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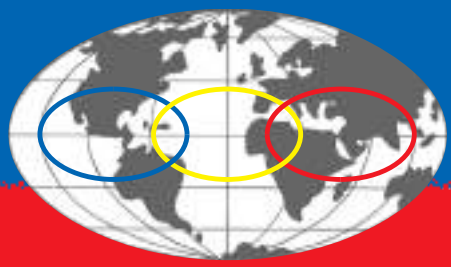

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Issue with supplement. Lacarrubba F, Musumeci Ml, Martorell A, Palmucci S, Petrillo G, Micali G. Role of the Imaging Techniques in the Diagnosis and Staging of Hidradenitis Suppurativa. G Ital Dermatol Venereol 2018;153 (3 Suppl 2), 20-5.

Books and monographs

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Books by one or more authors. Rossi G. Manual of Otorhinolaryngology. Turin: Edizioni Minerva Medica; 1987.
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Electronic material

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The foundations for this International Consensus Statement were laid down by the European Consensus Statement on the Prevention of Venous Thromboembolism developed at Windsor (UK) in 1991 with support from the European Commission.[1] The European Consensus Statement was subsequently updated by an international faculty and was forged into "The International Consensus Statement" by extensive evaluation of the literature and debate during the International Union of Angiology (IUA) World Congress in London in April 1995.[2] The latter was updated at the IUA European Congress in Rhodes in May 1999 and was published in "International Angiology" in 2001.[3] Subsequent work by the editorial committee and faculty reconvened at Windsor (UK) in January 2005 produced the publication of 2006.[4] This version was updated by the faculty at a special meeting at the Royal Society of Medicine, London, UK in July 2011, subsequent meetings in Chicago and Prague in July 2012 and was published in 2013.[5]

Due to COVID-19 restrictions the current version has been developed exclusively online in 2023.

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DISCLAIMER

GLOSSARY

aCL: Anticardiolipin antibodies
ANDA: Abbreviated new drug application
APCR: Activated protein C resistance
aPL: Antiphospholipid antibodies
APTC: Antiplatelet trialists collaboration
APTT: Activated partial thromboplastin time
APC: Activated protein C
APS: Antiphospholipid syndrome
ART: Assisted reproductive techniques
ASH: American Society of Hematology
AT: Antithrombin
ASCVD: Atherosclerotic cardiovascular disease
ATE: Arterial thromboembolism
BBLA: Biosimilar biologics license applications
BMI: Body mass index
CAPS: Catastrophic antiphospholipid syndrome
CDT: Catheter directed thrombolysis
CHMP: Committee human use medicinal products
CI: Confidence intervals
COC: Combined oral contraceptives
CrCl: Creatinine clearance
CRNMB: Clinically relevant non major bleeding
CRS: Caprini risk score
CUS: Compression ultrasound
CVD: Chronic venous disease
CVI: Chronic venous insufficiency
DOAC: Direct oral anticoagulant
DMIC: Define, Measure, Analyze, Improve, Control
DVT: Deep vein thrombosis
ECS: Elastic compression stockings
EMA: European medicine agency
EVAR: Endovascular aneurysm repair
EVF: European venous forum
FDA: Federal drug administration
FIT: Foot impulse technology
FUT: Fibrinogen uptake test
FVL: Factor V Leiden
GDP: Gross domestic product
GEC: Graduated elastic compression
KBC: Heparin bleeding site
HR: Hazard ratio
HIT: Heparin induced thrombocytopenia
HRT: Hormone replacement therapy
ICU: Intensive care unit
ICER: Incremental cost-effectiveness ratio
IgG: Immunoglobin G
IMiD: Immunomodulatory drug
INR: International normalized ratio
IPC: Intermittent pneumatic compression
IU: International units
IVC: Inferior vena cava
LDUH: Low dose unfractionated heparin
LMWH: Low molecular weight heparin
MPL: Myeloproliferative leukemia
MPN: Myeloproliferative neoplasms
NCCN: National comprehensive cancer network
NMES: Neuromuscular electrical stimulation
NMCR: Non major clinically relevant
NNH: Number needed to harm
NNT: Number needed to treat
NO: Nitric oxide
NPH: Nocturnal paroxysmal hemoglobinuria
NSAID: Non-steroidal anti-inflammatory drug
NSQIP: National surgical quality improvement program
MC: Mechanical compression
MHV: Mechanical heart valves
MNP: Myeloproliferative neoplasm
NPH: Nocturnal paroxysmal hemoglobinuria
OAC: Oral anticoagulants
OHSS; Ovarian hyperstimulation syndrome

OR: Odds ratio
PAI: Plasminogen activation inhibitor
PC: Protein C
PCDT: Pharmacomechanical catheter-directed thrombolysis
PE: Pulmonary embolism
PF4: Platelet factor 4
PLND: Pelvic lymph node dissection
Proximal DVT: DVT in popliteal or more proximal veins
PS: Protein S
PTS: Post-thrombotic syndrome
QALY: Quality adjusted life year
QoL: Quality of life
RAM: Risk assessment model
RCOG: Royal College of Obstetricians and Gynecologists
RCT: Randomized controlled trial
RR: Relative risk
RT: Radiotherapy
SCD: Sequential compression device
SCH: Subcutaneous heparin
SPECT: Single photon emission computerized tomography
SRA: Serotonin release assay
SVT: Superficial vein thrombosis
TBSA: Total burnt surface area
TEVAR: Thoracic endovascular aortic repair
TFPI: Tissue factor pathway inhibitor
TGA: Therapeutic goods administration
THA: Total hip arthroplasty
THR: Total hip replacement
TKA; Total knee arthroplasty
TKR: Total knee replacement
TURP: Transurethral prostatectomy
UFH: Unfractionated heparin
VKA: Vitamin K antagonist
VTE: Venous thromboembolism
WHO: World health organization
ZPI: Z-dependent protease inhibitor

POTENTIAL CONFLICTS OF INTEREST

Andreozzi GM: honoraria for lectures from Alfasigma and CoreTeam; **Antignani PL:** none; **Arcelus J:** educational lectures sponsored by Sanofi and Rovi; **Avgerinos E:** honoraria for lectures from INARI Medical, BD Medical, Boston Scientific, Gove Medical, Bentley, Philips, Servier; **Baekgaard N:** none; **Barber E:** research funding to her institution by Eli Lilly on Scientific Advisory Board of Merk; **Belcaro G:** none; **Black S:** consulting contracts with Cook, BD, BSCI, Gore, Philips, Medronic, Veryan and research funding from Medtronic and BSCI; **Bihari I:** none; **Benhamou AC:** none; **Bush RL:** none; **Carpentier P:** none; **Caprini J:** Sanofi, Janssen, Recovery Force, Arjo Inc.; **Catalano M:** none; **Clarke-Pearson DL:** none; **Davies A**: NIHR grants on VTE prophylaxis (CI-GAPS, CI-PETS, CI-THRIVE, Co App TIIIE, CI-GRACE); **Van Dreden P:** none; **Elalamy I:** grants from Sanofi and Leo Pharma, consulting fees from Sanofi, Leo Pharma, Bristol Myers Squibb, Pfizer, Viatris, Galapagos, support for attending meetings Sanofi, Leo-Pharma, Viatris, Gedeon Richter; **Eklof B:** none; **Fareed J:** none; **Fletcher J:** none; **Gasparis A:** honoraria from BD Bard, Medtronic, Boston Scientific, Philips, Cook Medical, Tactile Medical, SUN Scientific; **Gerotziafas G:** none; **Gibbs H**: none; **Geroulakos G**: none; **Giannoukas A:** honoraria/grants from Leo, Servier, Bard, Bayer; **Gohel MS**: honoraria for speaking/advisory/travel from Medtronic, BD, Cook Medical, research grants from Medtronic and Gore; **Goldhaber SZ:** research support for Bayer, BMS, Boston Scientific, BTG EKOS, Janssen, NHLBI, Pfizer, and consultant of Pfizer; **Griffin M:** none; **Gu Y**: none; **Gwozds A:** none; **Hadjianastassiou V:** none; **Heim D:** none; **Hussein EA:** none; **Iqbal O:** none; **Jawien A:** none; **Kakkar AK:** personal fees and research grants from Bayer AG, Sanofi S.A. and Anthos Therapeutics Inc.; **Kakkos S:** research grant from Sanofi Aventis and honorarium for lectures from Covidien; **Kantarcioglu B**: none; **Kolbel T:** none; **Labropoulos N:** none; **Lefkou E:** none; **Lichteberg M:** none; **Liew NC:** none; **Lopes RD:** research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, Portola; **Lugli M:** none; **Lurie F:** none; **Mansilha A:** none; **Malouf M:** none; **Mannello F:** honoraria for lectures from Alfasigma, Angelini, Servier; **Mendoza E:** Received honoraria for lectures from Bristol Myer Squibb, JuZo, Pfizer, Hartmann; **O Maleti:** none; **Mosti G:** none; **Nicolaides A:** honoraria from Cardinal Health, Servier, Pierre Fabre, Alfasigma; **Norgren L:** none; **Obi A:** PI preclinical research grant from Medtronic, Surmodics, and Advisory Board of Medtronic; **Palareti G:** none; **Papageorgiou C:** none; **Poredos P:** none; **Prandoni P:** honoraria from Sanofi, Italfarmaco, Alfasigma, Viatris; **Puggioni A:** none; **Raffetto J:** none; **Ramacciotti E:** research grants and consulting fees from Bayer and Pfizer, grants from the Brazilian Ministry of Science and Technology, and personal fees (educational) from Achē Pharma, Biomm Pharma, and Daiichi Sankyo; **Rao GH:** none; **Ricco JB:** none; **Robless P:** none; **Rognoni C:** none; **Sachev U:** none; **Spyropoulos AC:** research funding from Janssen, Astra Zeneca, advisory boards of Astra Zeneca, BMS Squibb, and

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SECTION 1

Introduction

Aims

This document aims to provide a clear and concise summary of the evidence regarding the efficacy or harm of various methods available to prevent and manage venous thromboembolism (VTE) and to provide recommendations based on such evidence.

Methodology of updating the document

This is the sixth revision of this document which was last published in 2013. A literature search was performed from January 2012 through September 2023 by searching Medline through its Pub-Med interface and the Cochrane library using standard key terms such as venous thrombosis, lower limb deep vein thrombosis (DVT), venous thromboembolism, pulmonary embolism (PE) and thrombosis with limits for: humans, clinical trial, randomized controlled trial, meta-analysis, and practice guidelines. Additional key terms were added that were specific to the subject for each part. Similar terms were used to search the Cochrane library. Randomized controlled trials (RCTs) and meta-analyses were the main sources used to determine efficacy and harm from different prophylactic and therapeutic methods. Observational studies or results from registries were used only when RCT were not available. Only fully published papers in peer review journals in English were used. Studies in which the diagnosis of DVT or PE was based on clinical findings without confirmation by an objective test were excluded. Abstracts that have not been subsequently published as full-length manuscripts were also excluded.

For each section of the document, members of the faculty were provided with the references and the first draft update as well as the opportunity to provide additional data. The updated section was then presented to the entire faculty for discussion and comment. Most changes were made at this time by the faculty. Parts that required major changes or additions were rewritten by a group and were presented again to the faculty for unanimous acceptance or suggestions for further changes. This process was iterative until the point when the entire faculty agreed.

Levels of evidence

Discrepancies regarding the significance or level of evidence were resolved by involving all faculty members. The following method for determination of levels of evidence was consistently used.

High level of evidence was provided by RCTs with consistent results, or systematic reviews that were directly applicable to the target population. In the past, single RCTs had not been accepted as adequate for high level of evidence and were considered to provide moderate evidence even when they were of a high quality and methodologically sound.[1-3] However, more recently, single randomized trials which have been rigorously performed, are methodologically reliable, and are sufficiently large to give clear results that apply to most patients in most circumstances have been accepted as high-level evidence.

Historically, RCTs of thromboprophylaxis studied an active agent *vs.* placebo or no prophylaxis. Following acceptance of routine thromboprophylaxis in moderate and high-risk patients in modern clinical practice, subsequent trials compared new agents with established prophylactic measures, *e.g.* direct oral anticoagulants (DOACs) with LMWH. If such trials give clear results for superiority, non-inferiority or inferiority that are applicable to most patients in most circumstances, they have been accepted as providing a high level of evidence.

Moderate level of evidence was provided by RCTs

with less consistent results, limited power or other methodological problems, which were directly applicable to the target population as well as by RCTs extrapolated to the target population from a different group of patients.

Low level of evidence was provided by well-conducted observational studies with consistent results that were directly applicable to the target population.

A review of the literature using the levels of evidence as defined above has revealed areas of lack of evidence or low-level evidence and several key questions that should be addressed by future studies. They are stated throughout the document and are summarized in the final section (Section 26).

Strength of recommendations

A strong recommendation is given when there is **evidence and/or general agreement** that a certain treatment is beneficial, useful, and effective.

A moderate recommendation is given when there is conflicting evidence and/or divergence of opinion, but the weight of the evidence or opinion is in favor of usefulness/efficacy.

A weak recommendation is given when there is conflicting evidence and/or divergence of opinion, but the usefulness/efficacy is less well established by evidence or opinion.

A specific treatment is not recommended when there is evidence or general agreement that a certain treatment is not useful or effective and, in some cases, may be harmful.

Costs of prevention or therapy

Since this is an international document, not focused on the clinical practice of one country or continent, and because of the variability in costs in different parts of the world, we have refrained from incorporating consideration of costs or cost-effectiveness in our recommendations. We believe that decisions about costs and resource allocations for healthcare interventions are more appropriately made by individual healthcare systems. However, recognizing that healthcare systems do not have unlimited resources, we have included a section that summarizes available cost-effectiveness evidence for primary prevention and treatment of VTE (Section 25) that can be used by appropriate decision-makers.

Outcomes

Evidence is presented for outcomes such as the incidence of asymptomatic DVT at screening, symptomatic DVT or PE, fatal PE, overall mortality and development of the post-thrombotic syndrome (PTS) when available. The decision to use asymptomatic DVT as well as symptomatic DVT or PE is a subjective one based on the following arguments.

a. Relationship between asymptomatic and symptomatic DVT and PE

The relationship between asymptomatic and symptomatic VTE, including PE has been known for some time.[4-6] Reduction in the incidence of asymptomatic DVT is associated with a reduction of symptomatic DVT and PE.[7-9] Large studies, such as the international multicenter trial, that were powered to study efficacy on fatal PE have demonstrated that reduction in asymptomatic DVT is accompanied by a reduction in symptomatic DVT, clinical PE and fatal PE.[10]

Another example is the meta-analysis of VKA in orthopedic surgery,[11] which showed a RR of 0.56 (95% CI 0.37 to 0.84) for DVT and 0.23 for PE (95% CI 0.09 to 0.59) compared with placebo. VKA were less effective than LMWH in preventing any DVT (RR 1.51; 95% CI 1.27 to 1.79) and proximal DVT (RR 1.51; 95% CI 1.04 to 2.17). The ratio between reduction in the incidence of DVT and incidence of PE observed in different general surgical, orthopedic, and medical patients because of different methods of prophylaxis is not constant, but this is not a valid argument to discard the endpoint of asymptomatic DVT. Thus, regulatory authorities have recognized asymptomatic proximal DVT as a valid endpoint of clinical trials and drug evaluation. As clinical practice and our knowledge base on VTE evolved, so did the regulatory requirements for product approval. A confounding factor is the use of symptomatic events to assess efficacy in trials where ultrasound or venography are also used to detect asymptomatic DVT, because these investigations introduce bias due to treatment of patients with the detected asymptomatic DVT, which suppresses and underestimates the true incidence of symptomatic PE and VTE. The same applies to the current opinion of regulatory bodies and authorities that favors weighting recommendations for effectiveness of prophylaxis or treatment based on symptomatic VTE and mortality. Treating symptomatic DVT (that is considered unethical not to treat) suppresses the true effect on PE and mortality.

Relatively few episodes of PE occur in patients with symptomatic DVT because appropriate treatment has been given. The majority of PE including fatal PE occur in patients with asymptomatic DVT. Thus, asymptomatic DVT

is an important stage of thromboembolic disease that has not yet manifested itself.

Sandler *et al.* performed a 5-year retrospective study on the general hospital patient population and all autopsy reports, also analyzing the clinical course during the hospital stay. Fatal in hospital PE was reported in 239 out of 2388 autopsies (10%). In this group of patients, lower limb DVT was confirmed in 83% patients at autopsy, of whom only 19% had had DVT symptoms and signs reported before death.[12]

b. Association between asymptomatic and symptomatic DVT to all-cause mortality

Two studies of thrombo-prophylaxis in patients hospitalized for acute medical illness have suggested that the presence of asymptomatic proximal DVT is associated with subsequent increased mortality.[13, 14] Using the data of the MAGELLAN study,[15] in a *post-hoc* defined analysis it was found that the incidence of all-cause mortality at 90 days was 4.8% in those that had no VTE; it was 11.4% in those with asymptomatic proximal DVT (HR 2.31; 95% CI 1.52 to 3.51; P<0.0001) and 29.2% in those with symptomatic VTE (HR 9.42; 95% CI 4.12 to 21.20; P<0.0001).[16] The authors concluded that asymptomatic proximal DVT is an indicator of clinically important VTE and is a useful outcome for evaluating efficacy in clinical trials of thromboprophylaxis in patients with acute medical illness.

c. Association between asymptomatic below knee DVT and post-thrombotic syndrome

Demonstration that asymptomatic below knee DVT is associated with subsequent development of PTS in 17% of patients,[17, 18] that 20% of asymptomatic calf DVT extend proximal to the knee if untreated[19] and that 17% of symptomatic calf DVT are associated with proximal extension or recurrence[20] also validates adoption of such endpoints for efficacy evaluation. Because PTS results in a marked reduction of Quality of Life (QoL) and because there is emerging evidence that it can be prevented by DVT prophylaxis, adequate treatment of lower limb DVT and prevention of DVT recurrence by extended prophylaxis,[21] we have devoted an entire section to this topic (Section 22).

Use of available evidence

Based on the above arguments, we have strived for objectivity in using the evidence present and available rather than absent (very few studies are powered for fatal PE or mortality as an endpoint), which results in many recommendations based on high level of evidence for preventing DVT, PE or recurrent VTE.[22] Such an approach provides clinically important distinctions to guide clinicians concerning prophylactic and treatment regimens.

This document presents the evidence in a concise format and explains how and why practice has changed in the last 30 years. It attempts to indicate not only the magnitude of the effect of different prophylactic regimens in terms of absolute, as well as, relative risk, but also the quality of the studies in terms of the level of evidence: high, moderate, or low. Safety information (clinically relevant and/or major bleeding and other adverse effects) is also provided. We believe that lack of evidence for mortality should not detract from objective evidence of morbidity.

Low molecular weight heparins (LMWHs)

Regulatory bodies in Europe and North America consider the various LMWHs (both original and generic) to be distinct drug products. They require clinical validation for specific indications for each drug. Each LMWH must be dosed according to the manufacturer's label and recommendations. Therapeutic interchange among these products is not appropriate. In our recommendations we have often used the term **LMWH dosed as per label** because different LMWHs are equally effective and because they have been grouped together in many meta-analyses. The choice of a particular LMWH should be made locally and should be based on the magnitude of clinical effect, level of evidence, approval by the regulatory authorities for each indication and cost.

Generic LMWHs

The approval process of generic LMWHs varies in different regulatory agencies. In United States of America (USA), the abbreviated new drug application (ANDA) pathway is exclusive for generic drug approvals while Biosimilar Biologics License Applications (BBLA) pathway is reserved for biosimilars. FDA considers unfractionated heparin and LMWHs a drug (not a biologic), therefore requires applicants to follow a new drug approval (NDA) pathway for new LMWHs and ANDA pathway for generic LMWH approval. An ANDA applicant is not required to submit clinical studies for re-establishing safety and efficacy of the generic drug product.[23] In contrast, other regulatory agencies such as European Medicine Agency (EMA), World Health Organization (WHO), Health Canada, and Therapeutic Goods Administration (TGA) of Australia consider LMWHs as biologically active products, therefore require the need for conducting clinical trials to evaluate the pharmacological effects of the LMWHs.[24] Thus, approval pro-

cesses show great variability in different authorities. Currently, only generic LMWHs are approved by FDA, and the biosimilar LMWHs are not available for commercial use in the US. The health authorities of the UK, Canada and Australia have also approved generic but not biosimilar LMWHs. Several generic and biosimilar LMWH products are approved and readily available in Europe, South America, Southeast Asia and other parts of the world.

Direct Oral Anticoagulants (DOACs)

For decades, VKAs were the only oral anticoagulants available for the treatment of patients. Although effective for the prevention of thromboembolism, their use required frequent monitoring and dose adjustments. Advantages of DOACs compared with VKAs include fewer monitoring requirements, less frequent follow-up, more immediate drug onset and offset effects (important for periprocedural and acute bleeding management: see Section 23), and fewer drug and food interactions.[25]

DOACs are categorized into two main classes: direct factor Xa inhibitors (*i.e.*, rivaroxaban, apixaban, edoxaban, and betrixaban) and direct thrombin inhibitors (*i.e.*, dabigatran). Dabigatran and rivaroxaban were approved by EMA in 2008.[26] This was followed by approval of several other DOACs in Europe. FDA approved its first DOAC, dabigatran in 2010, followed by rivaroxaban, apixaban, edoxaban, and betrixaban in the following years.[27] Betrixaban was withdrawn from the market in 2020 for independent business reasons. DOACs quickly became attractive alternatives to the long-standing standard of care VKA for prevention and treatment of VTE around the world. In addition, although DOACs are not yet available in US pharmacies, generic forms of DOACs have been approved by the FDA, EMA and other health authorities.

Implementation of guidelines

Creation of guidelines is necessary but not sufficient for implementation. We manage information and actionability in two basic methods: 1) day to day decision making in a busy clinical practice which often demands a more automatic, affect-based, fast, and a narrative process, known as type 1 thinking[28, 29] and 2) type 2 thinking which is slow, and probabilistic on which clinicians often rely.[13] Recognizing this bias can help us implement this guideline.

For facilitated change management a multidisciplinary unit, often including clinicians, quality control and administration shall trigger initiation of the implementation process by measuring the problem. Early institutional empowerment is necessary to allow physician champions to allocate time for feedback and amplification. The problem metrics shall trigger a unified message of urgency. These metrics shall also serve as accountable goals for follow-up after any changes in implementation.

Potential solutions will ideally undergo pilot testing while the main stakeholders share their opinion on potential barriers. Tactics for dissemination may often need to be contextualized to the problem and to the culture of the institution. There are multiple tools to follow an implementation process. Define, Measure, Analyze, Improve, Control (DMAIC) is a frequently discussed problem-solving tool used in Six Sigma, which is also used often in antimicrobial stewardship and other quality control projects.[30] The control mechanism may be assisted by simplification of pathways of care in the electronic medical system. Alert systems may help facilitate adoption and continuation of the practice changes.[31] Because meaningful use of electronic medical records remains low in many places, implementation teams need to remain resourceful with alternative tactics for system-based modifications. Ultimately, the implementation team will need to repeat the cycle (Plan-Do-Study-Act) of continuous quality improvement (see also "Health-system implementation of thromboprophylaxis" in Section 10).

Patient education

Successful implementation of VTE prophylaxis ultimately requires an alliance with the patient. Education can serve as the catalyst to form this necessary bond and trust. Patients know that anticoagulants can cause bleeding. Therefore, they may ask themselves whether the risk of bleeding is less important than the risk of clotting. Most will not be aware of the multiple rigorous clinical trials that support this pharmacological approach. Patient support groups and foundations dedicated to prevention of thrombosis are worthy collaborators in this mission to implement appropriate VTE prophylaxis. The North American Thrombosis Forum (NATF; www.thrombosis.org) comprises representatives from medicine, science, patients, families, government, and industry who have coalesced to endorse more widespread prevention efforts. As our knowledge of VTE prophylaxis progresses, multiple alliances using a team approach will propel us toward success.

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SECTION 2

The problem and the need for prevention

Incidence and complications of VTE

DVT and PE are major health problems with potentially serious outcomes. The annual incidence of symptomatic DVT and VTE (DVT plus PE) in the adult population is estimated to be 50-100 and 75-150 per 100,000 respectively and the incidence doubles for every 10-year increase in age.[1-3] Recurrent DVT rate is 10% in the first year and 25% at 5 years for unprovoked DVT. It is 5% and 15% respectively for provoked DVT with 4% of these events resulting in death.[4] Estimates of the overall annual costs of VTE vary from € 1.5 to 13.2 billion in the European Union[5] and $ 7 to 10 billion in the USA.[6]

The complications of DVT and PE may be significant and morbid. Acute PE may be fatal. Chronic thromboembolic pulmonary hypertension may complicate acute or recurrent PE. Post-thrombotic syndrome (PTS) occurs commonly following DVT because of the development of deep venous reflux and/or residual venous obstruction. PTS is associated with skin changes and ulceration and causes an adverse impact on quality of life and escalation of health care costs.

Predisposing factors

Virchow's triad of factors that predispose to VTE consists of venous stasis, alterations in blood constituents, and changes in the endothelium; these factors are as true today as when postulated in the 19th century. Principal clinical predisposing factors are immobilization, trauma, surgery, malignancy, autoimmune diseases, and previous history of venous thrombosis.[7] Other predisposing factors include age, obesity, infection, the postpartum period, varicose veins, dehydration, hormone replacement therapy, chronic heart failure, nephrotic syndrome, inflammatory bowel disease, and myeloproliferative disorders.[8-18] In addition, the predisposition due to a thrombophilia, which results in hypercoagulability or a prothrombotic state may also be a concurrent condition.[19, 20]

Patients admitted to hospital, both surgical and medical, are at particularly increased risk for VTE and the problem has been shown to continue after discharge.[21-25] Without prophylaxis, the incidence of DVT is high and depends, amongst others, on age, number of risk factors, and type and duration of surgery. The annual number of VTE-related deaths in six European countries has been estimated as 370,000 and three quarters of these were from hospital-acquired VTE.[26] VTE related events within 90 days after discharge from hospital represent a major cause of mortality and morbidity in the UK (60.4 cases per 100,000 admissions) and are associated with an estimated annual cost of £ 640 million when considering both hospital and community care.[27]

The very special group at significant risk of VTE is that of cancer patients. Approximately 20% of all VTE cases occur in oncology patients. According to autopsy studies, VTE can be expected in up to 20-50% of the cases, depending on the cancer type, disease advancement, location and applied therapy.[28, 29] In the VTE risk evaluation not only surgery but also other anticancer therapies should be taken into consideration including chemotherapy, immunotherapy as well as hormonal treatment. The risk of VTE remains especially high in some oncology patient cohorts, including hospitalized patients, patients undergoing systemic anticancer therapies as well as in patients with metastatic or in terminal phase of the disease. In some patients the occurrence of DVT or PE episode precedes the diagnosis of cancer, whereas in other subjects the VTE episode can be diagnosed at the same time as cancer or may occur

during the disease after the diagnosis of malignancy has been made[28, 30] (see Sections 11 and 17).

The need for education

Although VTE is an appealing target for maximally effective prevention, there is still a low rate of appropriate prophylaxis worldwide particularly for acute medically ill patients.[31-33] Continuing efforts to educate combined with hospital-wide protocols,[34] local audits for VTE prevention,[35] electronic alerts[25, 36] and the use of clinical nurse specialists[37] have been shown to result in a marked increase in the appropriate application of guidelines. The use of electronic medical alerts is particularly effective.[25, 36]

Another approach has been the mandatory implementation of evidence-based pathways for prophylaxis. The success of the UK program, which includes mandatory completion of a risk assessment tool, and implementation of an evidence-based pathway, is linked to reimbursement and has been shown to save more than 900 fatal PE events over 2 years.[38] Boston University introduced a program of mandatory implementation of an evidence-based pathway using the Caprini Risk Score which resulted in lowering the incidence of VTE by 84%. This institution has maintained a very low VTE incidence for more than 10 years with this program.[39] Preventing many fatal pulmonary emboli after surgery or hospitalization can be a reality using these methods.

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SECTION 3

Prevention in general, vascular, bariatric, plastic, cardiac and thoracic surgery

The risk

Risk in general surgery

Patients who undergo general surgical procedures are at risk of developing VTE.[1-6] In early studies performed in the absence of prophylaxis, the risk of asymptomatic DVT on screening was 25% (95% CI: 24% to 26%) in general surgery, 19% (95% CI: 15% to 25%) in abdominal vascular surgery, and 15% (95% CI: 9% to 23%) in peripheral vascular reconstructive procedures (Table 3.I).[3, 7-19]

In a meta-analysis of 32 studies involving 5091 general surgical patients without prophylaxis, the frequency of symptomatic PE was 1.6% (95% CI: 1.3% to 2.0%) and that of fatal PE was 0.8% (95% CI: 0.62% to 1.1%).[3]

Contrary to the belief that the incidence of postoperative DVT is rare in Asian patients, studies have demonstrated that this is not the case. The incidence of asymptomatic DVT was found to be 12.4% (95% CI: 10% to 15%) in Asians using the fibrinogen uptake test (FUT) in five studies.[7-11] In a meta-analysis of four studies, the overall ad-

TABLE 3.I.—*The frequency of all DVT in general and vascular surgery in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS). The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.*

Patient groups	Number of studies	Patients N.	DVT incidence (weighted mean)	95% CI
General surgery				
Clagett *et al.*, 1988[3]				
Total	54	4310	1084 (25%)	24% to 26%
General Surgery (Asian studies with FUT)				
Cunningham *et al.*, 1974[7]	68	8		
Nandi *et al.*, 1980[8]	150	4		
Shead *et al.*, 1980[9]	50	14		
Inada *et al.*, 1983[10]	256	39		
Phornphibulaya *et al.*, 1984[11]	74	9		
Total	4	598	74 (12.4%)	10% to 15%
Abdominal vascular surgery				
Hartsuck *et al.*, 1973[12]	26	7		
Angelides *et al.*, 1977[13]	88	18		
Belch *et al.*, 1980[14]	25	6		
Olin *et al.*, 1993[15]	50	9		
Killewich *et al.*, 1997[16]	48	1		
Hollyoak *et al.*, 2001[17]	21	9		
Total	6	258	50 (19%)	15% to 25%
Peripheral vascular reconstruction				
Hamer *et al.*, 1972[18]	21	9		
Passman *et al.*, 2000[19]	53	1		
Hollyoak *et al.*, 2001[17]	28	5		
Total	3	102	15 (15%)	9% to 23%

justed incidence of PE and fatal PE was 1.0% (95% CI: 0.0 to 2.0) and 0.4% (95% CI: 0.0% to 1.0%), respectively.[20] A multicenter study performed in Japan in 2006 using routine venography demonstrated that in the absence of prophylaxis, the incidence of postoperative DVT in patients having major abdominal surgery was close to that found in European patients (24%).[21]

The risk is increased by age, obesity, malignancy, history of VTE, and hereditary or acquired thrombophilia. This risk is also affected by the nature and duration of the operation, type of anesthesia, immobility, dehydration, sepsis, varicose veins, hormone replacement therapy and pregnancy.[22-26]

Risk assessment

Traditional risk stratification

The traditional classification of patients into high, moderate, or low risk of developing VTE is summarized in Table 3.II.[27]

Low risk category is defined when the frequency of calf vein thrombosis, proximal vein thrombosis or fatal PE is <10%, <1% and <0.1% respectively.

Moderate risk category is defined when the frequency of calf vein thrombosis, proximal vein thrombosis and/or fatal PE is 10-40%, 1-10% and 0.1-1.0%.

High risk category is defined when the frequency of calf vein thrombosis, proximal vein thrombosis and fatal PE is 40-80%, 10-30% and >1%, respectively.

In general surgery, patients can be allocated into these three risk categories according to the type of operation (major or minor), age and presence or absence of additional risk factors (Table 3.III). This simple risk classification model has been derived from a series of prospective studies of general surgical patients not receiving prophylaxis.[22-26]

The Rogers risk score

A risk assessment model (RAM) is the Rogers risk score published in 2007.[28] This risk prediction model was based on 183,069 patients undergoing vascular and general surgical operations. In this group of patients symptomatic VTE occurred in 1162 (0.63%) of patients and the 30-day mortality in patients with VTE was 11.19%. Based on 15 independent variables, a predictive model was developed for postoperative VTE (C statistic 0.76) as well as a risk score that can be used in the preoperative assessment of patients undergoing major operations. Based on this score patients can be classified into very low-risk (score <7), low-risk (score 7-10) and moderate risk (score >10). The problem of such a study performed in 2007 was that many of the patients were on prophylactic regimens for VTE and patients developing clinical DVT were treated by prompt therapeutic anticoagulation to prevent PE. Thus, most of the PE detected originated from silent DVT.

Table 3.II.—*The definition of risk categories in general surgical patients using FUT and in hospital pulmonary embolism. Although based on old studies the percentages shown in this table are still used to define the category of risk. Modified from: Salzman* et al.[27]

Category	Frequency of calf vein thrombosis	Frequency of proximal vein thrombosis	Frequency of fatal PE
High-risk	40-80%	10-30%	>1%
Moderate-risk	10-40%	1-10%	0.1-1%
Low-risk	<10%	<1%	<0.1%

Table 3.III.—*Risk categories according to clinical risk factors in general surgical patients.*

Risk	Category
High	Major General Surgery, age >60
	Major General Surgery, age 40-60 & cancer or history of DVT/PE or other risk factors including thrombophilia
Moderate	Major General Surgery, age 40-60 without other risk factors*
	Minor surgery, age >60
	Minor surgery, age 40-60 with history of DVT/PE or other risk factors
Low	Major General Surgery, age <40; No other risk factors*
	Minor surgery, age 40-60; No other risk factors*
	Minor surgery: Operations other than abdominal lasting less than 45 minutes
	Major surgery: Any intra-abdominal operation and all other operations lasting more than 45 minutes

*The risk is increased by infectious disease, presence of varicose veins, general immobility.

The Caprini risk score

Another approach is to use a scoring system based on empirical weighting of risk factors according to the strength of their association with thrombotic events.[29-32] The Caprini Risk Score (CRS) is based on many risk factors combined with a relative weight of each factor. CRS, which is the most validated risk score, has been reported in 284 publications involving more than 60 medical and surgical groups.[29-34] These studies demonstrated that as the numerical score increased, the VTE rate rose exponentially. In the validation study by Bahl *et al.*[29] published in 2010, which involved 8216 patients undergoing general, vascular and urologic operations, symptomatic VTE at 30 days was zero for score 0-1, 0.70% for score 2, 0.97% for score 3-4, 1.33% for score 5-6, 2.58% for score 7-8 and 6.51% for score ≥9. These findings led to a modification of the CRS

TABLE 3.IV.—*Caprini score thresholds and associated risk of VTE in general, vascular, plastic and thoracic surgery. Modified from: Lobastov* et al.[36]

Specialty	Caprini Risk Score	Risk of VTE
General surgery	0-2	<1%
	3-4	1%
	5-8	1.6%
	≥9	15.9%
Vascular surgery	0-6	<2%
	7-9	5.6%
	≥10	14.7%
Plastic surgery	0-6	0-1.4%
	7-8	2.3%
	≥9	5.6%
Thoracic surgery	0-4	0%
	5-8	10.5%
	≥9	38.6%

to include a separate "super high risk" group for patients with a CRS 9 or more.[29, 35]

A recent systematic review examined the thresholds of the CRS associated with increased risk of VTE in different specialties. The data from 202 publications demonstrated that the thresholds for highest CRS risk vary with different specialties.[36] Based on this data, in general surgery patients receiving prophylaxis, a CRS <5 is associated with a clinical VTE risk of <1% (low risk); a CRS of 5-6 with a VTE risk of 1-3% (moderate risk); a CRS of 7-8 with a risk of 3-6% (high risk), and a CRS of 9-11 with a risk of 26% (very high risk) (Table 3.IV).[36]

The Chao-Yang VTE risk assessment model

The most recently developed risk score is that obtained from the Chao-Yang VTE risk assessment model, which involved 533 patients undergoing thoracic surgery.[37] None of these patients received any perioperative prophylaxis. Lower limb ultrasonography was performed before and after operation. Patients with new postoperative DVT, symptoms of PE or high Caprini Score (>9) underwent pulmonary CT-angiography. The overall incidence of VTE was 8.4% (45 out of 533 patients). Of these 45 patients, 86.7% were DVT and 13.3% were PE. Factors associated with increased risk were age ≥60, American Society of Anesthesiologists score ≥2, cancer diagnosis, open operation, operative time >180 minutes, intraoperative bleeding (>200 ml), preoperative D-dimer >0.55 mg/L, RBC<4.0× 10^{12}/L and BMI ≥30 kg/m^2. VTE was 1.3% for score 0-4 (low risk), 8.4% for score 5-8 (moderate risk) and 20.4% for score ≥9 (high risk). The area under the ROC curve was 0.80.

Other risk assessment models

Other risk assessment models such as the Kucher, Padua, Intermountain and IMPROVE which have been developed specifically for medical patients are not applicable to surgical specialties (for these see section 10 on medical patients).

Risk after discharge from hospital

Studies in patients undergoing abdominal or pelvic surgery demonstrate that the risk continues following discharge from hospital.[38, 39] Moreover, in a recent case crossover study based on the French national input database, the risk of postoperative PE was significantly higher even 12 weeks after surgery in ranges of OR: 2.26 (95% CI: 1.81 to 2.82) for gastrointestinal operations to OR: 3.15 (95% CI: 2.25 to 4.41) for vascular operations.[40]

This finding has implications for the duration of thromboprophylaxis. Patients having abdominal or pelvic operations for cancer as well as extensive abdominal and pelvic surgery have been shown to benefit from 30 days of LMWH (for evidence, see "Duration of Prophylaxis" below).

Data from the RIETE database in 2008, and 2019 have shown that many medical and surgical patients suffer a VTE event following hospital discharge, and at least half of these individuals experience a VTE event when anticoagulation is stopped.[41, 42]

Based on data from the National Surgical Quality Improvement Program (NSQIP), Iannuzzi and co-workers developed a risk assessment model to predict the probability of VTE after hospital discharge. The study involved 844,159 patients who had general surgical, vascular, urologic, gynecologic, thoracic, cardiac, colorectal, breast, upper GI, hepatobiliary, pancreatic and neurosurgical procedures. Multivariable analysis was used to develop a model on two thirds of the patients that was then validated on the remaining one third. Age ≥58, operation duration ≥100 minutes, steroid use, functional status/dependent, BMI ≥30, smoking, malignancy, major postoperative inpatient complication, and days from operation to discharge were independent predictors for post discharge VTE. The model showed good predictive ability for the validation data (C-statistic of 0.713). The postdischarge risk of VTE was 1.35% in the high-risk group (5.3% of the population), 0.68% in the medium risk group (18.6% of the population) and 0.19% in the low-risk group (76.1% of the population).[43]

Risk in vascular surgery

Despite the use of intraoperative heparin or other peri-operative antithrombotic agents, patients undergoing major vascular surgery are at significant risk of VTE occurrence.

In the absence of postoperative prophylaxis, the incidence of asymptomatic DVT is 19% in patients having abdominal vascular surgery and 15% for those having peripheral vascular reconstruction (Table 3.I). In the absence of prophylaxis, the reported incidence of proximal DVT (DVT in popliteal or more proximal veins) in patients having abdominal vascular reconstruction is 4-6%[15, 17] and the incidence of symptomatic VTE within 90 days of major elective or urgent vascular procedures has been found to be 1.7% to 2.8%.[44] A prospective European registry of vascular surgical procedures showed that the incidence of symptomatic DVT was 0.9% following aortic procedures and 0.7% following femoro-distal bypass operations.[45] The National Impatient Sample (20% of all inpatients across the USA 1998-2001) demonstrated that the incidence of symptomatic VTE was 1.9% for CABG, 1.2% for abdominal aortic aneurysm, 1.1% for amputation, 0.87% for lower limb revascularization and 0.54% for carotid endarterectomy.[46] When routine screening with ultrasound was used in patients having abdominal aortic aneurysm repair with LMWH prophylaxis starting 1-5 days after surgery, the incidence of asymptomatic DVT was 10.2% if the repair was open and 5.3% if endovascular.[47] In a more recent survey of 2,669,772 patients who had surgical operations between 2005 and 2010 the incidence of symptomatic DVT in cardiac surgery was 2.07%, vascular surgery 0.99% and general surgery 0.66%. The odds ratio for developing DVT was 1.52 (95% CI: 1.44 to 1.61) for vascular surgery and 3.00 (95% CI: 2.48 to 4.07) for cardiac surgery when compared with general surgery (P<0.0001).[48]

In a series of 45,548 patients who underwent an elective vascular procedure identified in the National Surgical Quality Improvement Program (NSQIP) (2007-2009), symptomatic VTE was diagnosed in 1.3% of patients who had an aortic procedure. The incidence of VTE was 4.2% after open thoracoabdominal aortic aneurysm surgery, 1.7% after open abdominal aneurysm surgery and 2.2% and 0.7% after thoracic endovascular aortic repair (TEVAR) and endovascular aneurysm repair (EVAR) respectively. In patients who had infra-inguinal bypass grafting, the incidence of VTE was 1.0% whereas after carotid endarterectomy 0.2%. An important message from this observational study is that 41% of all VTEs were diagnosed after discharge from hospital. In addition, diagnosis of postoperative VTE was associated with a significant increase in mortality. In patients with diagnosed DVT the overall mortality increased from 1.5% to 6.2% and in patients with PE the risk of death increased from 1.5% to 5.7%.[49] The incidence of asymptomatic DVT in a prospective study in which patients undergoing abdominal aortic endovascular repair were screened with postoperative ultrasound imaging was 8%.[50]

In a more recent study involving 1,449 vascular surgery patients the postoperative incidence of VTE was 3.4%. In this series, a CRS of 7 as cut-off point stratified patients for development of VTE (7.7% *vs.* 1.6%). Earlier initiation of pharmacological prophylaxis was associated with a reduced risk of VTE development.[51]

Based on the data of the most recent review and meta-analysis, in vascular surgery patients, a CRS<6 is associated with a clinical VTE risk of <2% (low risk); a CRS of 6-7 with a VTE risk of 2-5% (moderate risk); a CRS of 7-9 with a risk of 5-6% (high risk), and a CRS of ≥10 with a VTE risk of 14% (very high risk) (Table 3.IV).[36]

Risk in laparoscopic surgery

The risk of VTE in patients undergoing laparoscopic surgery appears to be low. Two small prospective studies in which prophylaxis was not used showed an incidence of DVT detected by Duplex ultrasound or venography in the range of 0-2%.[52, 53] Other prospective studies in which some form of prophylaxis was used confirmed the low incidence[54-58] except for one in which 11 of 20 patients developed DVT.[59] Large series from surveys,[60-62] registries,[63-66] a literature review,[67] and a population study[44] indicate that the risk for clinical post-operative VTE after laparoscopic procedures is less than 1%. The use of prophylaxis in these studies is not reported in detail, but there appears to be a wide variation from none to LMWH in 80% of patients in some hospitals.

A retrospective study compared the incidence of clinical VTE in 46,105 open abdominal operations and that of 92,490 laparoscopic operations in four selected procedures: appendicectomy, cholecystectomy, anti-reflux surgery and gastric bypass surgery between 2002 and 2006.[68] The incidence of VTE was 0.59% in open cases compared with 0.28% in laparoscopic cases (P<0.01). The incidence varied enormously by severity of illness. In those who had a minor or moderate illness, the incidence of VTE was 0.18% for open procedures and 0.10% for laparoscopic procedures. However, in those who had severe illness, the incidence of VTE was 3.66% for open procedures and 2.74% for laparoscopic procedures.

Risk in bariatric surgery

Obesity is a known independent risk factor for sudden postoperative fatal PE.[69, 70] Bariatric surgery is associated with symptomatic DVT in 1.2% to 1.6% of cases and with PE in 0.8% to 3.2% depending on the objective

method used for the diagnosis despite the use of LMWH or LDUH.[71-80] In these patients VTE is the most common cause of readmission and mortality.

Using a private insurance claims database of 17,434 patients who underwent bariatric surgery, the incidence of VTE at one month after laparoscopically adjustable gastric banding was 0.8% compared with 2.7% after laparoscopic gastric bypass and 3.3% after open gastric bypass. Over 74% of the VTE events occurred after discharge from hospital. Risk factors for VTE included male sex (OR: 1.68, 95% CI: 1.37 to 2.07), age ≥55 (OR: 2.18, 95% CI: 1.56 to 3.03), smoking (OR: 1.86, 95% CI: 1.06 to 3.27) and previous VTE (OR: 7.48, 95% CI: 5.78 to 9.67).[81] Other studies reported transfusion, history of DVT, prolonged operative length, BMI >55, PTS, obesity hypoventilation syndrome, pulmonary hypertension, cardiomyopathy, and obstructive sleep apnea as risk factors.[78, 82]

Based on the NSQIP database, with over 95,000 patients, a model has been proposed to estimate the risk of VTE after discharge in bariatric surgery that includes the following independent risk factors: congestive heart failure, paraplegia, reoperation, resting dyspnea, surgical technique other than gastric band, age^3 59, BMI^3 50 Kg/m^2, hospital stay^3 3 days, and length of surgery^3 3 hours.[83] Among 45 examined variables, the final risk-assessment model contained 10 categorical variables including congestive heart failure, paraplegia, reoperation, dyspnea at rest, non-gastric band surgery, age ≥60 years, male sex, BMI ≥50 kg/m, postoperative hospital stay ≥3 days, and operative time ≥3 hours. The model demonstrated good calibration (Hosmer-Lemeshow goodness-of-fit test, P=0.71) and discrimination (C-statistic = 0.74).

A recent study used the CRS to select patients for extended prophylaxis after sleeve gastrectomy.[84] Patients received 5000 IU UFH or 7500 U UFH if BMI >40 preoperatively and these doses combined with IPC were continued throughout hospital stay. Following discharge, they received LMWH 40 mg once daily or 40 mg twice daily if BMI >40, for 7 days when scores were 5-8, or 30 days for scores of 9 or more. None of the patients discharged on extended VTE prophylaxis developed a VTE event. Likewise, no patient deemed to be at low risk for VTE based on their Caprini Scores developed a VTE event, and no episode of porto-mesenteric venous thrombosis (PMVT) occurred in the series.

Risk in plastic surgery

A systematic review on the reported incidence of VTE in patients undergoing plastic surgery has indicated that it is 0.3% for abdominoplasty, 0.8% for abdominoplasty and concomitant plastic surgery, 2.2% for abdominoplasty combined with intra-abdominal procedures and 3.4% for circumferential abdominoplasty.[85] In a survey involving 10,000 abdominoplasties not having prophylaxis the incidence of symptomatic PE was 1%.[86] In a large plastic surgery patient cohort, Panucci showed that the 60-day clinically relevant VTE incidence was related to the Caprini Score. The incidence of VTE was 1.3% in those with a score of 5-6, 2.7% in those with a score of 7-8 and 11.3% in those with a score of ≥9.[80] None of these patients had pharmacologic prophylaxis.

A few authors have suggested the CRS is not useful for certain plastic surgery procedures such as body contouring and face lifts.[87, 88] In contrast, the CRS was very valuable for patients undergoing sternal reconstruction.[89]

Pannucci published an interesting theory regarding risk assessment in Plastic Surgery patients where the overall VTE incidence is low. He states that "Most (96%) breast augmentation patients were at lower risk (Caprini ≤6) for VTE. Many (28%) had modifiable VTE risk factors. Monte Carlo simulation demonstrated that most VTE will occur among lower risk (Caprini ≤6) patients, because rare events in a very common population (96% are Caprini ≤6) are more likely to occur than frequent events in a rare population. The point of this study is that these patients with a low risk of VTE still should have a CRS performed to identify those with modifiable risk factors. In addition, patients with a past or family history of thrombosis or a history of obstetric complications can be identified and protected appropriately.[90]

An extremely thoughtful publication appeared combining the unique features of numerous plastic surgery procedures with inherent risk factors specific to everyone. An algorithm was suggested as a guide for when to apply prophylaxis based on the CRS with minor modifications specific to plastic surgery.[91] The authors indicated the need for further RCTs in plastic surgery patients so that eventually an international guideline, based on plastic surgical data, using a validated risk assessment model, which combines the surgical risk with the patient related risk.

Based on the data of the most recent review and meta-analysis in plastic surgery patients, a CRS <6 is associated with a clinical VTE risk of 0-1.4% (low risk); a CRS of 7-8 with a VTE risk of 2.3% (moderate risk); a CRS of ≥9 with a risk of 5.6% (high risk)[32] (Table 3.IV).[36]

Risk in cardiothoracic surgery

Cardiac surgery

Two post-mortem studies demonstrated that fatal PE accounts for approximately 11% to 20% of all unexplained

deaths after cardiac surgery, with at least 50% not diagnosed before death.[92, 93]

The incidence of **asymptomatic DVT** detected by routine ultrasound scanning in patients having coronary artery bypass grafting (CABG) in the absence of prophylaxis or prophylaxis for less than three days, was found to be 44.3%[94] and 17.4% respectively.[95] In two other studies in which patients had routine CT-pulmonary angiography, the incidence of **silent PE** was found to be 3.2%[96] and 6.2%.[97] Other studies showed that **symptomatic PE** occurred in 0.4% to 9.5% of patients after CABG and it was fatal in 0.3-1.7% of the series.[92, 98]

In one recent study both CT-pulmonary angiography and ultrasound scanning of the lower limbs was performed on the 7th (±3) postoperative day in a series of 100 patients having CABG. All patients were on aspirin but none on mechanical or heparin prophylaxis. PE was detected in 13% of the patients, simultaneous PE and DVT in 8% and isolated DVT in 4%, totaling 25% of the patients for VTE. Of the 12 DVTs all were below the popliteal vein but two extended proximally.[99]

Lung surgery

Two studies reported on the incidence of **clinical VTE** in patients having lung resection for cancer in the absence of prophylaxis. In a series of 77 lung resections, there were four (5.1%) PE and 11 (14.2%) DVTs, a total of 15 VTE cases (19.4%).[100] In the most recent one, which involved 372 lung resections, there were 7 (1.9%) symptomatic PE.[101]

In a meta-analysis of 19 studies, in which most of them were retrospective, the mean postoperative incidence of PE at 30 days was 2.0%, despite some forms of prophylaxis used in a proportion of patients.[102]

In a prospective study involving 157 patients receiving "guideline-based" thromboprophylaxis until hospital discharge and who had CT-pulmonary angiography and lower limb ultrasonography, there were 19 (12.1%) events: 14 (8.9%) PE, three (1.9%) DVT and one combined PE/DVT. The 30-day mortality in patients with VTE was 5.2%.[103]

The Caprini Risk Score has been validated in a series of 232 patients undergoing lung resection.[104] Clinical VTE at 60 days occurred in 12 (5.2%) patients. Four occurred post-discharge. Six of the 12 patients had PE, of which one was fatal in a patient with a score of 16. The VTE incidence increased with the Caprini Score. Scores in the low, moderate and high-risk groups were associated with a VTE incidence of 0%, 1.7% and 10.3%, respectively. These events occurred despite the administration of LDUH or IPC being used by 92% of patients in the moderate or high-risk groups.

In 1141 patients undergoing lung transplantation and receiving pharmacological prophylaxis, the incidence of symptomatic DVT was 8.8%, reaching 17.3% with routine screening.[105]

Esophagectomy

In a retrospective study of 1095 patients undergoing esophagectomy for cancer, the 30-day incidence of clinical **VTE** was 7.3% (6.1% for DVT and 2.4% for PE).[106] Risk factors for VTE in all patients (43,808) having cancer operations were age >60, BMI >35, recent steroid therapy, blood transfusion of ≥3 units, deep infection, re-intubation, postoperative sepsis, postoperative shock, cardiac arrest, hospital stay >1 week. In hospital post-esophagectomy mortality increased from 6.9% to 13.6% when VTE occurred.[107]

Based on the data of the most recent review and meta-analysis,[36] in thoracic surgery patients in the absence of prophylaxis, a CRS 0-4 is associated with a clinical VTE risk of 0% (low risk); a CRS of 5-8 with a VTE risk of 10.5% (high risk); and a CRS of ≥9 with a risk of 38.6% (very high risk) (Table 3.IV).[36]

Risk in breast surgery

The overall incidence of symptomatic VTE after breast surgery is low, around 0.3%. Depending on the surgical procedure, it varies from 0.13% for lumpectomy, to 0.29% for mastectomy, and 0.52% for mastectomy and breast reconstruction.[108, 109]

In 52,000 cases of mastectomy for cancer, the following factors increased the risk of VTE: respiratory disease, hypothyroidism, hospital stay >5 days, previous VTE, and autologous reconstruction.[110] The incidence of symptomatic VTE in patients without prophylaxis, depending on the Caprini Score was 0% in low to moderate risk patients, 1.3% in high-risk, and 1.6% in very high-risk patients.[111]

Prophylactic methods

General considerations

General surgery

Low dose unfractionated heparin

In the 1970s, low dose unfractionated heparin (LDUH) (5000 IU every 8 or 12 h subcutaneously) was found to reduce the incidence of both DVT and fatal PE in patients having general surgery.[112-114] In the International Multi-

center Trial which included 4,121 patients randomized to LDUH or no prophylaxis, there was a reduction in fibrinogen uptake test (FUT) detected DVT, symptomatic DVT, clinical PE, and fatal PE.[113, 114]

During the late 1980s, two meta-analyses compared LDUH with no prophylaxis or placebo (29 RCTs involving 8000 general surgical patients)[3, 4] showed that the incidence of asymptomatic DVT was reduced from 22% to 9% (RR: 0.41, 95% CI: 0.35 to 0.47) and fatal PE from 0.8% to 0.3% (RR: 0.39, 95% CI: 0.17 to 0.87). However, there was a small increase in bleeding complications, mainly wound hematomas, from 3.8% to 5.9% (RR: 1.56, 95% CI: 1.21 to 1.99).

LMWH

A multi-center study found that LMWH not only reduced the incidence of fatal PE but also the overall surgical mortality compared with controls without prophylaxis.[115] Two small, placebo controlled RCTs, one in patients having major oncological abdominal surgery[116] and the other on emergency abdominal surgery[117] also demonstrated the effect of LMWH in reducing the incidence of asymptomatic DVT.

LMWH *vs.* LDUH

Subsequently, 16 studies[118-133] and nine meta-analyses compared LMWH with LDUH.[134-142] Six studies compared different doses of LDUH or LMWH.[123, 143-147] There were some differences between the studies regarding selection of patients. Four of the meta-analyses reported that there was no difference in total mortality comparing LMWH with LDUH.[135, 137-139] Two meta-analyses reported a reduced incidence of symptomatic PE with LMWH from 0.70% to 0.31% (RR: 0.43, 95% CI: 0.33 to 0.54).[135, 137] and one showed a decrease in symptomatic VTE.[139] The overall conclusion was that although there was not a large difference between LMWH and LDUH in terms of DVT reduction, **LMWH was more effective than LDUH in reducing PE**. In addition, the latter had to be given 2-3 times daily whereas LMWH could be administered once daily.

LMWHs have a lower risk of heparin-induced thrombocytopenia (HIT) (see Section 20) than LDUH.[148, 149] High dose LMWH is more effective but is associated with a higher incidence of hemorrhagic complications than LDUH, whereas a low dose of LMWH has a similar efficacy with less bleeding.[137] In view of the above advantages of LMWH over LDUH, LDUH is no longer recommended unless LMWH is not available.

Regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. Dose interchange among these products is not appropriate.[150]

Fondaparinux

In a double-blind double-dummy RCT involving 2,927 patients having high risk major abdominal surgery, **fondaparinux 2.5 mg** once daily was found to be **at least as effective as peri-operative LMWH** (dalteparin 5 000 U once daily) in preventing venographically detected DVT without any increase in bleeding.[151] The incidence of DVT was 6.1% in the dalteparin group and 4.6% in the fondaparinux group (P=0.14). There was not any difference in major bleeding (2.4% *vs.* 2.8%) **when fondaparinux was administered at least six hours after operation.** However, in the subgroup of 1941 **patients with cancer, the incidence of DVT was reduced from 7.7% in the dalteparin group to 4.7% in the fondaparinux group (RR: 0.74, 95% CI: 0.40 to 0.93; P=0.02)**.

Antiplatelet agents

Antiplatelet agents, including aspirin in high doses (500-3000 mg per day) reduce DVT by 30% and PE by 50%. In a meta-analysis of 22 RCTs[152] involving 1459 general surgical patients where DVT was diagnosed by surveillance with fibrinogen uptake, the incidence of DVT was reduced from 27% in the control group to 19% in the antiplatelet therapy group (RR: 0.71, 95% CI: 0.62 to 0.82). In the same meta-analysis, data on PE were available in 26 RCTs involving 3419 patients. The incidence of PE was reduced from 1.7% in the control group to 0.5% in the antiplatelet group (RR: 0.28, 95% CI: 0.16 to 0.48). In view of the availability of more effective methods of prophylaxis and the potential side effects of high dose aspirin which was in the range of 600-3000 mg in several RCTs, aspirin is no longer considered as an alternative prophylaxis in European centers. However, it is used in lower risk patients in some centers in USA based on the above data and a cost benefit argument.

Graduated elastic compression

Graduated elastic compression (GEC) stockings reduce the incidence of asymptomatic DVT in general surgery by approximately 50-60% as shown by several studies (Figure 3.1),[10, 153-159] and three systematic reviews,[160-162] but the number of patients studied has been too small to be able to assess the effects on the development of PE. A Cochrane systematic review demonstrated that in ten studies involving 1486 general surgical patients, the incidence of DVT

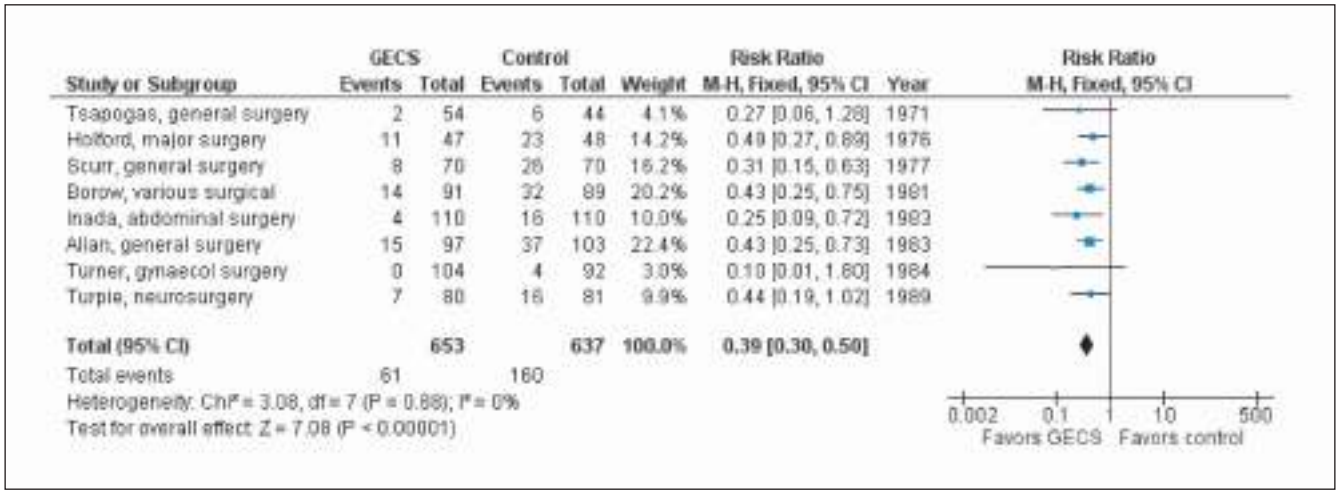

Figure 3.1.—Effect of graduated elastic compression stockings (GEC) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake and/or phlebography) in non-orthopaedic surgical randomized controlled studies.[153-159]

was reduced from 19.9% in the control group to 7.0% in the compression group (OR: 0.30, 95% CI: 0.22 to 0.41).[163]

Intermittent pneumatic compression

A meta-analysis of 11 RCTs (1318 patients) (Figure 3.2)[156, 164-173] demonstrated a reduction of the incidence of asymptomatic DVT from 25% in the control group to 7.9% in the IPC group (RR: 0.32, 95% CI: 0.24 to 0.42). A meta-analysis involving 2270 patients from 15 studies randomized to IPC or no prophylaxis conducted in orthopedic (5), general surgical (4), oncologic (3), neurosurgical (3) and urologic (1) specialties, showed that IPC reduced the risk of DVT by 60% (RR: 0.40, 95% CI: 0.29 to 0.56; P<0.001).[174]

The recent data about the use of IPC in high-risk surgical patients confirm the better efficacy of IPC as the

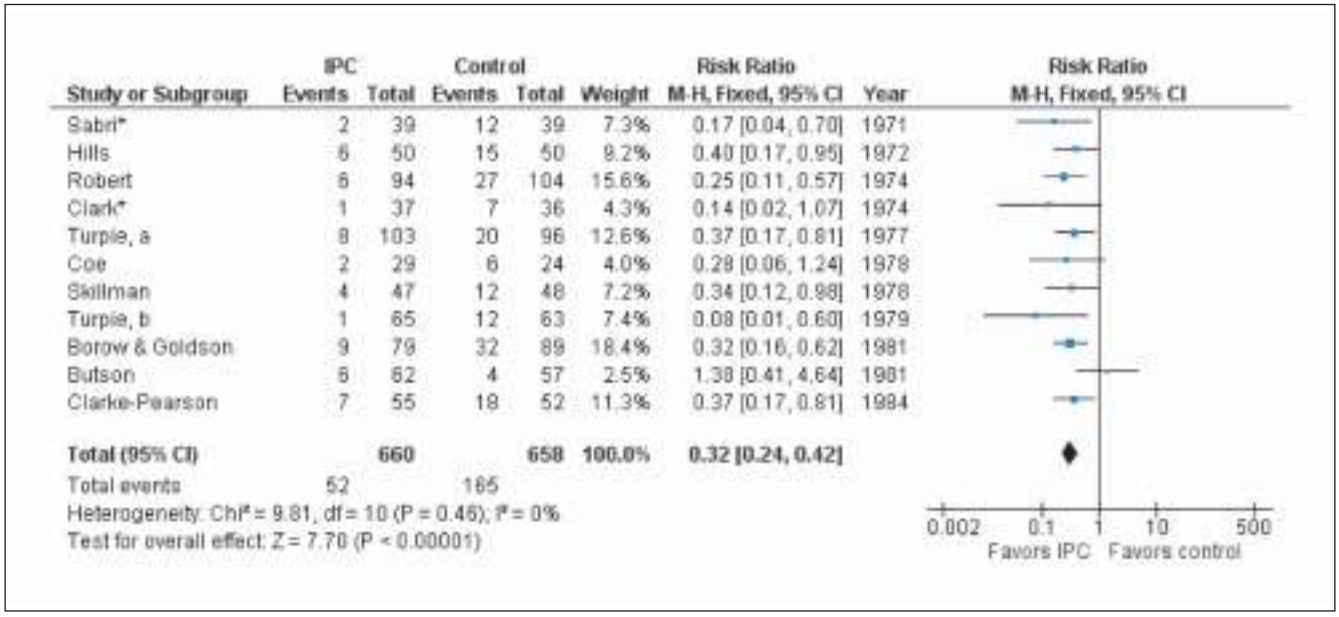

Figure 3.2.—Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test or phlebography) in non-orthopaedic surgical randomized controlled studies.[164-173]
*Contralateral leg was used as the control.

adjunctive prophylaxis method in comparison with IPC alone. In a RCT on 682 gastric cancer surgery patients, the VTE incidence in the group that received combined prophylaxis (LMWH+IPC) was significantly lower than the incidence of VTE in the patients that received IPC alone (0.6% *vs.* 3.6% P=0.008)[175] (see Section 12 on Combined Modalities).

IPC or GEC *vs.* heparin

A systematic review of 16 RCT of mechanical compression (MC), *i.e.*, GEC or IPC *vs.* prophylactic heparin *i.e.*, LDUH or LMWH published in 2010 demonstrated that the pooled RR: for MC compared with heparin was 1.07 (95% CI: 0.72 to 1.61) for DVT and 1.03 (95% CI: 0.48 to 2.22) for PE. MC was associated with significant reduction of postoperative bleeding compared with heparin (RR: 0.47, 95% CI: 0.31 to 0.70). Among the studies that used LDUH, there was a non-significant trend towards a lower risk of DVT with heparin compared with MC (RR: 0.71, 95% CI: 0.42 to 1.19). However, among the studies that used LMWH, there was a significant higher risk of DVT with MC (RR: 1.80, 95% CI: 1.16 to 2.79) compared with heparin, but LMWH was still associated with an increased risk of bleeding.[176]

Electrical calf stimulation

In the early 1970s two studies tested the efficacy of electrical calf stimulation during operation using one leg as control in general surgical patients. In the first study which involved 110 patients, the incidence of asymptomatic DVT was 21% in the unstimulated leg and 8.2% in the stimulated leg (OR: 0.33, 95% CI: 0.15 to 0.77).[177] In the second study which involved 60 patients, the incidence of asymptomatic DVT was 15% in the unstimulated leg and 1.6% in the stimulated leg (OR: 0.11, 95% CI: 0.01 to 0.90).[178] Subsequently, in a RCT, electrical calf stimulation was applied to both legs of 37 patients while 40 acted as controls. The incidence of asymptomatic DVT was 30% in the unstimulated group and 14% in the stimulated group (OR: 0.35, 95% CI: 0.90 to 1.16). In this RCT, perfusion lung scanning, and chest X-rays were performed the day before operation and 4-6 days after operation. The incidence of silent PE was 35% in the control group and 10% in the group receiving electrical stimulation (OR: 0.33, 95% CI: 0.11 to 0.97).[179]

In the most recent systematic review published in 2018, three meta-analyses were performed comparing intraoperative neuromuscular electrical stimulation (NMES) with controls (no thromboprophylaxis), NMES with LDUH, and NMES as an adjunct to heparin compared with heparin alone.[180] The first meta-analysis involved five RCTs (4 in general surgery and one in trauma with hip fractures) involving a total of 717 patients and performed between 1972 and 2012. The incidence of silent DVT was reduced from 25.5% in the absence of prophylaxis to 10.3% in the group having NMES (OR: 0.29, 95% CI: 0.13 to 0.65; P=0.003). The second meta-analysis involved three RCTs (two in general surgery and one in neurosurgery) including a total of 341 patients. The incidence of silent DVT was 23.9% in the NMES group and 13.4% in the LDUH group (OR: 2.00, 95% CI: 1.13 to 3.52; P=0.02). The third meta-analysis involved three RCTs (one in spinal cord injury, one in postoperative trauma surgery and one during total knee arthroplasty) including a total of 168 patients. The risk of developing silent DVT was lower in the combination therapy group (NMES plus LDUH or LMWH) than the heparin alone, but this was not statistically significant (15% *vs.* 34.1%) (OR: 0.33, 95% CI: 0.10 to 1.14; P=0.08).

During the period of 1970-1990 the equipment used for electrical calf muscle stimulation produced painful stimuli so that electrical stimulation could be used only intraoperatively as indeed was done in the above-mentioned studies. Modern equipment, now commercially available, produces muscle contractions because of electrical impulses that are painless and can be tolerated by patients throughout the day. The efficacy of such modern equipment used not only during surgery but also during the postoperative period should be determined in adequately powered RCT before any recommendations can be made.

Combined modalities

RCTs show that combinations of prophylactic methods are more effective than using each method singly. They include **LDUH with GEC** (Figure 3.3),[181-184] **GEC with IPC** and **LDUH with GEC** (Figure 3.4).[182-187]

GEC combined with IPC was more effective than IPC alone. It reduced the incidence of DVT from 12.2% to 2.8% (RR: 0.25; 95% CI: 0.09 to 0.73).[183]

The combination of LDUH with IPC was more effective than LDUH alone. It reduced the incidence of DVT from 26% to 1.5% (Figure 3.4).

In a double blind RCT in patients having abdominal surgery, the combination of **fondaparinux 2.5 mg once daily and IPC** (different devices) was compared with placebo combined with **IPC**. The combined modalities produced a further reduction of VTE from 5.3% to 1.7% (RR: 0.31, 95% CI: 0.12 to 0.69; P=0.004) and proximal DVT from 1.7% to 0.2%; P=0.037. Major bleeding occurred in 1.6% in the combined group and 0.2% in the intermittent pneumatic compression group.[188]

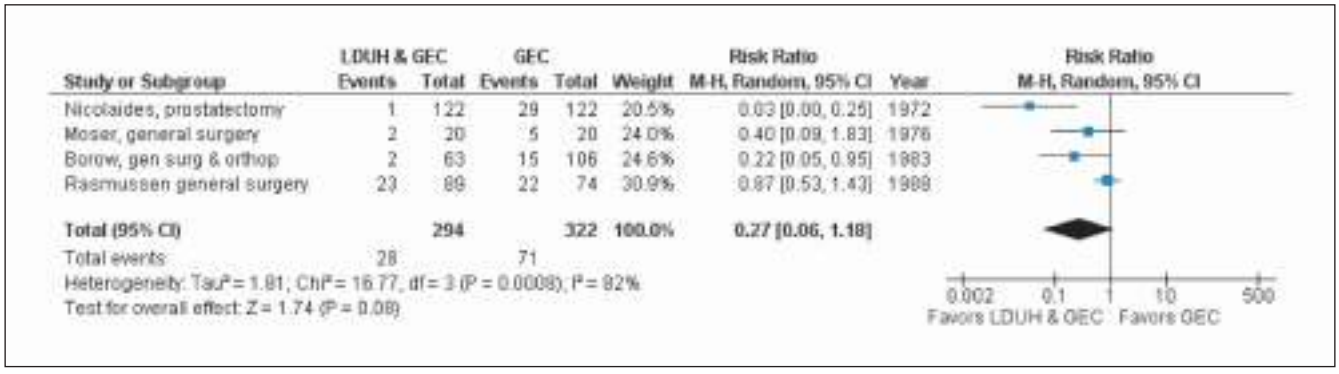

Figure 3.3.—Effect of graduated elastic compression (GEC) stockings *versus* low dose unfractionated heparin (LDUH) plus GEC in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).[181-184]

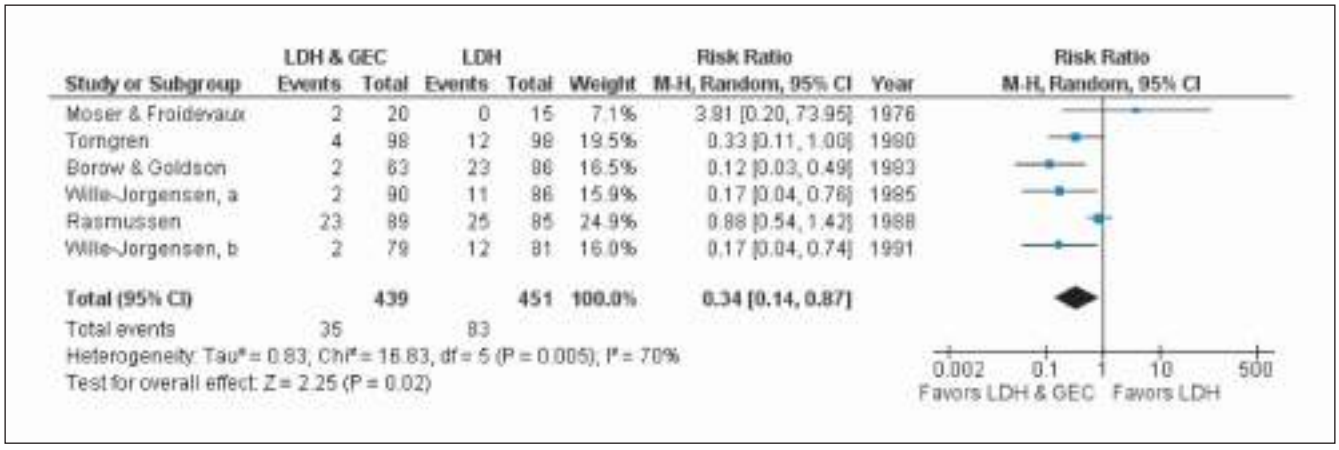

Figure 3.4.—Effect of low dose unfractionated heparin (LDUH) *vs.* LDUH plus graduated elastic compression (GEC) in the prevention of DVT in non-orthopaedic surgical patients diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).[182-187]

A RCT involving 2,551 patients undergoing **cardiac surgery** demonstrated reduction in the incidence of PE from 4% in the LDUH group to 1.5% in the group receiving **LDUH combined with IPC** (RR: 0.37, 95% CI: 0.22 to 0.63).[189]

The additive role of mechanical and pharmacological modalities suggests that venous stasis and hypercoagulability are independent risk factors. Elastic compression prevents endothelial damage which tends to occur when veins dilate during anesthesia resulting in endothelial tears.[190] IPC reduces venous stasis by producing active flow enhancement[191, 192] and also increases the plasma levels of tissue factor pathway inhibitor (TFPI)[193] while LDUH and LMWH inhibit factors II and Xa. The different mechanisms of action are probably responsible for the improved results shown when mechanical prophylaxis (GEC or IPC were combined with LDUH, or even GEC combined with IPC).

A meta-analysis of RCTs comparing pharmacological prophylaxis (mainly LMWH) with pharmacological prophylaxis combined with GEC (mainly in orthopedic studies) performed after 2004 has casted doubts on the validity of the results due to a high degree of heterogeneity.[194]

The GAPS study published in 2020 randomized a total of 1858 patients undergoing elective upper gastrointestinal, obstetric/gynecologic and lower gastrointestinal surgery to LMWH or LMWH combined with GEC. The incidence of clinical VTE was 1.7% in the LMWH group and 1.4% in the combined modality group (P>0.05). LMWH alone was confirmed to be non-inferior. The authors concluded that GEC might be unnecessary in most patients undergoing elective surgery.[195] A possible explanation offered by the authors could be the shorter length of hospital stay and earlier mobilization in comparison to historical studies that were using a combination of LDUH with GEC. As indicated above LMWH is more effective

in reducing VTE (especially PE) than LDUH. It might be due to the fact that pharmacological prophylaxis in general and abdominal surgery is mainly provided by LMWH or fondaparinux and the hospital stay is shorter in the current era, so that the addition of GEC might be unnecessary.

A recent trial from Japan compared IPC with IPC plus enoxaparin in 400 patients undergoing laparoscopic surgery for gastric and colon cancer. The incidence of VTE detected by surveillance with contrast-enhanced CT scans on the lower limb and chest was 4.8% with IPC, and 3.3% with the combination, without reaching a statistically significant difference.[196]

The most recent Cochrane database systematic review and meta-analysis published in 2022, involving 14,931 patients from 34 studies, which included general surgical, orthopedic and cardiac surgical patients, demonstrated the efficacy of combined modalities in the prevention of DVT and PE.[197] The incidence of DVT was reduced from 9.3% in the anticoagulant group to 5.5% in the heparin plus IPC groups (OR: 0.38, 95% CI: 0.21 to 0.70) and PE from 1.8% to 0.9% (OR: 0.46, 95% CI: 0.30 to 0.71), respectively. The incidence of DVT was reduced from 3.8% when IPC was used alone to 2% when IPC was combined with heparin (OR: 0.51, 95% CI: 0.36 to 0.72) and PE from 1.34% to 0.65% (OR: 0.51, 95% CI: 0.29 to 0.91) respectively (see Section 12 on combined modalities).

Lobastov *et al.* demonstrated that, in very high-risk patients with a CRS of 9 or 10, the frequency of symptomatic VTE was as high as 11%, and in those with scores of 11 or greater, the incidence of asymptomatic VTE events approach 59% despite the combination of elastic compression stockings (ECS) and LMWH prophylaxis. The authors postulated that this extremely high-risk group required improvements in their VTE preventive protocol. They randomized 407 patients to receive either GEC/LMWH alone or combined with (IPC). Only one (0.5%) of 204 patients in the combined group compared with 34 (16.7%) of 203 patients in the GEC/LMWH group (P<0.001) developed VTE. Three cases of fatal PE were seen in the GEC/LMWH group and none in the combination group.[198]

Laparoscopic surgery

There are no RCTs of prophylaxis *vs.* no prophylaxis in patients having laparoscopic surgery. However, two RCTs investigated the need for post discharge prophylaxis. In the first RCT, 209 consecutive patients received prophylaxis consisting of GEC and variable doses of dalteparin based on their risk score. At discharge, patients were randomly allocated either to continue dalteparin for one week or to not to receive any further prophylaxis. Duplex scanning was performed four weeks after discharge. The incidence of DVT was 0% in the dalteparin group and 0.95% in the control group (P=1.0).[199]

In the second RCT, 225 patients who underwent laparoscopic surgery for colorectal cancer and received LMWH prophylaxis for 8 days and did not have any DVT on ultrasound were randomized to one week or four weeks of extended heparin prophylaxis. A repeat ultrasound examination at four weeks demonstrated the presence of DVT in 11(9.7%) of 113 patients in the short heparin prophylaxis group and none in the patients randomized to the extended heparin prophylaxis (P=0.001). DVT was proximal and symptomatic in two patients. The remaining nine patients had asymptomatic distal deep vein thromboses. The median age of the patients was 66 (range 28-89). Age over 70 years was an independent predictor of DVT at multivariable analysis (HR: 3.77, 95% CI: 1.13 to 12.55; P=0.03).[200]

Bariatric surgery

In a survey of members of the American Society for Bariatric Surgery, 95% of surgeons routinely used some form of thromboprophylaxis.[201] Prospective and retrospective non-controlled studies found a low incidence of VTE (less than 1.2%) in patients undergoing bariatric surgery given LMWH or LDUH.[202-205]

In several studies on LDUH administration, the dose modification proposals up to 7500 IU three times daily can be found. However, in other patient cohorts standard 5000 U sc. three times daily dosage were still used.[204, 206]

LMWH appears to be at least as effective as LDUH and is associated with a more convenient and stable profile of anticoagulant activity.[206, 207]

A double-blind pilot RCT involving 175 bariatric surgical patients compared postoperative **fondaparinux 5 mg daily with preoperative LMWH** (Enoxaparin 40 mg twice daily). Routine magnetic resonance venography (MRV) performed at 2 weeks demonstrated 2 patients with DVT in each arm of the study. No major adverse events occurred in either group. In this study adequate anti-Xa levels were more common with fondaparinux (74.2%) than with enoxaparin (32.4%). The authors concluded that **both regimens appeared to be equally effective at reducing the risk of DVT**. However, further studies are needed to determine the optimal prophylaxis regimen in bariatric surgery.[208]

Several observational and comparative studies suggest-

ed that 60 mg of enoxaparin twice daily is effective and well tolerated by patients with morbid obesity.[209]

Comparison of 40 *vs.* 60 mg of enoxaparin twice daily showed a similar rate of VTE in both series (0.8 *vs.* 0%), and postoperative bleeding was 3.2% in the low dose group compared with 1% in the higher dose group.[209] Other observational studies showed similar results and concluded that a higher dose of LMWH should be considered in bariatric patients at high risk for VTE.[210, 211]

A limited number of observational studies and comparisons with historical controls suggest that IPC is effective in reducing DVT in bariatric surgery.[212-215]

In two consecutive groups of patients, a **higher dose of LMWH (enoxaparin 40 mg twice daily) in combination with GEC and IPC was associated with fewer thrombotic events compared with a lower dose group** (enoxaparin 30 mg twice daily) in combination with GEC and IPC (0.6% *vs.* 5.7%; P<0.01).[216] Bleeding was rare occurring in one patient in each group.

Plastic surgery

In the absence of RCTs in **high-risk patients having plastic surgery,** recommendations are based on extrapolation from general surgery and observational studies. A series of 1458 patients having plastic surgery and receiving postoperative prophylactic doses of LMWH while in hospital was compared with a group of 1876 historical controls who did not have any prophylaxis. All patients were stratified according to the Caprini Score. In the presence of a Caprini Score of less than 7 the incidence of VTE was 1.2% in both groups. In the group with Caprini Score 7-8 the incidence of VTE was 2.5% in the control group and 1.15% in the LMWH group. In the presence of a Caprini Score >8 the incidence of VTE in the control group was 8.5% and in the LMWH group 4.1%.[217] Thus, in high-risk patients **LMWH or fondaparinux starting 24 hours after surgery or a combination of LMWH with IPC and GES** are often used.

Cardiac surgery

A systematic review and meta-analysis by Ho *et al.* in 2015 identified five RCTs involving a total of 725 patients, which compared one method of prophylaxis (IPC, LDUH, aspirin and leg elevation) against placebo or no prophylaxis and used ultrasound to detect asymptomatic DVT.[218] The results of this part of the meta-analysis were of borderline significance (OR: 0.64, 95% CI: 0.38 to 1.09). These results were driven by one positive RCT by Mirhosseini *et al.*[219] who randomized 120 patients having off-pump CABG surgery into a group receiving aspirin 80 mg daily combined with LDUH three times a day and a group receiving the same dose of LDUH. The incidence of asymptomatic DVT was reduced from 16.6% in the LDUH group to 3.3% in the group receiving combined therapy (P=0.015). There was no significant difference in the rate of bleeding (four cases *vs.* one case).

In the above-mentioned review by Ho *et al.*[218] there was another meta-analysis of six RCT which compared one method of prophylaxis (warfarin, aspirin or IPC) with placebo or no prophylaxis and involved a total of 3,248 patients with symptomatic VTE as an endpoint. There was a significant reduction in VTE rates in the group receiving prophylaxis (OR: 0.44, 95% CI: 0.28 to 0.71). The results of this meta-analysis were mainly driven by the study of Ramos *et al.*[189] who randomized 2,551 patients in two groups comparing IPC combined with LDUH 12-hourly with LDUH alone. Clinical PE was reduced from 4% in the LDUH group to 1.5% in the group receiving IPC combined with LDUH (62% reduction) (P<0.001).

It is interesting to observe that the only two RCTs that demonstrated a significant benefit for DVT or PE were using combined prophylaxis: IPC with LDUH in the study by Ramos *et al.*[189] and LDUH combined with low-dose aspirin (80 mg/day) in the study by Mirhosseini *et al.*[219] Further studies are needed to determine the optimum prophylaxis in cardiac surgery.

Thoracic surgery

We are not aware of any RCTs comparing one method of prophylaxis against no prophylaxis with statistically significant reduction in DVT or PE frequency, although there are several observational studies available.[220]

According to the Cochrane analysis of 2015, in 6 studies focusing on thoracic surgery patients (only some of the patients had cancer), 15 symptomatic VTE episodes among 2890 patients were identified (0.51%).[221] According to the authors all studies had major study design flaws and most lacked a placebo or no treatment control group. They could not pool data because of the different comparisons or the lack of the data. Thus, recommendations below are by extrapolation from RCT from other specialties.

Duration of prophylaxis

In most of the studies, the duration for prophylaxis was 5-7 days. However, several studies suggested that the risk continues after discharge from hospital.[38, 39, 41, 222-225] Recent evidence suggests that the risk of postoperative VTE persists several weeks after the procedure and continues

even after the hospital discharge. For example, an analysis of the RIETE registry has evaluated over 3000 patients with symptomatic VTE after non-orthopedic surgery for non-cancer procedures, finding that the median interval between surgery and the detection of VTE was 16 days (IQR 8-30), with almost 80% of the episodes occurring after the 7th postoperative day, and 27% after 30 days. Interestingly, 75% of the VTEs occurred after pharmacological prophylaxis had been discontinued.[42]

In the United Kingdom, Lewis-Lloyd *et al.* evaluated over 100,000 patients undergoing colectomy with a 3-month follow-up. The overall incidence of postoperative symptomatic VTE after hospital discharge was 0.63%, increasing three times in cases of emergency surgery. Besides, in the first four postoperative weeks, the incidence of VTE was significantly higher after emergency surgery for benign conditions, especially inflammatory bowel disease, than for elective colon cancer surgery.[226]

RCTs have demonstrated that extending prophylaxis from one week to one month reduces asymptomatic DVT by 50-70%.[147, 227-230] In the study by Lausen *et al.*,[147] approximately 70% of patients were operated on for malignancy. The other studies had only pelvic/abdominal malignancies included. In three meta-analyses,[231-233] there was a relative risk reduction for VTE of 60-70%. The numbers were too small to allow conclusions for an effect on the incidence of fatal PE. There were no significant differences for major or minor bleeding between the two regimens.

Further support for the effect and safety of extended prophylaxis in abdominal cancer was obtained in a study on bemiparin, a second generation LMWH.[234] In this study, extended prophylaxis was associated with an 88% reduction in proximal DVT and a 24% reduction in the composite endpoint of any DVT, nonfatal PE and death from any cause. Thus, in surgery for abdominal/pelvic malignancy, extended prophylaxis to four weeks does reduce the frequency of VTE and is safe.

A meta-analysis published in 2019 identified seven RCTs involving 1728 patients undergoing abdominal and pelvic surgery, which compared prolonged thromboprophylaxis using LMWH with control or placebo.[235] The incidence of VTE was 13.2% in the control groups compared with 5.3% in the patients receiving out-of-hospital LMWH (OR: 0.38, 95% CI: 0.26 to 0.54). There were similar reductions for all DVTs (OR: 0.39, 95% CI: 0.27 to 0.55), for proximal DVT (OR: 0.22, 95% CI: 0.10 to 0.47) and symptomatic DVT which was not significant (OR: 0.30, 95% CI: 0.08 to 1.11) (incidence 1.0% in the control group and 0.1% in the LMWH group). There was no significant difference in the incidence of bleeding between control and LMWH group (2.8 *vs.* 3.4%) (OR: 1.10, 95% CI: 0.67 to 1.81 and mortality (3.8% *vs.* 3.9%) (OR: 1.15, 95% CI: 0.72 to 1.84). The authors concluded that prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE compared with thromboprophylaxis during hospital admission only, without increased bleeding complications or mortality after abdominal or pelvic surgery. The quality of the evidence is moderate and supports the routine use of prolonged thromboprophylaxis.

In a RCT of 225 patients having laparoscopic surgery for colorectal cancer, LMWH prophylaxis for four weeks was more effective than one week. The incidence of ultrasound detected DVT at 28 days was 9.7% in the one-week prophylaxis group and zero in the 28 days prophylaxis group (P=0.005). The rate of bleeding was similar in the two groups.[200]

In a pilot randomized open label study of patients undergoing laparoscopic surgery for colorectal cancer and LMWH prophylaxis for one week, 569 patients were randomized to extended prophylaxis with rivaroxaban (10 mg once daily) or placebo for a further three weeks. Extended prophylaxis reduced the primary outcome (symptomatic DVT, asymptomatic ultrasonography detected DVT or VTE related death) at 28 days from 3.9% to 1.0% (OR: 0.26, 95% CI: 0.07 to 0.94). Major bleeding occurred in none of the patients in the placebo group and in two (0.7%) patients in the rivaroxaban group (P>0.05). The authors concluded that rivaroxaban was more effective than placebo for extended prevention of DVT after laparoscopic surgery for colorectal cancer without an increase in major bleeding.[236]

Further studies are needed to determine the optimal duration of extended prophylaxis and whether mortality is influenced. There are no studies on extended prophylaxis after vascular surgery.

Extended duration of pharmacological prophylaxis (>7 days) should be considered if patients develop complications such as infection during the postoperative hospitalization period.[237, 238]

Obese patients undergoing bariatric surgery should also be evaluated for post discharge VTE risk and may be considered for extended pharmacological prophylaxis.[239]

Recommendations

Patients undergoing general surgery

Low-risk patients are those without risk factors undergoing minor surgery. The data are insufficient to make any recommendations. Based on risk/benefit ratio and extrapo-

lation from studies in moderate-risk patients, it is common practice in some countries to use **GEC stockings** in addition to early ambulation and adequate hydration (**Level of evidence low, recommendation weak**).

Moderate-risk patients are those over the age of 40 years undergoing major surgery for benign disease in the absence of additional risk factors. The use of **LMWH** (initiated and dosed according to labelling) is recommended (**Level of evidence high, recommendation strong**). An alternative method, especially in patients at risk for or with active bleeding, is **GEC with IPC** used continuously until the patient is fully ambulant (**Level of evidence high, recommendation strong**). LMWH may be added when the risk of bleeding is minimized.

LDUH may be used instead of LMWH if the latter is not available (**Level of evidence high, recommendation strong**).

High- risk patients are those over the age of 60 undergoing major surgery for benign disease or any patient with additional risk factors. **LMWH** or **fondaparinux** initiated and dosed according to labelling is recommended (**Level of evidence high, recommendation strong**).

LMWH or **fondaparinux** should be combined with **IPC, particularly in the presence of cancer or other risk factors** (**Level of evidence high; recommendation strong**).

An alternative method to the pharmacological thromboprophylaxis, especially in patients at high risk for bleeding or with active bleeding, is **GEC with IPC till the time when pharmacological prophylaxis will be acceptable** (**Level of evidence high, recommendation strong**).

If LMWH is initiated after surgery, the intraoperative use of GEC with IPC is advised (**Level of evidence low, recommendation strong**).

Laparoscopic surgery

Patients undergoing laparoscopic surgery who do not have any additional risk factors should receive **GEC or GEC with intraoperative IPC** (**Level of evidence: low, recommendation weak**). In the presence of additional risk factors, they should receive **LMWH, fondaparinux or IPC** (**Level of evidence low, recommendation strong**). In patients at very high risk the combination of the pharmacological methods and IPC should be applied (**Level of evidence low; recommendation strong**).

Patients undergoing abdominal or pelvic major surgery for cancer and do not present contraindications to extended prophylaxis should receive **LMWH up to one month after operation** (**Level of evidence moderate, recommendation strong**). Rivaroxaban would be an alternative when approval for this indication becomes available (**Level of evidence moderate, recommendation moderate**).

Patients undergoing bariatric surgery

Patients at low risk undergoing bariatric surgical procedures should receive **IPC or LMWH** (**higher dosage**) alone or **fondaparinux** (as per label) (**Level of evidence low, recommendation strong**).

Patients at high risk should receive a **combination of LMWH and IPC** (**Level of evidence moderate, recommendation strong**) or **LMWH** (**enoxaparin-40 mg twice daily**). Another alternative is **enoxaparin** (**40 mg twice daily**) **started before surgery followed by fondaparinux started after surgery** (**Level of evidence moderate; recommendation strong**).

Extended prophylaxis is recommended for patients at high risk of VTE up to four weeks after discharge (**Level of evidence moderate, recommendation strong**).

Patients undergoing vascular surgery

Patients undergoing major vascular surgery should receive **LMWH** (**Level of evidence moderate, recommendation strong**). In other vascular surgery cases the decision on VTE prophylaxis should be based on the individual VTE prophylaxis benefit/risk evaluation.

GEC is contraindicated in patients with peripheral arterial disease because of anecdotal reports of gangrene (**Level of evidence low, recommendation low**).

Patients undergoing plastic surgery

High-risk patients having plastic surgery should receive **LMWH or LMWH in combination with IPC** (**Level of evidence moderate, recommendation strong**).

In patients at high risk of bleeding and high risk of VTE, **IPC with GEC should be used perioperatively** at least till the moment when an implementation of the pharmacological prophylaxis will be considered safe (**Level of evidence low, recommendation strong**).

An alternative to LMWH, is the use of fondaparinux starting after operation (**Level of evidence moderate, recommendation weak**).

Patients undergoing cardiac surgery

Patients having cardiac surgery **should receive** IPC combined with LMWH which is started 12 hours after completion of surgery **or when satisfactory hemostasis has been achieved** (**Level of evidence moderate, recommendation strong**).

Patients undergoing thoracic surgery

In the absence of malignancy, patients should receive **IPC. In the presence of risk factors or cancer, LMWH** prophylaxis should be added when satisfactory hemostasis has been achieved and continued for at least the duration of hospital stay (**Level of evidence moderate, recommendation strong**).

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SECTION 4

Prevention in urologic surgery

The risk

In the 1970s and 1980s, the incidence of DVT diagnosed with surveillance methods, in the absence of prophylaxis, was 33% in patients having open urologic surgery and 9% in patients having transurethral procedures (Table 4.I).[1-11] In a study, performed in 2011 and using ultrasound examination of the lower limb veins on the 7th postoperative day, 538 consecutive patients had urologic cancer surgery (nephrectomy in 177 participants, radical cystectomy in 86 participants and radical prostatectomy in 275 participants); the incidence of DVT was 7.4%. DVT was asymptomatic in 92% and limited to calf veins in 80%. There were 12 (2.2%) PEs, of which 4 (0.7%) of them were fatal.[12] These thromboembolic events occurred despite the use of heparin and mechanical prophylaxis prior to patient ambulation.

A review of 1,653,275 surgical cases registered in the California Patient Discharge Data Set between January 1, 1992, and September 30, 1996, reported that the incidence of symptomatic VTE was 3.7% after radical cystectomy, 2.0% after nephrectomy for malignancy compared with 0.4% in non-cancer patients, and 1.5% after radical prostatectomy.[13] Urologic procedures with a low incidence of VTE included transurethral resection of the prostate (TURP) and incontinence operations.

The incidence of symptomatic DVT and symptomatic PE after urologic endoscopic surgery in 2002 was reported

TABLE 4.I.—*The frequency of all DVT in patients undergoing urologic surgery in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS).*

Patient groups	Number of studies	Patients N.	DVT incidence	95% CI
Open urological operations				
Becker *et al.*, 1970[1]		187	39	
Mayo *et al.*, 1971[2]		41	21	
Nicolaides *et al.*, 1972[3]		25	7	
Hedlund *et al.*, 1975[4]		40	18	
Rosenberg *et al.*, 1975[5]		32	11	
Sebeseri *et al.*, 1975[6]		31	18	
Kutnowski *et al.*, 1977[7]		25	12	
Coe *et al.*, 1978[8]		8	1	
Bergqvist & Hollböock, 1980[9]		19	6	
Vandendris *et al.*, 1980[10]		33	13	
Hedlund & Blomback, 1981[11]		28	13	
Total	11	469	159 (33%)	29% to 38%
Transurethral prostatectomy				
Hedlund, 1975[4]		101	10	
Mayo *et al.*, 1971[2]		20	2	
Nicolaides *et al.*, 1972[3]		29	2	
Total	3	150	14 (9%)	5% to 15%

The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

to be 0.11% and 0.45%, respectively.[14] The data from the National Prostatectomy Audit also demonstrated that the incidence of VTE was 0.3% in patients undergoing prostate interventions, where 85% of the patients underwent TURP (including DVT in 0.2% and PE in 0.1%).[15]

Similar rates of symptomatic VTE between 0.3-4.8% have been reported for laparoscopic urologic surgery,[16-20] which was shown in a single comparative study to be as hazardous as open urologic surgery.[16]

In the absence of VTE prophylaxis the DVT risk in patients undergoing kidney transplantation ranges from 5 to 8%.[17, 21]

The incidence of symptomatic VTE is currently reported to be in the range of 0.2-24%, and PE is the most common cause of postoperative death.[12, 22-24] In observational studies performed after 2000, the risk of VTE was 0-0.4% for transurethral ureteroendoscopy, 0.2-2.9% for nephrectomy, 2.6-22.6% for nephrectomy for advanced/high-risk disease (stage 3 or 4 malignancy), 0.2-0.9% for radical prostatectomy without extensive lymph node dissection, 3.9-15.7% for radical prostatectomy with extensive lymph node dissection, 6-24.4% for radical cystectomy and 0-1% for retroperitoneal lymph node dissection.[24]

Prophylactic methods

IPC

Two small, randomized studies involving 153 patients undergoing open urologic procedures compared **IPC with controls**.[8, 25] Asymptomatic DVT was numerically reduced from 14.9% to 6.3% (RR: 0.43, 95% CI: 0.15 to 1.17; P=0.085).

LDUH

LDUH was effective in reducing asymptomatic DVT in eight RCTs in which the control groups did not have prophylaxis (Figure 4.1).[3-7, 9-11] The overall incidence of DVT was reduced from 39% to 16% (RR: 0.41, 95% CI: 0.24 to 0.71).[3, 4, 6-8, 10, 11, 26] A study of 579 patients having radical prostatectomy did not find any difference in the number of pelvic lymphoceles or blood loss between those receiving LDUH and those not having prophylaxis.[27]

LMWH *vs.* fondaparinux

RCTs to study the efficacy of LMWH for VTE prevention in patients undergoing urologic surgery have yet to be performed. Also, RCTs using any prophylactic modality in patients having transurethral resection are not available.

A RCT compared **fondaparinux** with **LMWH** in 298 patients undergoing radical prostatectomy (N.=244) or radical nephrectomy (N.=32) for malignancy. All patients had LDUH for the first 24 hours starting 6 hours after surgery and were then randomized to fondaparinux 2.5 mg daily or LMWH (enoxaparin) 2000 IU 12-hourly. In addition, all patients received mechanical prophylaxis until ambulant. The incidence of VTE was 0.7% in the LMWH group and zero in the fondaparinux group (P>0.05). There was no significant difference in the rate of major bleeding (0.7% *vs.* 1.3%) or minor bleeding (5.5% *vs.* 6.6%) between the LMWH and fondaparinux groups. **The authors concluded that fondaparinux was safe and non-inferior to LMWH**.[28] Actually, this study was a comparison of two prophylactic regimens of combined modalities, since mechanical thromboprophylaxis was used in all patients until

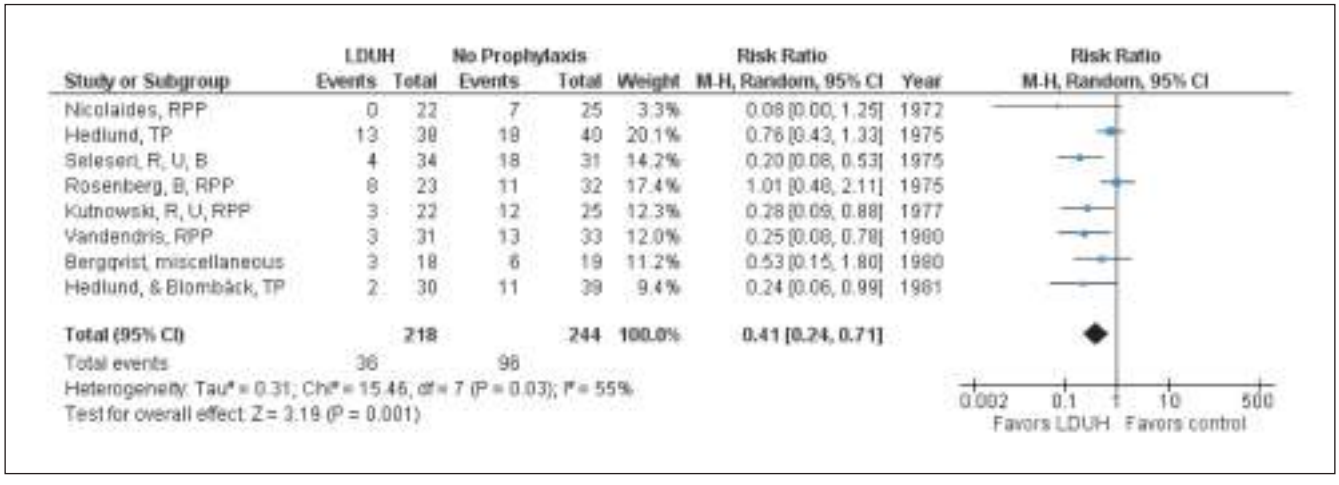

Figure 4.1—Effect of low dose heparin (LDUH) *vs.* no prophylaxis in the prevention of DVT in patients having urologic surgery diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).[3-7, 9-11]

fully ambulatory (see combined modalities for general surgery in Section 3 and Section 12).

In the absence of any other RCT, Tikkinen *et al.* performed a series of systematic reviews and meta-analyses addressing baseline perioperative risks i.e., determining the risk in the absence of thromboprophylaxis and important adverse outcomes (VTE or bleeding requiring reoperation).[29] This was done for specific procedures in both non-cancer and cancer urologic surgery.[30, 31] They produced a model of relative risk that could be applied to each procedure. **Low risk (1x)** was in the absence of any risk factors; **moderate risk (2x)** if any one of the following was present: age ≥75, BMI≥35 kg/m^2, VTE in first-degree relative; and **high risk (4x)** if there was a history of prior VTE or any combination of two or more risk factors. Based on this model, and with the information regarding the risks of VTE and bleeding that was derived from the meta-analysis, they were able to provide a means of calculating the risk/benefit ratio for each patient undertaking a specific procedure.

For non-cancer surgery, the authors concluded that although the inferences were limited owing to low-quality evidence, their findings suggested that extended prophylaxis was warranted for some procedures (*e.g.*, kidney transplantation in high-risk patients) but not in others (TURP and reconstructive female pelvic surgery in low-risk patients).[30] For cancer surgery, they concluded that extended thromboprophylaxis was warranted in some procedures (*e.g.*, open and robotic cystectomy) but not in others (*e.g.*, robotic prostatectomy without PLND in low-risk patients). For intermediate risk procedures, decisions would depend on values and preferences regarding VTE and bleeding.[31]

Recommendations

For low-risk patients undergoing transurethral urologic procedures, routine pharmacologic prophylaxis is not recommended, but IPC combined with early mobilization is suggested (**Level of evidence low, recommendation weak**).

For patients undergoing TURP, who due to the high risk of VTE may potentially benefit from pharmacologic thromboprophylaxis, the use of UFH or LMWH is suggested (**Level of evidence moderate, recommendation moderate**).

For high-risk patients having major urologic procedures LDUH (**Level of evidence high, recommendation strong**), LMWH **extrapolated from trials in patients having general surgery** (**Level of evidence moderate, recommendation strong**) or fondaparinux **are recommended** (**Level of evidence moderate, recommendation strong**).

In patients with increased risk of bleeding, **IPC with GEC is recommended,** also by extrapolation from trials in patients having general surgery (**Level of evidence moderate, recommendation strong**).

Duration of prophylaxis

In surgical urologic patients with malignancy and without high risk of bleeding **extended therapy with LMWH for four weeks** after discharge home is recommended (**Level of evidence moderate, recommendation strong**). This is by extrapolation from cancer patients having abdominal or pelvic surgery (see section 11 on prevention in surgical patients with cancer).

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SECTION 5

Prevention in gynecologic surgery

The risk

Incidence of asymptomatic DVT

Studies in the 1970s and 1980s demonstrated that asymptomatic DVT after gynecologic surgery occurred with approximately the same frequency as for general surgery (Table 5.I).[1-7] PE was a leading cause of death following gynecologic cancer surgery[8] and accounted for approximately 20% of peri-operative hysterectomy deaths.[9]

In a prospective cohort study published in 2001, 266 consecutive patients undergoing gynecologic laparoscopy had compression ultrasonography (CUS) to establish the incidence of asymptomatic DVT and clinical assessment to determine clinical PE.[10] There were no CUS detected DVT or clinically relevant VTE during follow-up. No patient died of fatal pulmonary embolism. The authors concluded that gynecologic laparoscopy in non-cancer patients is a low-risk procedure for postoperative VTE.

Incidence of symptomatic DVT

Early studies indicated that the incidence of symptomatic VTE appeared to be minimal for benign laparoscopic gynecologic surgery,[11, 12] and as high as 13-16% in surgery for ovarian cancer even when receiving prophylaxis.[13-15]

A prospective multicenter study investigated the incidence of complications in 1265 major and advanced laparoscopic procedures, including 364 cases of laparoscopic hysterectomy, 280 cases of pelvic floor repair and Burch colposuspension, 354 cases of excisional endometrio-

TABLE 5.I.—*The frequency of all DVT in patients having gynecologic surgery in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS).*

Patient groups	Number of studies	Patients N.	DVT incidence (weighted mean)	95% CI
Gynecological surgery				
Malignancy				
Ballard *et al.*, 1973[1]		55	15	
Walsh *et al.*, 1974[2]		45	16	
Taberner *et al.*, 1978[3]		48	11	
Clarke-Pearson *et al.*, 1983[4]		97	12	
Clarke-Pearson *et al.*, 1984[5]		52	17	
Clarke-Pearson *et al.*, 1990[6]		103	19	
Total	6	400	90 (22.5%)	19% to 27%
Benign disease				
Ballard *et al.*, 1973[1]		55	16	
Bonnar & Walsh, 1972[7]		140	15	
Taberner *et al.*, 1978[3]		48	11	
Walsh *et al.*, 1974[2]		217	21	
Total	4	460	63 (14%)	11% to 17%

The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

sis surgery, 177 cases of adnexal surgery and 75 cases of adhesiolysis. Symptomatic VTE occurred in 4 patients (0.3%).[16]

In another prospective study involving 849 patients undergoing laparoscopic gynecologic surgery, six patients (0.7%) developed symptomatic VTE.[17] VTE was diagnosed in three of 662 (0.5%) patients undergoing intermediate complexity procedures and three of 106 (2.8%) patients undergoing high complexity procedures. One patient had DVT only, four had pulmonary emboli without an identified DVT, and one had both. There was no associated death.

The risk of VTE was also investigated in 60,013 women who underwent laparoscopic hysterectomy listed in the Perspective Database, in which more than 500 acute care hospitals in the USA contributed data on inpatient hospital admissions.[18] There were 579 (1.0%) VTE events. Symptomatic DVT was documented in 546 (0.9%) women and 45 women had PE (0.1%). The rate of VTE was 0.9% for benign procedures and 2.3% for laparoscopic hysterectomy for cancer. VTE rate was 2.1% in women aged 60 years or over, 2.9% in patients in the highest comorbidity strata and 2.3% in patients with cancer. The incidence of symptomatic VTE in patients older than 65 years with endometrial cancer was 8.1% at 6 months and the overall mortality was higher in patients with VTE (HR: 1.60, 95% CI: 1.51 to 1.70).[18]

The @RISTOS Study was a prospective registry organized by 31 Italian surgical departments with a high rate of cancer operations.[19] Its aim was to evaluate the incidence of clinical VTE. It recruited a total of 2373 patients of which 52% were from general, 29% from urologic and 19% from gynecologic surgery. The 30-day incidence of VTE was 2.83% in general surgery, 2.0% in gynecologic surgery and 0.87% in urologic surgery. Forty percent of the events occurred later than 21 days from surgery. The death rate was 1.72%, and in 46.3% of these cases death was caused by VTE.

Risk factors specific to women

A common risk factor for VTE is estrogen contained in **combined oral contraceptives (COC)**,[20] which had been used by 18% of women in a UK study.[21] The COC increased the risk of VTE.[20] However, the absolute risk is small and represents an increase from 5 to 15-30 per 100,000 women years.[22] The latter is lower than the risk of VTE in pregnancy, which is estimated at 100 cases per 100,000 maternities. The risk of postoperative VTE showed an increase from 0.5% to 1% for pill users *vs.* non-users in early studies.[23] The absolute excess risk in COC users must be balanced against the risk of stopping the pill 4-6 weeks before surgery which includes unwanted pregnancy, the effects of surgery and anesthesia on a pregnancy, and the risks of subsequent termination. Each case should be assessed in relation to additional risk factors. Before major surgery, COC should be discontinued for at least four weeks and alternative contraception advised. If it is elected not to discontinue COC, then the patient should receive prophylaxis as for at least a moderate-risk patient. Other estrogen-containing preparations should be considered to carry the same risk as COC at least until studies become available. In emergency surgery or when COC have not been discontinued, VTE prophylaxis should be given to patients at least as a moderate-risk VTE category. COC do not need to be discontinued before minor surgery without immobilization. Progestogen-only oral contraceptives need not be discontinued even when immobilization is expected.[8] For other contraceptive preparations, consult the manufacturers' data information.[24]

Hormone replacement therapy (HRT) should be included as a risk factor for VTE when assessing patients for elective or emergency surgery.[25] HRT does not need to be stopped routinely prior to surgery provided that appropriate thromboprophylaxis is used such as LMWH.[26] An individual assessment is required in each woman to balance the risks of postoperative VTE against the changes in the quality of life which may result from cessation of therapy. Transdermal HRT has less effect on blood coagulation and appears to have a substantially lower VTE risk than oral HRT.[27]

In assisted reproduction, ovarian stimulation is used resulting in a hyperestrogenic state and activation of coagulation. The risk of venous thrombosis is increased and even upper extremity DVT extending to subclavian and internal jugular veins can occur. In women with ovarian hyperstimulation syndrome, thromboprophylaxis with standard dosage of LMWH is advised.[28]

Risk assessment

Patients undergoing major gynecologic surgery (*e.g.*, over 30 min duration) aged 40 years or over have a significant risk of postoperative VTE. The risk is increased by age, obesity, malignancy, history of VTE, immobility and hereditary or acquired thrombophilia.[29, 30] This risk is also affected by the nature and duration of the operation, type of anesthesia, dehydration, sepsis, varicose veins and hormone therapy.[31-33] Known clinical risk factors allow for classification of patients into high, moderate, and low risk of developing VTE (Table 5.II).[34]

TABLE 5.II.—*Risk categories according to clinical risk factors in gynecologic surgical patients.*

Risk category	
High	
Major gynecologic surgery	age >60
Major gynecologic surgery	age 40-60 and cancer or history of DVT/PE or other risk factors including thrombophilia
Moderate	
Major gynecologic surgery	age 40-60 without other risk factors
Minor gynecologic surgery	age <40 on estrogen therapy
Minor surgery	age >60
Low	
Major gynecologic surgery	age <40 without any other risk factors
Minor gynecologic surgery	age 40-60 without any other risk factors

Minor surgery: operations other than abdominal lasting less than 45 minutes; major surgery: any intra-abdominal operation and all other operations lasting more than 45 minutes. Modified from: Committee on Practice Bulletins-Gynecology, American College of Obstetricians and Gynecologists.[34]

Validation of the Caprini Risk Score (CRS) was attempted in a retrospective study of 1123 gynecologic oncology patients during the years 2004-2010.[35] Ovarian cancer was present in 39% of patients. IPC prophylaxis was used in all patients with 40% receiving additional LMWH prophylaxis. The overall incidence of VTE was 3.3%. Based on the Caprini scoring model, 92% of patients scored in the "Highest Risk" category. The Caprini Risk Assessment model (RAM) accurately predicted all 37 VTE, all of which occurred in the "Highest Risk" category (Score ≥5). The percentage of patients that received combined prophylaxis increased with time from 12% in 2004 to 63% in 2010. However, 25 of the 37 VTEs (68%) did not receive prophylaxis with combined modalities.

The limited utility of the CRS and Rogers score in gynecologic oncology patients was demonstrated in a subsequent study which included 17,713 patients undergoing surgery for cervical, ovarian, uterine, vaginal, and vulvar cancers between 2008 and 2013 as identified from the National Surgical Quality Improvement Database.[36] Of 17,713 patients, 1.8% developed VTE. No patients were classified by the Caprini score as low risk, 0.1% were moderate risk, 3.0% were higher risk (score 4), and 96.9% were in the highest risk (score ≥5). The Caprini score groupings did not correlate with VTE. The high-risk group had an incidence of VTE of 2.5% which was close to the highest risk group, 1.7% (P=0.40). For the Rogers Score, only 0.2% of patients were low risk. The authors concluded that gynecologic oncology patients score very high on current VTE risk assessment models. Established scores are limited in their ability to stratify gynecologic oncology patients according to risk because 97% are classified in the highest-risk category.

The risk of VTE may persist beyond 4 weeks after gynecologic surgery in the very high-risk patients, such as those with a history of previous VTE or those undergoing operations for ovarian cancer.[37]

Prophylactic methods

Graduated elastic compression (GEC)

A RCT involving 196 patients[38] demonstrated a lower rate of asymptomatic DVT with the use of **GEC** compared with **no prophylaxis** (0 *vs.* 4%; P<0.05) in women undergoing major gynecological surgery. Based on the risk-benefit ratio in this study and extrapolation from data from moderate-risk patients in general surgery (8 RCTs and 3 meta-analyses showing a 50-60% reduction in DVT) (see Section 3), mechanical prophylaxis with GEC stockings should be used in addition to early ambulation and adequate hydration in low-risk patients.

LDUH

Two RCTs involving 207 patients having surgery predominantly for benign gynecologic disease showed that **LDUH** (5,000 IU, twice daily) reduced asymptomatic DVT from 25% to 4.8% (RR: 0.19, 95% CI: 0.07 to 0.48).[1, 3] In a double blind RCT involving 215 patients, **LMWH** (initiated and dosed according to the labeling) was equally effective as **LDUH** (5000 IU, 12 hourly) in preventing DVT.[39]

In patients having gynecologic surgery for malignancy, **LDUH administered twice daily** was not effective[4] but **LDUH administered three times daily** was effective.[6] The latter reduced asymptomatic DVT from 18.4% in the control group to 8.7% in the LDUH group (RR: 0.47, 95% CI: 0.22 to 0.98).

LMWH *vs.* LDUH

Subsequent RCTs in patients having gynecologic oncology did not demonstrate any difference in efficacy between **LMWH given once a day and LDUH given three times daily** for thromboprophylaxis against DVT or PE and no difference in the risk of bleeding.[40-42]

In the ENOXACAN study 1115 patients over 40 years of age undergoing planned elective curative abdominal or pelvic surgery for cancer were randomized into **LDUH or LMWH** (enoxaparin) but venograms were inadequate in 460 (41.3%).[40] Of 631 evaluable patients, a total of 104 (16.5%) developed VTE. The frequency was 18.2% in the LDUH group and 14.7% per cent in the enoxaparin group

(P>0.05). There were no differences in bleeding events or other complications. One patient in the LDUH group developed severe thrombocytopenia. There were no differences in mortality at either 30 days or 3 months.

In a second double blind RCT 102 patients undergoing gynecologic cancer surgery with pelvic and paraaortic lymphadenectomy were given LMWH (enoxaparin) once daily or LDUH three times daily.[41] No patient developed symptomatic DVT, wound hematoma or intra-abdominal bleeding. There was no significant difference in bleeding complications between the two regimens.

In a third study, 80 patients undergoing pelvic or abdominal surgery for cancer were randomized to **LDUH** (Calciparin) three times daily or **LMWH** (dalteparin) once daily for 10 days.[42] In the **LDUH** group, two patients (5%) developed postoperative PE and none in the **LMWH** group. Two patients in the **LMWH** group (5%) developed DVT detected by the ^{125}I-Fibrinogen Test, which was not confirmed by phlebography. Important postoperative bleeding (one patient in the **LDUH** group and two patients in the **LMWH** group) was similar in both groups. **Moderate and minor bleeding were significantly lower in the LMWH group**. It was concluded that, over a 10-day period, a **once daily 5000 U LMWH dose was as effective and safe as thrice daily 5000 IU LDUH** injections. In the above studies the risk of wound hematomas appeared to be reduced by avoiding subcutaneous injections near the wound. LMWH had the advantage of once daily injection and was less likely to cause HIT.

IPC *vs.* no prophylaxis

An RCT, involving 107 patients undergoing major surgery for gynecologic malignancy, compared **IPC** for 5 days with **no prophylaxis**. Patients were prospectively screened for DVT with impedance plethysmography and ^{125}I-fibrinogen leg counting. **The incidence of VTE** (DVT and/or PE) **was 34.6% in the control group and 12.7% in the IPC group** (RR: 0.28, 95% CI: 0.11 to 0.66; P<0.005).[5, 43]

IPC *vs.* LDUH or LMWH

An RCT, involving 208 patients undergoing surgery for gynecologic malignancy, compared IPC with LDUH.[44] All patients were evaluated with ^{125}I-fibrinogen scanning of the legs. Clinical and laboratory variables associated with bleeding complications were recorded prospectively. DVT occurred in seven patients receiving LDUH and four in the IPC group (P=0.54). LDUH patients received more blood transfusions postoperatively (P=0.02), had increased volume of retroperitoneal drainage (P=0.02), and the activated partial thromboplastin time was more frequently prolonged (P=0.001).

A subsequent RCT involving 211 patients undergoing surgery for gynecologic malignancy compared IPC, starting with induction of anesthesia, and continued for 5 days, with LMWH (dalteparin 5000 units once daily). All patients had bilateral ultrasound scans of the legs on days 3-5 and a follow-up interview 30 days after the operation. DVT occurred in two patients in the LMWH group and one patient in the IPC group. The number of required perioperative transfusions and estimated intraoperative blood loss were similar between the two groups.[45]

Systematic review of all RCT prior to 2017 in gynecologic oncology surgery

A systematic review of all the RCTs performed in patients having gynecologic cancer surgery published prior to 2017 identified seven studies involving 1001 patients.[15] Most studies had a low risk of bias. The results were as follows: **IPC maintained for 5 days or until full ambulation significantly lowered DVT risk** (RR: 0.33, 95% CI: 0.16 to 0.66). **There was no difference in the incidence of DVT between IPC and heparin** (LDUH or LMWH) **groups** (RR: 1.19, 95% CI: 0.42 to 3.44). Six studies reported on PE. There was no significant effect on PE reduction by any method. Three trials mentioned perioperative transfusion rate in IPC *vs.* heparin groups. Compared with LDUH, IPC was associated with a lower postoperative transfusion rate (RR: 0.53, 95% CI: 0.32 to 0.89). Compared with LMWH, IPC had a similar transfusion rate in the operating room (RR: 1.06, 95% CI: 0.69 to 1.63).

IPC combined with LDUH or LMWH

Combined prophylaxis has not been studied in any RCTs in patients undergoing gynecologic surgery.

A 2022 Cochrane review update evaluated the efficacy of combined modalities, **intermittent pneumatic compression** (**IPC) and pharmacological prophylaxis** (treatment group) against single modalities alone (control group) to prevent PE and DVT in patients at high risk for VTE[46] Thirty-four studies that included 14,931 patients were identified, of which 25 were RCTs. The studies evaluated orthopedic patients (N.=14), urology patients (N.=3), and general surgery, cardiothoracic and other types of patients (N.=17). Compared with IPC alone, combined modalities significantly reduced the incidence of both symptomatic PE from 1.34% to 0.65% (OR: 0.51, 95% CI: 0.29 to 0.91) and DVT from 3.81% to 2.03% (OR: 0.51, 95% CI: 0.36 to 0.72). Compared with pharmacological prophylaxis alone,

combined modalities significantly reduced the incidence of PE from 1.84% to 0.91% (OR: 0.46, 95% CI: 0.30 to 0.71). Compared with pharmacological prophylaxis alone, combined modalities significantly reduced the incidence of DVT from 9.28% to 5.48% (OR: 0.38, 95% CI: 0.21 to 0.70).

Thromboprophylaxis with IPC (SCD) combined with LDUH three times daily or LMWH once daily until discharge has been compared with historic controls in one observational study involving patients having gynecologic operations for cancer.[47] Prior to this regimen patients were given IPC starting before induction of anesthesia and continuing until discharge from hospital. The new regimen of combined modalities reduced the incidence of VTE from 6.5% (19 out of 294 patients) to 1.9% (6 out of 311 patients) (P=0.007). There was no increase in bleeding complications. The authors concluded that the protocol of dual thromboprophylaxis with prolonged thromboprophylaxis in high-risk patients was associated with a significant reduction in the rate of VTE.

Based on the above observations and by extrapolation from other specialties it has been suggested that in the presence of two out of three identified risk factors (*e.g.*, age older than 60, cancer, prior VTE) that place patients in the highest risk category for VTE prophylaxis with both IPC and LMWH should be considered.[48, 49]

Extended prophylaxis

LMWH

A large national quality study demonstrated that of 9,948 patients who underwent hysterectomy for the treatment of endometrial cancer, 61.9% underwent minimally invasive surgery and 38.1% underwent open surgery. Patients undergoing minimally invasive surgery had a lower VTE incidence (0.7%, N.=47) than open surgery patients (2.2%, N.=80) (P<0.001). In the patients diagnosed with postoperative VTE the diagnosis was made after hospital discharge in 73% of those having minimally invasive surgery and 43% of those having open surgery.[50]

The ENOXACAN II, a double-blind RCT, which involved 332 patients undergoing open abdominal or pelvic operations for malignancy demonstrated that the incidence of VTE (routine venographic DVT or PE confirmed by V/Q scan or pulmonary angiography) decreased from 12% in the group that had only inpatient prophylaxis to 4.8% in the group that LMWH was given for 4 weeks (P=0.02)[51] This difference persisted for three months (13.8% *vs.* 5.5%; P=0.03). There were no significant differences in the rates of bleeding in the two groups.

A Cochrane meta-analysis published in 2019 identified seven studies of prolonged thromboprophylaxis with LMWH for abdominal or pelvic surgery involving 1728 patients[52] The incidence of VTE after major abdominal or pelvic surgery was 13.2% in the control group compared with 5.3% in the patients receiving LMWH out-of-hospital (OR: 0.38, 95% CI: 0.26 to 0.54). Prolonged thromboprophylaxis with LMWH was associated with a statistically significant reduction in the incidence of all DVTs (OR: 0.39, 95% CI: 0.27 to 0.55). There was a similar reduction when analysis was limited to the incidence in proximal DVT (OR: 0.22, 95% CI: 0.10 to 0.47). There was no difference in the incidence of bleeding and no difference in mortality between the control and LMWH group.

Apixaban vs. *LMWH*

A recent RCT involving 400 patients undergoing surgery (either by laparotomy or laparoscopy) for gynecologic malignancy compared **apixaban 2.5 mg twice daily for 28** days with **LMWH (enoxaparin) 40 mg daily for 28 days**.[53] Prior to randomization, all patients received LDUH (5000 units) three times daily on the first postoperative day until patients were deemed safe for randomization by the operating surgeon. Patients were then randomized to oral apixaban (2.5 mg twice daily) for 28 days or LMWH (enoxaparin 40 mg daily) for 28 days. **There were no statistically significant differences between the apixaban and LMWH groups in terms of venous thromboembolic events** (1.0% *vs.* 1.5%; OR: 1.57, 95% CI: 0.26 to 9.50; P=0.68), rates of major bleeding events (0.5% *vs.* 0.5%; OR: 1.04, 95% CI: 0.07 to 16.76; P>0.99), clinically relevant non major bleeding events (5.4% *vs.* 9.7%; OR: 1.88, 95% CI: 0.87 to 4.1; P=0.11), adverse events, medication adherence, or quality of life between the groups.

Rivaroxaban vs. *LMWH*

In a recent study (VALERIA), patients undergoing major gynecological cancer surgery who had thromboprophylaxis with LMWH during hospitalization were randomized at hospital discharge to receive rivaroxaban 10 mg once daily or enoxaparin 40 mg once daily for 30 days.[54] The primary efficacy outcome (combination of symptomatic VTE and VTE-related death or asymptomatic VTE at day 30) occurred in 3.51% of patients assigned to rivaroxaban and in 4.39% of patients assigned to enoxaparin (RR: 0.80, 95% CI: 0.22 to 2.90; P=0.734). Patients assigned to rivaroxaban had no primary bleeding event, and 3 patients (2.63%) in the enoxaparin group had a major or CRNM bleeding event (HR: 0.14, 95% CI: 0.007 to 2.73; P=0.196). Al-

though, the power was limited due to not reaching the intended sample size of 440 patients, the authors concluded that the results supported the hypothesis that DOACs might be an attractive alternative strategy to LMWH to prevent VTE in this high-risk population.

Recommendations (see Table 5.II[34] for levels of risk)

Cessation of combined oral contraception (COC) or hormone replacement therapy (HRT) four weeks prior to major gynecologic surgery should be considered **(Level of evidence low, recommendation moderate)**. If not discontinued the patient should receive appropriate **VTE prophylaxis based on the individual risk assessment appropriate for a moderate risk patient (Level of evidence low, recommendation strong)**.

Low-risk patients

Thromboprophylaxis with GEC (Level of evidence moderate, recommendation moderate) in addition to early ambulation and adequate hydration are recommended.

Moderate risk patients

LDUH (5000 IU, three times daily), **LMWH** (initiated and dosed according to labeling) or **IPC** are recommended (**Level of evidence high, recommendation strong**). **LMWH,** is the preferred method because it has the advantage of once daily injection and is less likely to cause HIT.

IPC is the method of choice in patients with a high risk of bleeding **(Level of evidence high, recommendation strong)**.

High-risk patients

LMWH (initiated and dosed according to labeling) **(Level of evidence high, recommendation strong)**, **fondaparinux (Level of evidence low, recommendation weak)**, **LDUH (5000 IU three times daily) (Level of evidence high, recommendation moderate)** or **IPC** (throughout hospital stay) **(Level of evidence high, recommendation strong)** are recommended.

IPC as the sole prophylactic method is the method of choice in patients with a high risk of bleeding **(Level of evidence high, recommendation strong)**.

Combined therapy of **LMWH** or **LDUH with IPC** provide optimal prophylaxis and should be the method of choice in high-risk patients **(Level of evidence moderate, recommendation strong)**.

Extended prophylaxis with LMWH should be given after hospital discharge with LMWH for up to 28 days especially in patients with cancer **(Level of evidence moderate, recommendation strong)** extrapolated from general surgery.

Until further evidence is available, patients undergoing complex laparoscopic surgery should be provided with prophylaxis in accordance with risk category like patients undergoing open procedures **(Level of evidence low, recommendation weak)**.

Initial prophylaxis with **LDUH three times a day** followed by **apixaban 2.5 mg twice daily** starting at end of the first postoperative day in the absence of any bleeding and continued for 28 days is a studied and effective prophylactic regimen that may be more acceptable to patients. However, apixaban has not yet been approved by FDA for this indication **(Level of evidence moderate, recommendation moderate)**.

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SECTION 6

Prevention in obstetrics

The risk

Introduction

Despite a relatively low absolute risk of VTE of 1.2 per 1000 pregnancies, VTE remains the leading cause of maternal mortality in developed countries.[1, 2] There is a five-fold increase in risk during pregnancy and up to 60-fold increase *postpartum* which persists for six weeks compared with age-matched non-pregnant women.[3, 4]

Pregnancy is a prothrombotic state, characterized by significantly increased levels of fibrinogen, factors VII, VIII, IX, X and XII, factor von Willebrand and decreased levels of Protein S compared with non-pregnant women. Fibrinolysis is also altered during pregnancy, due to an altered balance between the plasminogen activation inhibitors (PAI-1 and PAI-2) and t-PA in favor of reduced fibrinolysis.[5, 6] These alterations are adaptive modifications which warrant embryo development and effective hemostasis during delivery. In addition, during late pregnancy there are some venous flow changes due to increase of venous capacity and compression effects which increase stasis particularly in the lower limb veins.[7]

Nevertheless, routine administration of thromboprophylaxis to all pregnant women is not justified. Regular risk assessment for VTE is necessary to identify pregnant women at increased risk for VTE as soon as pregnancy is confirmed, throughout its evolution and *postpartum*.

Risk factors for pregnancy associated VTE

Table 6.I lists the various intrinsic, maternal-related risk factors and/or triggering risk factors which amplify the risk of pregnancy associated VTE.[8-20] The co-existence of multiple risk factors has an amplifying effect on the risk.

Risk stratification scores

Several risk assessment models (RAM) have been proposed for the evaluation of pregnancy associated VTE risk in *antepartum* and *postpartum*. A recent prospective case-control study compared the accuracy of 11 models to identify women at high risk of *postpartum* VTE.[21] The study included 55 women with and 165 women without puerperal VTE. The predictive value of different risk assessment methods for puerperium VTE varied greatly. Considering the sensitivity and specificity, available data and acquired experience we propose the use of the Royal College of Obstetricians and Gynecologists (RCOG) RAM[21] and the Swedish tool[22] for the evaluation of VTE risk during pregnancy. In *postpartum* we propose the use of the Swedish tool for the evaluation of VTE risk.

Risk of VTE in patients having assisted reproductive techniques

A meta-analysis of 14 studies involving women undergoing assisted reproductive techniques (ART) showed that the overall frequency of VTE associated with ART was 0.23% (95% CI, 0.07 to 0.46).[23] Pregnant women following ART had a two-fold increased risk of VTE compared with those who had spontaneous pregnancy (RR: 2.66, 95% CI: 1.60 to 4.43).

The frequency of VTE specifically related to ovarian hyperstimulation syndrome (OHSS) was <0.001%. The risk of VTE after ART complicated by OHSS compared with ART without OHSS, was higher but not statistically significant (RR: 14.83, 95% CI: 0.86 to 255.62). Risk factors of VTE associated with ART were *in-vitro* fertilization procedure (OR: 4.99, 95% CI: 1.24-20.05), hyperhomocysteinemia (OR: 15.2, 95% CI: 2.0 to 115.0), polycystic

TABLE 6.I.—*Risk factors for pregnancy associated VTE.*

Intrinsic risk factors		Triggering risk factors			
Mother related risk factors		Pregnancy related risk factors		Delivery related risk factors	
Risk factor	OR	Risk factor	OR	Risk factor	OR
Age >35 years	1.3	Intrauterine Growth Restriction	3.8	Preterm delivery	2.28
Parity ≥3	2.4	Preeclampsia	2.9-3.1	Prolonged labour	NA
BMI ≥30 kg·m^{-2}	1.8-5.3	Multiple pregnancies	1.7-4.2	Instrumental delivery	NA
Smoker (10-30 cigarettes per day.)	2.1-3.4	Immobility	7.7-10.8	Caesarean section Emergence CS	1.8-3.6 2.7
Comorbidities	1.6-8.7	Assisted reproduction	2-4.3	Stillbirth	6.4
Varicose veins	2.4	Gestational diabetes	1.79	Manual removal of placenta	2.2
Thrombophilia	3.2-34.4			*Postpartum* haemorrhage ≥1000 mL	4.1
Prior VTE	24.8			Infection	4.1-6.1
Factor V Leiden heterozygous	4.6			BMI≥25kg/m^2 + *antepartum* immobilization	62.3
Factor V Leiden homozygous	15.2				
Factor II G20210A heterozygous	3.1				
Combined heterozygous mutations Factor V Leiden and Factor II G20210A	47				
Antithrombin deficiency severe	49				
Protein C deficiency	2.3 - 5.5				
Protein S deficiency					
Mild	2.6				
Severe	9.7				
Family history of VTE in 1st degree	3.3				
Family history of VTE	NA				
Lupus	7				
Chron disease	2.49				
Cancer	6.50				
Other autoimmune disease	1.33				
Antiphospholipid syndrome	5-12				
HIV	2.8-3.4				
Disability	1.5-3.3				
COVID-19	3.8				
Smoking,	2.38				
Hypertension	2.14				
Diabetes	2-3.5				
Recent long duration flight	2				
Recent hospitalization for acute medical infection or surgery (<3 months	2				
Sickle cell disease	6.7				

ovarian syndrome (PCOS) (RR: 4.8, 95% CI: 1.7-13.4), and successful ART leading to pregnancy (OR: 13.94, 95% CI: 1.41 to 137.45).

Prophylactic methods

Meta-analysis of RCTs

A Cochrane review, published in 2021 included 29 RCTs, involving 3839 pregnant women at high VTE risk and **analyzed the efficacy and safety of *antepartum* and *postpartum* thromboprophylaxis with LMWH or UFH *vs.* placebo.**[24] A limitation of the studies was the small number of reported events because studies were underpowered. For the primary outcomes symptomatic thromboembolic events including pulmonary embolism (PE) and/or deep vein thrombosis (DVT), and the critical outcome of adverse effects sufficient to stop treatment, the evidence was very uncertain.

The authors concluded that the evidence was very uncertain about benefits and harms of VTE thromboprophylaxis in women during pregnancy and the early postnatal period at increased risk of VTE. Further high-quality very large-scale RCTs are needed to determine effects of currently used treatments in women with different VTE risk

factors. As sufficiently large definitive trials are unlikely to be funded, secondary data analyses based on high-quality registry data are important.

The Highlow RCT

In a multicenter open-labelled RCT, 1110 pregnant women with a history of VTE and gestational age of 14 weeks or less were **assigned to either weight adjusted intermediate-dose or fixed low dose LMWH.** The primary efficacy outcome was objectively confirmed VTE (DVT, PE or unusual site venous thrombosis).[25]

VTE occurred in 11(2%) of 555 women in the weight-adjusted intermediate-dose group and in 16 (3%) of 555 in the fixed low-dose group (RR: 0·69, 95% CI: 0·32 to 1·47; P=0·33). VTE occurred *antepartum* in five (1%) women in the intermediate-dose group and in five (1%) women in the low-dose group, and *postpartum* in six (1%) women and 11 (2%) women. On-treatment, major bleeding occurred in 23(4%) of 520 women in the intermediate-dose group and in 20(4%) of 525 in the low-dose group (RR: 1·16, 95% CI: 0·65 to 2·09). The authors concluded that low-dose LMWH for thromboprophylaxis during pregnancy is the appropriate dose for the prevention of pregnancy-related recurrent VTE. However, an advantage of weight-adjusted over fixed low-dose LMWH in the *postpartum* period cannot be excluded.

Observational studies

A recent observational study evaluated thromboprophylaxis with LMWH (nadroparin).[26] The study included 91 pregnant women at high or intermediate risk of VTE. In women at high risk treated with nadroparin, the incidence of VTE was 7.0% (95% CI: 2.9 to 16.7) *postpartum* and 1.8% (95% CI: 0.4-9.2) *antepartum*. The rate of severe *postpartum* hemorrhage (defined as blood loss of >1000 mL) was 9.1% (95% CI: 4.7 to 16.9) and 6 women received transfusions.

A retrospective, observational study of 123 women (172 pregnancies) who had received LMWH prophylaxis for prevention of VTE during the period of 1999-2014 because of a previous history of VTE, reported the development of 2 (1.2%) episodes: one SVT in varicose veins and one DVT during the *antepartum* period.[27] The rate of severe *postpartum* hemorrhage was 9.3%. Bleeding events occurred following Cesarean delivery.

In another retrospective analysis 409 women (502 pregnancies) at increased risk of VTE were prescribed thromboprophylaxis in accordance with RCOG guideline of the time.[28] The most prevalent risk factors were: presence of thrombophilia (43%), personal history of VTE (36%), body mass index >30 kg/m^2 (19%), family history of VTE (13%), age >35 years (12%), and parity >3 (11%). Most women (76%) were prescribed enoxaparin 40 mg daily dose in line with their weight. Bleeding was reported in 7.2%, with epistaxis being most common. All bleeding events were classed as minor and were reported at routine hematology clinic follow-up. Twelve (2.4%) women had thromboembolic events with 10 of these women having a prior history of VTE. It is important to note that 4 of these events occurred >6 weeks *postpartum*, when thromboprophylaxis had ceased.

Another retrospective cohort study included 129 pregnancies, who received thromboprophylaxis for VTE prevention.[29] Women with intermediate-risk pregnancies and medical comorbidities or multiple low-risk pregnancies, received thromboprophylaxis with fixed low-dose enoxaparin *antepartum* and for a median of 4 weeks *postpartum*. Women with high-risk pregnancies, with a history of previous VTE, received enoxaparin doses adjusted with regular measurement of the anti-Xa levels at 4 hours after subcutaneous injection during *antepartum* and for a median of 6 weeks *postpartum*. In women with high-risk pregnancies the rate of VTE during the *antepartum* period was 1.4%. In those with intermediate-risk pregnancies the rate of VTE was 3.4%. Bleeding events occurred in 7.1% of intermediate and 8.5% of high-risk pregnancies. Of these bleeding events, 3.1% were classified as major bleeding. On univariate analysis, no independent predictors of bleeding were identified.

A retrospective single center observational study published in 2023, included 208 women with at least one previous VTE and one pregnancy thereafter.[30] No thrombosis or major bleeding was recorded in 138 pregnancies conducted with LMWH, whereas 10 (14%) VTE events occurred in 70 pregnancies conducted without thromboprophylaxis. Nine (90%) women with recurrent VTE had had a previous hormone-related event. The incidence of miscarriage was lower in pregnant women who received LMWH than in those who did not receive LMWH (11% *vs*. 26%), (RR: 0.4, 95% CI: 0.2 to 0.8). Late obstetrical complications and terminations were similar in the two groups. The prevalence of terminations was doubled in women with thrombophilia (12%) than in those without (6%). The authors concluded that LMWH prophylaxis during pregnancy appears to be effective and safe for the prevention of recurrent VTE and may reduce the incidence of miscarriage.

A prospective open-label study using a sequential

group allocation method, included 7020 pregnant women at high risk of VTE according to the RCOG 2009 RAM.[31] Women delivered vaginally or abdominally. Women who delivered by elective Cesarian section were included if they had one or more additional risk factors. In addition, all women who delivered by emergency Cesarian section were included in the study. **Patients were stratified to receive *postpartum* thromboprophylaxis with bemiparin 3500 anti-Xa IU, or enoxaparin 4000 anti-Xa IU once daily for 7 days. The third arm of the study (control group) did not receive any thromboprophylaxis**. In each group 2340 patients were included. The first dose of LMWH was injected 6 hours or 8 hours after delivery (vaginal or cesarian section) under general anesthesia or under spinal anesthesia respectively. **Symptomatic, objectively confirmed VTE** was the primary efficacy endpoint. Side effects and wound complications were the secondary study endpoints. Symptomatic VTE, was documented in one (0.043%) woman in the bemiparin group, two (0.085%) in the enoxaparin group, and nine (0.384%) in the control group. All cases of VTE occurred within the first week after delivery. The number of women experiencing mild side effects (pain and ecchymosis) was significantly lower in the bemiparin group than in the enoxaparin group. **The incidence of symptomatic VTE was significantly lower in the two combined intervention groups (0.64 per 1000 deliveries) than in the control group (3.8 per 1000 deliveries) (RR: 0.166, 95% CI: 0.045 to 0.614; P=0.004)**. One woman died during the study period. She had a twin pregnancy and underwent emergency Cesarian section owing to fetal distress. She developed severe dyspnea and cyanosis 5 hours after delivery (1 hour before administration of LMWH). She was in the bemiparin group and died within 10 minutes of resuscitation due to PE.

Recommendations

Risk assessment

Routine risk assessment for pregnancy associated VTE is recommended for all women in early pregnancy using the RCOG RAM as soon as pregnancy is confirmed, and then regularly every trimester; also, if new risk factors appear or complications occur, or the patient is hospitalized for any reason. **The Swedish RAM should be used after either vaginal delivery or Cesarian section (Level of evidence moderate, recommendation strong)**.

For the evaluation of pregnancy associated risk of VTE and interpretation of the Swedish and RCOG RAMs see Supplementary Digital Material 1 (Supplementary Table 6.I, 6.II, 6.III, 6.IV).[22, 32]

Thromboprophylaxis during pregnancy and puerperium

LMWH is the method of choice during pregnancy and *postpartum* (Level of evidence moderate, recommendation strong) (see Table 6.II for prophylactic doses of LMWH according to the body weight).

GEC should be considered in addition to LMWH in selected high-risk patients **(Level of evidence low, recommendation weak)**.

Initiation and duration of thromboprophylaxis

The recommendations for the prevention of pregnancy associated VTE and the modalities of thromboprophylaxis in particular situations are summarized in Supplementary Digital Material 2 (Supplementary Table 6.V).

Management of delivery in patients on prophylactic LMWH

Patients on LMWH antenatally and who wish epidural anesthesia should have heparin prophylaxis discontinued with the onset of labor **(Level of evidence low, recommendation moderate)**.

In patients undergoing epidural anesthesia the last prophylactic dose of LMWH should be given not later than 12 hours before epidural puncture **(Level of evidence moderate, recommendation strong)**.

Notes on implementation

Regarding the perinatal management of the antithrombotic treatment, the general advice is to administer the injection of LMWH from 9 to 11 in the morning. This practice

TABLE 6.II.—*Doses of the most widely used LMWHs for the prevention of pregnancy associated VTE adapted according to the body weight status.*

Body weight	Bemiparin (anti-Xa IU o.d. s.c. /24h)	Dalteparin (anti-Xa IU o.d. s.c. /24h)	Enoxaparin (o.d. s.c. /24h)	Tinzaparin (o.d. s.c. /24h)
<50 kg	2.500	2.500	2000	3.500
50-90 kg	3.500	5.000	4000	4.500 IU
91-130 kg	5.000	7.500	6000	7.000
131-170 kg	7.500	10.000	8000	9.000
>170 kg	10.000	75 anti-Xa IU/kg	60 anti-Xa IU/kg	75 anti-Xa IU/kg

allows one to get the benefit of the circadian rhythm of oxytocin secretion (it is secreted only during the night or early morning) resulting in spontaneous unprovoked labor during the night or early morning. Thus, pregnant women should be advised at least at the last trimester, to have the injection in the morning, after ensuring that they do not have any symptoms of onset of labor. With this advice the great majority of women can have a normal unprovoked labor with epidural anesthesia, without the need of inducing labor or elective Cesarean section.

When an induced labor is decided by the obstetrician then the last dose of LMWH should be given the day before the scheduled induction.

Epidural or spinal anesthesia is not advised for at least 12 hours after prophylactic LMWH administration and 24 hours after therapeutic doses have been discontinued.[33] LMWH should not be given for at least four hours after the epidural catheter has been inserted or removed and the catheter should not be removed within 10 to 12 hours of the most recent injection.[34]

At least 6 hours after the end of the Cesarian section, and in the absence of active bleeding or hemorrhagic risk, thromboprophylaxis with LMWH should be initiated **(Level of evidence low, recommendation strong)**.[35, 36]

There is an increased risk of wound hematoma following Cesarean section with LMWH. The subcutaneous injections should be given in the flank well away from the incision to minimize wound hematoma.

Management of the puerperium

The first *postpartum* daily prophylactic dose of LMWH should be given 6-8 hours after delivery provided hemostasis is obtained. *Postpartum* anticoagulation should be continued for a minimum of six weeks in high-risk patients (Table 6.II). In other patients not at high-risk, prophylaxis should continue for 10 days, and the need for prophylaxis should be reviewed if the hospital stay continues beyond seven days **(Level of evidence moderate, recommendation moderate)**.

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Supplementary data
For supplementary materials, please see the HTML version of this article at www.minervamedica.it

SECTION 7

Prevention in orthopedic surgery and trauma

A. General considerations

Timing of prophylaxis

VTE prophylaxis involves a balance of risks and benefits. Chemical prophylaxis poses a dilemma: the closer it is administered to surgery for a given dose, the better the thromboprophylaxis but the greater is the risk of bleeding complications.[1] If a given dose of the drug is administered too long before surgery, then, intra-operative blood levels would be inadequate for effective prophylaxis, whereas if given too close to surgery then surgical bleeding is a threat.

It has already been stated in the introduction (Section 1), that regulatory bodies in Europe and North America consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug. Each LMWH must be dosed according to the manufacturer's label and recommendations. Therapeutic interchange among these products is not appropriate. Thus, administration should be used as per label.

When LMWHs were first introduced for VTE prophylaxis, the results of the clinical trials brought a longstanding controversy between North America and European clinical practice regarding the timing and dosing regimens of LMWHs.[2] In Europe, LMWH was given at a lower dose (40 mg once daily) 12 hours prior to operation providing a moderate anticoagulant effect to counteract the intra-operative activation of coagulation factors and venous stasis. This was based on the natural history of DVT demonstrated by the ^{125}I-fibrinogen Test and routine phlebography. It was found that most of the thrombi started in the calf during operation and remained asymptomatic, with most of them resolving when the patient became ambulant, but with 20% extending into the popliteal and more proximal veins often without symptoms.[3, 4] Venographic studies in patients having hip arthroplasty also demonstrated that a second "batch" of isolated DVT occurred in the femoral and pelvic veins at 12-15 days after the operation.[5]

In North America, LMWH was given at least 12-24 hours after surgery at a higher dose and more frequently (30 mg twice daily). The premise of this approach was to reduce the risk of surgical bleeding, although intra-operative thrombogenesis would not be prevented and thrombi may have had already begun forming.[6]

A systematic review and meta-analysis of six RCTs, which involved 987 patients having elective hip arthroplasty, published in 1999, compared preoperative initiation of LMWH (enoxaparin 40 mg daily, initiated 10-12 hours before surgery) with postoperative initiation **of the same LMWH** (enoxaparin 30 mg every 12 hours initiated within 24 hours after surgery). All patients had routine ascending contrast venography performed before or at the time of discharge from hospital. **Treatment with LMWH initiated preoperatively was associated with a DVT frequency of 10.0% compared with 15.3% when LMWH was initiated postoperatively (P=0.02)**. Major bleeding occurred in 0.9% of patients receiving preoperatively initiated LMWH compared with 3.5% in those receiving postoperatively initiated higher dose of LMWH (P=0.01).[7]

A systematic review and meta-analysis of 11 trials involving 3545 patients having elective hip arthroplasty, published in 2001, assessed the relative efficacy and safety of three LMWH initiation times although different LMWHs were used: **1) preoperative, starting 12 hours before surgery** (enoxaparin 40 mg, dalteparin 5000 IU, and tinzaparin 4500 IU in 11 studies involving 1926 patients); **2) postoperative starting 12-48 hours after surgery** (enoxaparin 40 mg; 4 studies involving 694 patients); and

3) perioperative given between two hours before or up to 4 hours after surgery (enoxaparin 20 mg one hour after surgery followed by 40 mg daily, dalteparin 2,500 IU 4 hours after surgery followed by 5,000 IU daily, dalteparin 2,000 IU 2 hours after surgery followed by 5,000 IU daily and dalteparin 2500 IU evening of the operation followed by 5,000 IU daily; 4 studies involving 925 patients).[8] The diagnosis of DVT was based on routine venography in all patients. **The incidence of DVT was 19.2% (95% CI: 17% to 21%) in the preoperative group, 12.4% (95% CI: 10% to 14%) in the perioperative group and 14.4% (95% CI: 12 to 17%) in the postoperative group. The rate of major bleeding was 1.4% (95% CI: 1% to 2%) in the preoperative group, 6.3% (95% CI: 5% to 7%) in the perioperative group and 2.5% (95% CI: 1% to 3%) in the postoperative group**. The authors concluded that there was no convincing evidence that preoperative prophylaxis was associated with a lower incidence of VTE than starting postoperatively. **Perioperative regimens may lower the risk of postoperative DVT, but if so, this positive effect is offset by an increase in postoperative major bleeding**.

IPC and foot impulse technology (FIT) sleeves are available in sterile packages that allow for intra-operative use, reducing both the risk of bleeding and the duration that the patient is not under prophylaxis.[9-11]

Spinal and epidural anesthesia

Meta-analyses show that **spinal and epidural anesthesia** reduce both thromboembolism and perhaps mortality in hip fracture surgery[12, 13] and total knee arthroplasty (TKA).[14-16] This method does not reduce risk sufficiently on its own but should be regarded as a useful adjunct. Initial European experience suggested that neuraxial anesthesia could be safely used in the presence of LMWH.[17] However, more recently there have been concerns that a spinal hematoma may develop on rare occasions.[18, 19] Guidelines had suggested that LMWH could be given safely four hours after removal of the epidural catheter.[20-22] However, on November 6, 2013, the FDA released a Drug Safety Communication updating recommendations to decrease the risk of neuraxial bleeding and paralysis in patients on LMWHs[23] It stated that for enoxaparin, placement or removal of a spinal catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of DVT. Longer delays (24 hours) were recommended for patients receiving higher therapeutic doses of enoxaparin (1 mg/kg twice daily or 1.5 mg/kg once daily). A post-procedure dose of enoxaparin should not be administered sooner than 4 hours after catheter removal.

Fondaparinux should be avoided whilst a continuous postoperative neuraxial block is in place.

Duration of prophylaxis in elective orthopedic surgery

Studies in patients having total hip arthroplasty (THA)[1, 24-32] demonstrate that there is prolonged risk, with 45-80% of all symptomatic events occurring after discharge from hospital.[26, 33-35]

RCTs in patients having THA indicate that **prolonged thromboprophylaxis with LMWH** for up to 35 days is safe and effective irrespective of LMWH used. It decreases the frequency of venographically detected total DVT, proximal DVT and symptomatic VTE after the seventh day by more than 50%.[32, 36-40]

One RCT compared warfarin prophylaxis (INR 2-3) for 9 days with warfarin extended for one month after hospital discharge. VTE occurred in 5.1% of in-hospital prophylaxis patients and 0.5% in those having extended prophylaxis (RR: 9.4, 95% CI: 1.2 to 73.5).[41] This study was prematurely terminated because of the superiority of prolonged prophylaxis. As indicated above, it has been subsequently demonstrated that extended prophylaxis with warfarin is associated with more hemorrhagic complications than with LMWH.[42]

The RECORD2 Study,[43] which compared extended thromboprophylaxis (35 days) using rivaroxaban with short term enoxaparin (10-14 days) followed by placebo further confirmed the benefits of extended prophylaxis after THA suggested by the RECORD1 Study.[44]

A systematic review and meta-analysis published in 2012 investigated the benefits and harms of prolonged (≥ 21 days) *vs.* standard duration (7 to 10 days) thromboprophylaxis after major orthopedic surgery in adults.[45] The methods of thromboprophylaxis in the studies that were included in this meta-analysis were comprised of LMWH, fondaparinux or VKAs. Compared with standard-duration therapy, prolonged prophylaxis resulted in fewer cases of PE (5 trials; OR: 0.14, 95% CI: 0.04 to 0.47), asymptomatic DVT (4 trials; RR: 0.48, 95% CI: 0.31 to 0.75), symptomatic DVT (4 trials; OR: 0.36, 95% CI: 0.16 to 0.81), and proximal DVT (6 trials; RR: 0.29, 95% CI: 0.16 to 0.52). There were more minor bleeding events with prolonged prophylaxis (OR: 2.44, 95% CI: 1.41 to 4.20), and insufficient evidence from 1 trial on hip fracture surgery suggested more surgical-site bleeding events (OR: 7.55, 95% CI: 1.51 to 37.64) with prolonged prophylaxis.

A Cochrane meta-analysis published in 2016 evaluated

the extended duration (five to seven weeks) of anticoagulants following total hip or knee arthroplasty or hip fracture.[46] In this meta-analysis, which included 16 studies involving 24,930 patients, extended duration of heparins (UFH or LMWH) did not show any difference in symptomatic VTE, symptomatic DVT, symptomatic PE and major bleeding compared with placebo. Minor bleeding was increased in the heparin group (OR: 2.01, 95% CI: 1.43 to 2.81; 2500 participants). However, extended duration **DOACs showed reduced symptomatic VTE (OR: 0.20, 95% CI: 0.06 to 0.68; 2,419 participants; one study) and symptomatic DVT (OR: 0.18, 95% CI: 0.04 to 0.81; 2,459 participants; two studies) compared with placebo**. There was no difference in symptomatic PE (OR: 0.25, 95% CI: 0.03 to 2.25; 1733 participants), major bleeding (OR: 1.00, 95% CI: 0.06 to 16.02; 2457 participants), clinically relevant non-major bleeding (OR: 1.22, 95% CI: 0.76 to 1.95; 2457 participants) and minor bleeding (OR: 1.18, 95% CI: 0.74 to 1.88; 2457 participants). The authors concluded that moderate quality evidence suggests extended duration anticoagulants to prevent VTE for people undergoing hip arthroplasty, although the benefit should be weighed against the increased risk of minor bleeding.

Further studies are needed before recommendations can be made for prophylaxis beyond 35 days. The optimal duration of prophylaxis is unknown. Epidemiologic data on postoperative death rates indicate a much longer duration of risk in subgroups such as emergency patients (*e.g.*, hip fracture) and patients with co-morbidities (*e.g.*, rheumatoid arthritis) in which vascular deaths dominate.[47, 48]

B. Elective hip arthroplasty

The risk

In the absence of prophylaxis, patients undergoing major elective hip arthroplasty and those with hip fracture have a 40-50% risk of asymptomatic DVT as shown in studies performed in the 1970s, 1980s and 1990s[26, 49, 50] (Table 7.I).[51-118] Similarly high rates of VTE were found in the placebo groups of two more recent dose ranging studies for enoxaparin and fondaparinux performed in Japan.[119, 120] The frequency rates of proximal DVT (Table 7.II)[72-74, 76-78, 121, 122] and PE (Table 7.III,[121, 123] Table 7.IV[124, 125]) were also high, and symptomatic events ranged from 2-5%.[126] In a population-based study in Scotland the incidence of VTE including fatal PE for the years 1999-2001 was 2.27% for primary hip arthroplasty and 1.79% for total knee arthroplasty.[127]

As indicated above, the risk of clinical DVT and PE continues after hospitalization over a period of approximately three months[26, 27, 126, 128] (Table 7.V).[25, 129-132] Mortality studies have confirmed a reduced survival for 2-3 months following elective surgery with the highest death rate early after operation.[47, 133]

There is a high incidence of proximal DVT (18-36%) in patients having THA[56, 59-61, 65, 134-137] in contrast to patients having TKA in whom the preponderance of thrombosis is distal.[75-77, 138, 139]

Modern THA is performed with a continuing reduction in hospital stay (3-6 days) so that patients are discharged while still at risk. Thus, most clinical events appear after hospital discharge, giving a false impression of a decreasing problem.[27, 128, 140]

A meta-analysis of 10 RCTs that used venography in patients having THA treated by LMWH found that for every five patients with asymptomatic DVT in a screening program, one patient experienced symptomatic VTE within three months of the operation.[141] The consistency of this finding with previous reports strengthens the belief that asymptomatic DVT is a surrogate for symptomatic DVT and PE.

Prophylactic methods and recommendations

General considerations

Prophylactic methods that have been investigated in patients having THA include aspirin, fixed-dose LDUH, LMWH, fondaparinux, heparinoids, recombinant hirudin, oral direct -Xa inhibitors, oral direct thrombin inhibitors, fixed mini-dose, and adjusted doses of VKAs, GEC, IPC and FIT. To determine the risk reduction for each prophylactic method, only RCTs with systematic screening tests for DVT have been used for the purposes of this document[1, 56, 72, 74, 123, 142-147] (Table 7.VI,[123] Table 7.VII,[123] Table 7.VIII;[9, 78, 139, 148-154] Figure 7.1,[56, 60, 142, 155] Figure 7.2,[72, 143, 155] Figure 7.3[1, 74, 144-147]).

LDUH

LDUH (5000 IU 8 or 12 h) was found to be effective in reducing DVT from 46.8% to 23.3% (RR: 0.50, 95% CI: 0.43 to 0.58) (meta-analysis of 20 RCTs in patients having elective THA)[124] and was the method of choice in the 1980s.

LMWH

LMWH has been subsequently demonstrated to be superior to LDUH for elective THA, reducing DVT from 21.2% to 13.8% (RR: 0.66, 95% CI: 0.52 to 0.84) and PE from 4.1% to 1.7% (RR: 0.4, 95% CI: 0.19 to 0.84).[39, 137, 156-163] Thus, **LDUH** is no longer recommended.

TABLE 7.I.—*The frequency of all DVT in orthopedic surgery and trauma, in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS).*

Patient groups	Number of studies	Patients N.	DVT incidence	95% CI
Elective hip replacement				
Belch *et al.* 1982[51]		36	20	
Bergqvist *et al.* 1979[52]		71	45	
Dechavanne *et al.* 1974[53]		27	13	
Dechavanne *et al.* 1975[54]		20	8	
Evarts *et al.* 1971[55]		56	30	
Gallus *et al.* 1983[56]		47	25	
Hampson *et al.* 1974[57]		52	28	
Harris *et al.* 1977[58]		51	23	
Hoek *et al.* 1992[59]		99	56	
Hull *et al.* 1990[60]		158	77	
Ishak & Morley 1981[61]		41	22	
Kalodiki *et al.* 1996[62]		14	13	
Mannucci *et al.* 1976[63]		51	22	
Morris *et al.* 1974[64]		32	16	
Turpie *et al.* 1986[65]		50	21	
VTCSG 1975[66]		30	11	
Welin-Berger *et al.* 1982[67]		16	5	
Total	17	851	435 (51%)	48% to 54%
Multiple trauma				
Freeark *et al.* 1967[68]		124	4	
Geerts *et al.* 1994[69]		349	201	
Kudsk *et al.* 1989[70]		38	24	
Shackford *et al.* 1990[71]		25	1	
Total	4	536	270 (50%)	46% to 55%
Total knee replacement				
Hull *et al.* 1979[72]		29	19	
Kim 1990[73]		244	80	
Leclerc *et al.* 1996[74]		57	31	
Lynch *et al.* 1988[75]		75	28	
Stringer *et al.* 1989[76]		55	31	
Stulberg *et al.* 1984[77]		49	41	
Wilson *et al.* 1992[78]		32	22	
Total	7	541	252 (47%)	42% to 51%
Hip fracture				
Ahlberg *et al.* 1968[79]		45	16	
Checketts & Bradley 1974[80]		26	13	
Darke 1972[81]		66	11	
Galasko *et al.* 1976[82]		50	23	
Gallus *et al.* 1973[83]		23	11	
Kakkar *et al.* 1972[84]		50	20	
Lahnborg 1980[85]		69	28	
Montrey *et al.* 1985[86]		81	22	
Morris & Mitchell 1976[87]		74	50	
Morris & Mitchell 1977[88]		76	49	
Myhre & Holen 1969[89]		55	22	
Powers *et al.* 1989[90]		63	29	
Rogers *et al.* 1978[91]		37	19	
Svend-Hansen *et al.* 1981[92]		65	28	
Xabregas *et al.* 1978[93]		25	12	
Total	15	805	353 (44%)	40% to 47%
Spinal cord injury				
Bors *et al.* 1954[94]		99	58	
Brach *et al.* 1977[95]		10	9	
Rossi *et al.* 1980[96]		18	13	
Silver 1974[97]		32	8	
Watson 1974[98]		234	42	
Frisbie & Sasahara 1981[99]		17	1	

(To be continued)

TABLE 7.I.—*The frequency of all DVT in orthopedic surgery and trauma, in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS) (continues).*

Patient groups	Number of studies	Patients N.	DVT incidence	95% CI
Merli *et al.* 1988[100]		17	8	
Myllynen *et al.* 1985[101]		9	9	
Yelnik *et al.* 1991[102]		22	12	
Total	9	458	160 (35%)	31% to 39%
Isolated lower limb injuries				
Hjelmstedt & Bergwall 1968[103]		76	34	
Abelseth *et al.* 1996[104]		82	18	
Kujath *et al.* 1993[105]		127	21	
Kock *et al.* 1995[106]		163	7	
Lassen *et al.* 2002[107]		159	29	
Jorgensen *et al.* 2002[108]		77	10	
Lapidus *et al.* 2007[109]		96	27	
Goel *et al.* 2009[110]		111	14	
Total	8	891	160 (18%)	16% to 21%
Elective spinal surgery				
West *et al.* 1992[111]		41	6	
Oda *et al.* 2000[112]		110	17	
Total	2	151	23 (15%)	10% to 22%
Knee arthroscopy				
Stringer *et al.* 1989[76]		48	2	
Demers *et al.* 1998[113]		184	33	
Williams *et al.* 1995[114]		85	3	
Jaureguito *et al.* 1999[115]		239	5	
Delis *et al.* 2001[116]		102	8	
Wirth *et al.* 2001[117]		111	5	
Michot *et al.* 2002[118]		63	10	
Total	7	832	66 (8%)	6% to 10%

The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

TABLE 7.II.—*The frequency of proximal DVT in the absence of prophylaxis diagnosed by surveillance with objective methods (fibrinogen uptake test or venography).*

Patient group	Number of studies	Number of patients	Incidence of DVT	95% CI
Elective hip replacement	25	1436	330* (23%)	20.8 to 25.2%
Imperiale *et al.* 1994[121]				
Total knee replacement	7	536	41 (7.6%)	5.5 to 10.1%
Hull *et al.* 1979[72]				
Kim, 1990[73]				
Leclerc *et al.* 1996[74]				
Mckenna *et al.* 1976[122]				
Stringer *et al.* 1989[76]				
Stulberg *et al.* 1984[77]				
Wilson *et al.* 1992[78]				

*This number is an estimate from the percentage given in the paper.

TABLE 7.III.—*The frequency of clinical pulmonary embolism* in the absence of prophylaxis.*

Patient group	Number of studies	Number of patients	Clinical PE	95% CI
Elective hip replacement	25	1436	57** (4%)	3.0 to 5.1%
Imperiale *et al.* 1994[121]				
Traumatic orthopedic surgery	11	494	34 (6.9%)	4.8 to 9.5%
APTC, 1994[123]				

*In most of the studies using an objective method of screening for DVT, patients found to have proximal thrombosis were treated with anticoagulants; the true incidence of clinical pulmonary embolism in series without such screening and intervention is unknown; **this number is an estimate from the percentage given in the paper.

TABLE 7.IV.—*The frequency of fatal pulmonary embolism without prophylaxis.**

Patient group	Number of studies	Number of patients	Incidence of fatal PE	95% CI
Elective hip replacement	12	485	8 (1.65%)	0.38% to 2.7%
Collins *et al.* 1988[124]				
Fractured neck of femur	23	1195	48 (4.0%)	3.0% to 5.3%
Lassen *et al.* 1994[125]				

*In most of the studies using an objective method of screening for DVT, patients found to have proximal thrombosis were treated with anticoagulants; the true incidence of fatal pulmonary embolism in the absence of intervention is unknown.

TABLE 7.V.—*Mortality after elective hip replacement in the absence of routine pharmacological prophylaxis.*

Author	Number of patients	Follow-up	Total deaths	95% CI	Fatal PE	95% CI	Anticoagulant use
Seagroatt *et al.* 1991[129]	11600	90 days	93 (1.10%)	0.87 to 1.31%	–	–	Very low
Sheppeard *et al.* 1981[130]	3016	Inpatient	19 (0.63%)	0.38 to 0.98%	12 (0.40%)	0.20 to 0.70%	20%*
Warwick *et al.* 1995[25]	1162**	90 days	15 (1.30%)	0.73 to 2.10%	4 (0.34%)	0.09 to 0.90%	11%*
Wroblewski *et al.* 1992[131]	18104	1 year	362 (2.0%)	1.80 to 2.20%	1.27 (0.70%)	0.58 to 0.82%	–
Fender *et al.* 1997[132]	2111	42 days	19 (0.91%)	0.05 to 1.42%	4 (0.19%)	0.05 to 0.49	65%

–: information not available.
*High risk patients received anticoagulation; **all patients wore thigh-length elastic stockings.

TABLE 7.VI.—*Effect of antiplatelet therapy (e.g. aspirin) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake in general surgery and phlebography in orthopedic surgery) in randomized controlled studies (Antiplatelet Trialists' Collaboration, 1994).*[123]

Type of patient	Control groups*			Antiplatelet groups			
	Number of trials with data	Number of patients	DVT (%)	Number of patients	DVT (%)	RR	95% CI
Orthopedic							
Traumatic	10	444	186 (42%)	454	163 (36%)	0.86	0.73 to 1.0
Elective	13	436	232 (53%)	427	160 (37%)	0.70	0.61 to 0.82
High risk medical	8	266	61 (23%)	261	39 (15%)	0.65	0.45 to 0.94

*In most trials patients were allocated evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparison between percentages adjusted control totals were calculated, (actual DVT incidence in surgical controls 700/2050; all medical trials evenly balanced).

TABLE 7.VII.—*Effect of antiplatelet therapy (e.g. aspirin) in the prevention of PE in randomized controlled studies in orthopedic patients(Antiplatelet Trialists' Collaboration, 1994).*[123]

Type of patient	Control groups*			Antiplatelet groups			
	Number of trials with data	Number of patients	PE	Number of patients	PE	RR	95% CI
Orthopedic							
Traumatic	11	494	34 (6.9%)	504	14 (2.8%)	0.40	0.22 to 0.71
Elective	16	537	29 (5.4%)	529	14 (2.6%)	0.49	0.26 to 0.92
High risk medical	9	280	8 (2.9%)	275	3 (1.1%)	0.38	0.10 to 1.42

*In most trials patients were allocated evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparison between percentages adjusted control totals were calculated, (actual DVT incidence in surgical controls 700/2050; all medical trials evenly balanced).

RECOMBINANT HIRUDIN

RCTs have shown that **recombinant hirudin** (desirudin) is more effective than LDUH[164-166] or LMWH.[165] Of 2079 patients studied, 1587 were included in the primary efficacy analysis. Asymptomatic DVT was reduced from 25.5% in the LMWH group (enoxaparin 40 mg daily) to 18.45% in the hirudin group (15 mg twice daily) (P=0.001; RR: 28.0%). The safety profile was the same in both groups.

LMWH *vs.* VKA

Several randomized controlled trials have compared **LMWH** with **VKAs**. LMWH was found to be more effective[1, 144, 167, 168] or at least as effective as VKA[145] for prevent-

TABLE 7.VIII.—*Effect of prophylaxis using the combination of foot impulse technology (FIT) with graduated elastic compression (GEC) on proximal DVT, in orthopedic patients.*

Author	Diagnostic method	Prophylaxis	N.	Control		Foot impulse technology plus additional method of prophylaxis	
				Proximal DVT	Method of prophylaxis	N.	Proximal DVT
Hip surgery							
Bradley *et al.* 1993[9]	VG	GEC	44	11 (25%)	FIT+GEC	30	2 (6.7%)
Fordyce *et al.* 1992[148]	VG	GEC	40	13 (32%)	FIT+GEC	39	2 (5%)
Santori *et al.* 1994[149]	US	LDUH	65	13 (20%)	FIT+GEC	67	2 (3.0%)
Warwick *et al.* 1998[150]	VG	LMWH+GEC	138	27 (17.4%)	FIT+GEC	136	12 (9%)
Pitto *et al.* 2004[151]	US	LMWH	100	6 (6%)	FIT+GEC	100	3 (3%)
Knee surgery							
Blanchard *et al.* 1999[152]	VG	LMWH	60	2 (3.3%)	FIT only	48	4 (8.3%)
Wilson *et al.* 1992[78]	VG	Nil	32	6 (19%)	FIT only	28	0
Westrich *et al.* 1996[139]	VG	Aspirin	83	49 (59%)	FIT + Aspirin	81	22 (27%)
Warwick *et al.* 2002[153]	VG	LMWH	99	57 (58%)	FIT	98	48 (54%)
Hip fracture							
Stranks *et al.* 1992[154]	US	GEC	39	9 (32%)	FIT+GEC	41	0

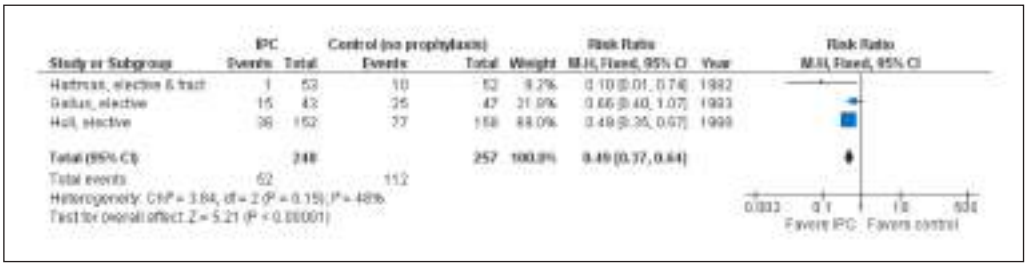

Figure 7.1.—Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with phlebography or duplex ultrasound[155] in randomized controlled studies of patients having hip replacement.[56, 60, 142]

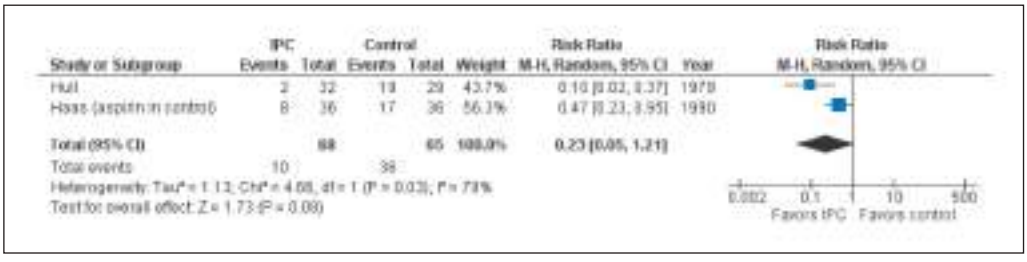

Figure 7.2.—Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with phlebography or duplex ultrasound[155] in randomized controlled studies of patients having knee replacement.[72, 143]

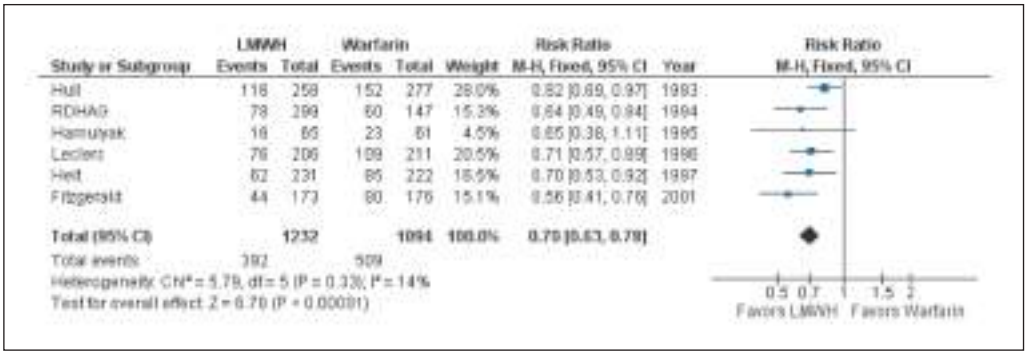

Figure 7.3.—Effect of warfarin versus low molecular weight heparin (LMWH) in the prevention of DVT diagnosed by surveillance with phlebography in patients having knee surgery.[1, 74, 144-147]

ing asymptomatic DVT. However, this was at the expense of a slight increase in hemorrhagic complications. When LMWH was started before or immediately after surgery, there was a marked reduction of proximal DVT from 3% to 0.8% (RR: 0.28, 95% CI: 0.1 to 0.74).[8] Symptomatic DVT was also reduced from 4.4% in the VKA group to 1.5% in the LMWH group (RR: 0.32, 95% CI: 0.12 to 0.88).

In a meta-analysis VKAs were less effective than LMWH in preventing any DVT (RR: 1.51, 95% CI: 1.27 to 1.79) and proximal DVT (RR: 1.51, 95% CI: 1.04 to 2.17), although the risk of wound hematoma was increased from 3.3% in the VKA recipients to 5.3% in LMWH recipients (RR: 2.29, 95% CI: 1.09 to 7.75).[169]

In a clinical trial for THA,[42] 1279 patients were randomized on the third postoperative day to LMWH or to warfarin for the subsequent six weeks. The primary endpoint was the overall clinical failure rate, *i.e.*, symptomatic VTE (radiologically confirmed), major hemorrhage or deaths. The failure rate was 3.7% in the LMWH group and 8.3% in the warfarin group (P=0.01). Major bleeding occurred in 1.4% and in 5.5%, respectively. It appears that reduced bleeding seen initially after surgery due to the slow onset of action for warfarin is offset by long-term increased risk of bleeding. Furthermore, national drug registries have shown warfarin to be a major cause of readmission and fatal bleeding.[170, 171] With these data, and because of the need for monitoring, their narrow therapeutic window and the risk of drug interactions, some surgeons find it difficult to see an advantage for VKA over LMWH, and VKA is no longer considered first line therapy for thromboprophylaxis.

Fondaparinux *vs.* LMWH

In contrast to LMWH, the pentasaccharide **fondaparinux** is a pure synthetic chemical compound. It is a potent indirect inhibitor of factor Xa acting by a catalytic effect facilitating antithrombin binding to activated factor X and represents one of many attributes of heparins. The drug is administered by subcutaneous injection once daily. It has been registered internationally for major orthopedic surgery.

Two large RCTs compared fondaparinux to enoxaparin.[172, 173] Reduction of asymptomatic DVT was 26% (RR: 0.74, 95% CI: 0.47 to 0.89) and symptomatic PE was 56% (RR: 0.44, 95% CI: 0.27 to 0.66) with fondaparinux. For the two studies combined, the incidence of major bleeding was 3% in the fondaparinux and 2.1% in the enoxaparin patients (P>0.05). Fondaparinux may accumulate and increase bleeding in patients with impaired renal function.

Antiplatelet therapy *vs.* placebo

A meta-analysis published in 1994[123] demonstrated that **antiplatelet therapy** in elective hip surgery is only moderately effective for protection against DVT (RR: 0.70, 95% CI: 0.61 to 0.82) (Table 7.VI)[123] but the observed reduction in the risk of PE was substantial (RR: 0.49, 95% CI: 0.26 to 0.92) (Table 7.VII).[123]

The subsequent PEP study[174, 175] showed that aspirin is not as valuable as suggested by the meta-analysis. Over 13,000 hip fracture patients were randomized to have either aspirin or placebo. The overall death rate was identical in each group. Risk reduction for symptomatic VTE was from 2.5% to 1.6% and this was only one-half of that expected from LMWH and one-third from fondaparinux. The reduced risk of VTE was matched by an increased risk of blood transfusion, gastro-intestinal bleeding and wound bleeding. (For extended therapy using aspirin see the relevant section below).

GEC

The Cochrane database[176] and an earlier meta-analysis[177] show that **GEC** is effective in reducing DVT in hospitalized patients, but there are few robust studies specific to orthopedic surgery.[61, 178] Because other methods of prevention are more effective, GEC stockings on their own are not recommended.

IPC

IPC is effective in patients having THA[56, 60, 142] (Figure 7.1[56, 60, 142, 155]) reducing asymptomatic DVT from 43.6% in the control groups to 21% in the compression groups (RR: 0.48, 95% CI: 0.36 to 0.64). Modern technology has made IPC devices light, silent, more portable and more effective in preventing stasis by sensing venous volume so that the compression period follows immediately after venous refilling. In addition, different sleeve designs and materials have been used to improve patient compliance.[179]

IPC combined with aspirin *vs.* LMWH

In a study involving 392 evaluable patients having THA in which **IPC combined with aspirin 81mg daily was compared with LMWH** initiated 12 to 24 hours after operation, the incidence of asymptomatic (ultrasound screening on 10-12 days) and symptomatic postoperative DVT was found to be 3% in both groups.[180] The incidence of PE was 1% in both groups. There were no major bleeding events in the IPC/aspirin group and a 6% rate of major bleeding in the LMWH group (P<0.001).

In another study involving 121 evaluable patients having THA or TKA, in which IPC plus aspirin 100 mg daily was also compared with LMWH, the incidence of postoperative venographic DVT was found to be 6.6% in the IPC plus aspirin group and 28.3% in the LMWH group (RR: 0.23, 95% CI: 0.08 to 0.65).[181]

IPC combined with LMWH *vs.* LMWH

Three RCTs have compared **combined modalities** with LMWH. In the first study in 131 patients having THA and TKA, the combination of LMWH plus IPC was more effective than LMWH plus GEC stockings (DVT incidence 0% *vs.* 28%).[182]

In the second study involving 277 patients, the combination of LMWH plus IPC was more effective than LMWH (DVT incidence 6.6% *vs.* 19.5%).[183]

In the third study involving 1,803 patients having various orthopedic operations, the combination of LMWH with IPC was also more effective than LMWH alone (DVT incidence 0.4% *vs.* 1.7%). In the subgroup of 306 patients having THA the incidence of DVT was 0% in the combined modalities group and 5.2% in the LMWH group (P<0.001).[184] (see additional information in section 12 on combined modalities).

FIT combined with GEC

FIT combined with GEC is effective in reducing the incidence of proximal DVT in patients having THA or TKA (Table 7.VIII)[9, 78, 139, 148-154] with less bleeding and swelling. Direct comparisons with chemical prophylaxis are sparse; there is probably superiority to LDUH[149] and equivalence with LMWH for THA[151, 185] but not for TKA.[152]

IPC and FIT offer an alternative for patients with contraindications to chemical prophylaxis (Figure 7.1;[56, 60, 142, 155] Table 7.IX).[123]

Systematic review and meta-analysis of combined modalities

A 2022 Cochrane review update evaluated the efficacy of combined modalities, **IPC and pharmacological prophylaxis** (treatment group) **against single modalities alone** (control group, separate analyses by prophylaxis modality) **to prevent PE and DVT in patients at high risk for VTE**.[8] Thirty-four studies that included 14,931 patients were identified, of which 25 were RCTs. The studies evaluated **orthopedic patients (N.=14)**, urology patients (N.=3), and general surgery, cardiothoracic and other types of patients (N.=17).[186]

The addition of pharmacological prophylaxis to IPC compared with IPC alone reduced the incidence of symptomatic PE from 1.34% in the IPC group to 0.65% in the combined group (OR: 0.51, 95% CI: 0.29 to 0.91). The incidence of DVT was 3.81% in the IPC group and 2.03% in the combined group showing a reduced incidence of DVT in favor of the combined group (OR: 0.51, 95% CI: 0.36 to 0.72).

The addition of pharmacological prophylaxis to IPC, however, increased the risk of any bleeding compared to IPC alone: 0.95% in the IPC group and 5.88% in the combined group (OR: 6.02, 95% CI: 3.88 to 9.35). Major bleeding followed a similar pattern: 0.34% in the IPC group compared with 2.21% in the combined group (OR: 5.77, 95% CI: 2.81 to 11.83).

Tests for subgroup differences between orthopedic and non-orthopedic surgery participants were not possible for the incidence of PE as no PE events were reported in the orthopedic subgroup. No difference was detected between orthopedic and non-orthopedic surgery participants for the incidence of DVT (P=0.19).

The use of combined IPC and pharmacological prophylaxis modalities compared with pharmacological prophylaxis alone reduced the incidence of PE from 1.84% in the pharmacological prophylaxis group to 0.91% in the combined group (OR: 0.46, 95% CI: 0.30 to 0.71). The incidence of DVT was 9.28% in the pharmacological prophylaxis group and 5.48% in the combined group (OR: 0.38, 95% CI: 0.21 to 0.70).

Increased bleeding side effects were not observed for IPC when it was added to anticoagulation (any bleeding:

Table 7.IX.—*Effect of antiplatelet therapy (e.g. aspirin) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake in general surgery and phlebography in orthopedic surgery) in randomized controlled studies (Antiplatelet Trialists' Collaboration, 1994).*[123]

Type of patient	Control groups*			Antiplatelet groups			
	Number of trials with data	Number of patients	DVT (%)	Number of patients	DVT (%)	RR	95% CI
Orthopedic							
Traumatic	10	444	186 (42)	454	163 (36)	0.86	0.73 to 1.0
Elective	13	436	232 (53)	427	160 (37)	0.70	0.61 to 0.82

*In most trials patients were allocated evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparison between percentages adjusted control totals were calculated, (actual DVT incidence in surgical controls 700/2050; all medical trials evenly balanced).

OR: 0.87, 95% CI: 0.56 to 1.35; major bleeding: OR: 1.21, 95% CI: 0.35 to 4.18).

No difference was detected between the orthopedic and non-orthopedic surgery participants for PE incidence (P=0.82) or for DVT incidence (P=0.69).

Rivaroxaban

Rivaroxaban is an oral direct Xa inhibitor. Two studies (RECORD1 and RECORD2) **compared rivaroxaban with enoxaparin** in patients having THA.[43, 44]

In RECORD1 Study which involved 3153 evaluable patients, both prophylactic regimens were given for 31-39 days.[44] Superior efficacy of rivaroxaban was demonstrated, with an incidence of **venographic VTE of 3.7% in the enoxaparin group and 1.1% in the rivaroxaban group (P< 0.001)**. The incidence of major and non-major clinically relevant bleeding was 2.5% in the enoxaparin group and 3.2% in the rivaroxaban group (P>0.05).

The RECORD2 Study investigated the efficacy of extended thrombophylaxis (35 days) with rivaroxaban compared with short term enoxaparin (10-14 days) followed by placebo.[43] **The incidence of venographic VTE was 9.3% in the enoxaparin group and 2.0% in the rivaroxaban group (P<0.0001)**. The incidence of major and non-major clinically relevant bleeding was 2.8% in the enoxaparin group and 3.3% in the rivaroxaban group (P>0.05).

Apixaban

Apixaban is another oral direct Xa inhibitor. In a double-blind placebo-controlled study involving 5407 patients having THA, **apixaban at a dose of 2.5 mg orally twice daily was compared with enoxaparin at a dose of 40 mg subcutaneously every 24 hours.** Apixaban therapy was initiated 12 to 24 hours after closure of the surgical wound; enoxaparin therapy was initiated 12 hours before surgery.[187] Prophylaxis was continued for 35 days after surgery, followed by bilateral venographic studies. The incidence of the **primary efficacy outcome** (asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause during the treatment period) **was 1.4% in the apixaban group and in 3.9% in the enoxaparin group (RR: 0.36, 95% CI: 0.22 to 0.54; P<0.001)** for both non-inferiority and superiority. The incidence of major and clinically relevant non-major bleeding was 4.8% in the apixaban group and 5.0% in the enoxaparin group (P>0.05).

Edoxaban

Edoxaban is an oral direct Xa inhibitor that is 10,000-fold more selective for factor Xa than thrombin.[188] In the double-blind, double-dummy RCT (STARS J-V) (N=503), **edoxaban (30 mg once daily) resulted in a significantly smaller VTE rates than enoxaparin (20 mg twice daily) (2.4% *vs.* 6.9%; P=0.0157 for superiority)**.[189] The difference between the incidence of major and clinically relevant non-major bleeding events between edoxaban (2.6%) and enoxaparin (3.7%) was not statistically significant (P=0.475).

In the multicenter double blind, STARS E-3 and STARS J-V RCTs, a total of 1326 patients with total knee or hip arthroplasty received edoxaban 30 mg once daily or enoxaparin 20 mg twice daily for 11 to 14 days.[190] The studies were conducted in Japan and Taiwan and enoxaparin dosing was based on Japanese label recommendations. The primary efficacy endpoint was the incidence of VTE and the safety endpoint was major or clinically relevant nonmajor (CRNM) bleeding. **The incidence of VTE was 5.1% for edoxaban and 10.7% for enoxaparin (P<0.001)**. The incidence of combined major and CRNM bleeding was 4.6% and 3.7% for edoxaban and enoxaparin, respectively (P=0.427). The authors concluded that edoxaban was superior to enoxaparin in prevention of VTE following TKA and THA, with comparable rates of bleeding events. Relative to enoxaparin, edoxaban significantly reduced D-dimer, F_{1+2}, and SFMC.

The most recent review and meta-analysis of nine RCTs involving 4274 patients having total knee or hip arthroplasty compared the short term (7-14 days) efficacy of edoxaban in the prevention of VTE (DVT identified by bilateral venography, symptomatic DVT and PE) compared with other drugs (LMWH, 5 studies; fondaparinux, 2 studies), or placebo (physiotherapy,1 study, placebo 1 study).[191] **VTE was reduced by edoxaban compared with the control groups (RR: 0.49, 95% CI: 0.31 to 0.74)**. There was no statistical difference between edoxaban and controls in the incidence of clinically relevant non-major or minor bleeding events (RR: 1.41, 95% CI: 0.97 to 2.06). However, there was a statistically significant increase in all bleeding events (RR: 1.43, 95% CI: 1.10 to 1.85).

Dabigatran

Dabigatran is an oral direct inhibitor of thrombin. Two double blind non-inferiority trials evaluated the efficacy and safety of dabigatran in patients having elective THA. In the first study (RE-NOVATE), there were three groups of patients receiving dabigatran 150 mg, dabigatran 220 mg or enoxaparin 40 mg for 25-35 days (median 33 days) when bilateral venography was performed. **The primary endpoint of VTE and all-cause mortality in the three**

groups was 8.6%, 6.0% and 6.7% of the respectively (P<0.0001 for non-inferiority of each group *vs.* enoxaparin).[192] In the second study (RE-NOVATE II) 220 mg of dabigatran was compared with 40 mg enoxaparin administered for the same period.[193] **The primary endpoint of total VTE and all-cause mortality occurred in 7.7% in the dabigatran group and 8.8% in the enoxaparin group (P<0.0001 for non-inferiority of dabigatran *vs.* enoxaparin)**. There was no significant difference in major bleeding events between the various groups in either study.

Extended duration of thromboprophylaxis using aspirin

The interest in the use of aspirin after orthopedic surgery has been renewed after the publication of several studies[194-197] including the American College of Chest Physicians 2012 Guidelines, which included aspirin among the methods of prophylaxis in patients undergoing major orthopedic surgery.[194] This was based on the EPCAT-1 RCT, in which **the efficacy of aspirin was compared with LMWH** after THR in 778 patients. All patients received dalteparin 5000 units subcutaneously for 10 days followed by random allocation to continue dalteparin or to start aspirin, 81 mg daily, for **28 more days**.[195] **The primary efficacy outcome was symptomatic VTE within 90 days post-randomization.** Five (1.3%) of 398 patients assigned to dalteparin and 1 (0.3%) of 380 (0.3%) patients assigned to aspirin had VTE (absolute difference, 1.0 percentage point [95% CI, 0.5 to 2.5 percentage points]). Aspirin was noninferior (P<0.001) but not superior (P=0.22) to dalteparin. Clinically significant bleeding occurred in 5 patients (1.3%) receiving dalteparin and 2 (0.5%) receiving aspirin. The authors concluded that extended prophylaxis for 28 days with aspirin was non-inferior to and as safe as dalteparin for the prevention of VTE after THA in patients who initially received dalteparin for 10 days.

In EPCAT-2 Trial, a total of 3424 patients (1804 undergoing THA and 1620 undergoing TKA) received rivaroxaban 10 mg daily for 5 days and were then randomly allocated to continue rivaroxaban or to start aspirin, 81 mg daily, for **9 additional days after knee arthroplasty or 30 additional days after hip arthroplasty**.[196] **Symptomatic VTE** occurred in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% confidence interval [CI]: −0.55 to 0.66; P<0.001 for noninferiority and P=0.84 for superiority). Bleeding complications including major bleeding were not significantly different between groups. The authors concluded that the extended prophylaxis with aspirin was not significantly different from rivaroxaban in patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty.

A recent crossover RCT (CRISTAL Trial) evaluated the effect of aspirin on **symptomatic VTE** compared with enoxaparin therapy in patients undergoing hip or knee arthroplasty using background IPC and GEC.[198] In this study, the **primary outcome was symptomatic VTE within 90 days, including PE and DVT (above or below the knee)**. The noninferiority margin was 1%. Six secondary outcomes are reported, including death and major bleeding within 90 days. A total of 13,717 patients that were enrolled to the trial were randomized to receive **aspirin (100 mg once daily) or enoxaparin (40 mg daily) for 35 days after THA** and for 14 days after TKA surgery. Within 90 days of surgery, symptomatic VTE occurred in 256 patients, including PE (79 cases), above-knee DVT (18 cases), and below-knee DVT (174 cases). **The symptomatic VTE rate in the aspirin group was 3.45% and 1.82% in the enoxaparin group it was 1.82% (estimated difference: 1.97%, 95% CI: 0.54% to 3.41%). This failed to meet the criterion for noninferiority for aspirin and was significantly superior for enoxaparin (P=0.007)**. The result of the primary outcome was driven by the incidence of below knee DVT which was occurred in 129 (2.4%) out of 5415 patients in the aspirin group and in 45 (1.2%) out of 3787 patients in the enoxaparin group (RR: 0.51, 95% CI: 0.36 to 0.71) (P=0.004). The authors concluded that in patients undergoing hip or knee arthroplasty for osteoarthritis, aspirin compared with enoxaparin resulted in a significantly higher rate of symptomatic VTE within 90 days, defined as below- or above-knee DVT or PE.

Systematic review and meta-analysis

A recent systematic review and meta-analysis, which was published in 2020 and included 13 RCTs evaluated the clinical efficacy and safety of aspirin with other anticoagulants (UFH, LMWH, VKA and DOAC) after THA and TKA.[199] **Three of the studies relied on symptomatic DVT and PE confirmed by objective tests. The remaining 10 studies relied on routine screening for the diagnosis of DVT as well as symptomatic DVT and PE.** The daily dose of aspirin was 81-100mg in four studies, 200-350 in three studies, 600-650 in two studies and 1200-3000 in four studies. The duration of prophylactic therapy was 7-14 days in 8 studies and 28-42 days in five studies.

The RR of VTE after THA and TKA was 1.12 (95% CI: 0.78 to 1.62) for aspirin compared with other anticoagulants. The results were similar for DVT (RR: 1.04,

95% CI: 0.72 to 1.51) and PE (RR: 1.01, 95% CI: 0.68 to 1.48). The risk of adverse events, including major bleeding, wound hematoma, and wound infection, was not statistically significantly different in patients receiving aspirin *vs.* other anticoagulants. When analyzing THAs and TKAs separately, there was no statistically significant difference in the risk of VTE, DVT, and PE between aspirin and other anticoagulants. Aspirin had a VTE risk not statistically significantly different from LMWH (RR: 0.76, 95% CI: 0.37 to 1.56) or rivaroxaban (RR: 1.52, 95% CI: 0.56 to 4.12). The authors concluded that there was no statistically significant difference with aspirin from other anticoagulants in terms of clinical efficacy and safety profile when they are used for thromboprophylaxis after THA and TKA.

Recommendations

In patients undergoing elective hip replacement LMWH initiated and dosed according to the manufacturer's recommendations **(Level of evidence high, recommendation strong), fondaparinux (Level of evidence high, recommendation strong), rivaroxaban (Level of evidence high, recommendation strong), apixaban (Level of evidence high, recommendation strong) dabigatran (Level of evidence high, recommendation strong) and VKAs (Level of evidence high, recommendation moderate)**.

IPC or **FIT combined with GEC** stockings are an equivalent alternative **(Level of evidence high, recommendation moderate)** to LMWH **(Level of evidence high, recommendation strong)** for those surgeons or anesthetists concerned about bleeding. These devices can be used as long as tolerated and then replaced with chemical prophylaxis starting as soon as it is safe and continued for the rest of the 5-week period of risk.

Desirudin is approved for short-term prophylaxis in approximately 20 European countries and the US and can be used in patients with HIT **(Level of evidence high, recommendation strong)**.

LMWH combined with IPC is more effective than either prophylactic modality used alone and should be considered in all cases **(Level of evidence strong, recommendation strong)**.

Prophylaxis with LMWH should be initiated either before or after surgery depending on the adopted regimen **(Level of evidence high, recommendation strong)**.

Fondaparinux should be started at least 6-8 hours after surgery. Prophylaxis should be continued for 4-6 weeks with LMWH (Level of evidence: high, recommendation strong) or fondaparinux (Level of evidence moderate, recommendation weak) (extrapolation from a hip fracture trial).

Aspirin may be considered for extended prophylaxis **(Level of evidence high for reduction in mortality and PE, but low for DVT prevention** and by inference reduction in PTS, **recommendation weak)** (see Section D on hip fracture below).

C. Elective knee arthroplasty

The risk

Data from THA should not be extrapolated to TKA. The incidence of asymptomatic DVT detected by venography is higher in patients having TKA than THA. However, the incidence of proximal DVT is lower in TKA than in patients having THA (see section B on THA above).

Prophylactic methods and recommendations

General considerations

IPC

IPC is effective in patients having TKA (RR: 0.27, 95% CI: 0.14 to 0.49) (Table 7.VIII).[9, 78, 139, 148-154] One small RCT demonstrated that **IPC reduced the incidence of asymptomatic DVT from 65% to 6%**.[72] A subsequent RCT found IPC to be more effective than aspirin for preventing of venographically-detected DVT (22% *vs.* 47%; P<0.02) in unilateral operations.[143] In yet another RCT, IPC was found to be less effective than warfarin for preventing venographically detected DVT (32% *vs.* 19%).[200]

FIT AND IPC *vs.* LMWH

FIT was effective in two studies[78, 139] but showed inferiority when compared with LMWH in two other studies[152, 153, 201] (Table 7.VIII).[9, 78, 139, 148-154] In a subsequent study involving 136 patients having THA or TKA, in which a mobile IPC device was also compared with LMWH, the incidence of postoperative venographically-detected DVT was found to be 6.6% in the IPC group and 28.3% in the LMWH group. Proximal DVT was detected in 1.6% in the IPC group and 10% in the LMWH group.[181]

LMWH

A RCT demonstrated that **LMWH** was more effective than placebo. It reduced venographically detected DVT from 65% in the placebo group to 19% in the LMWH group (RR: 0.30, 95% CI: 0.16 to 0.58).[202] Subsequent studies demonstrated that LMWH was more effective than LDUH

(RR: 0.75, 95% CI: 0.58 to 0.92)[203, 204] or warfarin (RR: 0.68, 95% CI: 0.62 to 0.76) (Figure 7.3).[1, 74, 144-147]

Fondaparinux

Fondaparinux (2.5 mg once daily starting 6 h after surgery) was more effective than enoxaparin (30 mg twice daily, starting 12-24 h after surgery) in one study.[205] VTE (defined as venographically detected DVT, symptomatic DVT or symptomatic PE) was reduced from 27.8% in the enoxaparin group to 12.5% in the fondaparinux group (RR: 0.45, 95% CI: 0.32 to 0.62). However, major bleeding was more common with fondaparinux (2.1% *vs.* 0.2%; P=0.006). This increased rate of bleeding with fondaparinux was driven by a minority of patients given fondaparinux within 6 h of surgery.

Systematic review and meta-analysis of fondaparinux studies

The efficacy of fondaparinux was confirmed in a meta-analysis[206] which included the above study and three other RCTs comparing fondaparinux (2.5 mg daily starting 6-hours after surgery) with enoxaparin in patients having orthopedic surgery (elective hip arthroplasty, elective major knee surgery, and surgery for hip fracture (N=7344).

The primary efficacy outcome was VTE up to day 11, defined as DVT detected by mandatory bilateral venography or documented symptomatic DVT or PE. The primary safety outcome was major bleeding.

The incidence of VTE by day 11 was reduced from 13.7% in the enoxaparin group to 6.8% in the fondaparinux group (RR: reduction of 55.2%, 95% CI: 45.8% to 63.1%; P<0.001). This beneficial effect was consistent across all types of surgery and all subgroups. Although major bleeding occurred more frequently in the fondaparinux-treated group (P=0.008), the incidence of clinically relevant bleeding (leading to death or reoperation or occurring in a critical organ) did not differ between groups.

Rivaroxaban

Two studies (RECORD3 and RECORD4) **compared rivaroxaban with enoxaparin** in patients having TKA.

In RECORD3 study which involved 2531 evaluable patients, both prophylactic regimens were given for 10-14 days. **LMWH 40 mg daily started 12 hours before surgery and rivaroxaban 10 mg daily starting 6-8 hours after surgery.** Mandatory venography was performed between day 11 and 15. The primary outcome, which was a composite of any DVT, non-fatal PE or death was 18.9% in the enoxaparin group and 9.6% for rivaroxaban, (P<0.001). There was no significant difference in the incidence of major and non-major clinically relevant bleeding in the two groups.[207]

The RECORD4 study **compared the efficacy and safety of rivaroxaban with the commonly used North American regimen of enoxaparin 30 mg twice daily** until days 11 to 15 when bilateral venography was performed.[208] The incidence of the composite endpoint, venographic VTE, PE or death was reduced from 10.1% in the enoxaparin group to 6.9% in the rivaroxaban group (RR: 0.69, 95% CI: 0.51 to 0.92). There was no significant difference in the incidence of major and non-major clinically relevant bleeding in the two groups.

Apixaban

Two double blind RCTs compared apixaban with enoxaparin.

The first study, which involved 3195 patients having TKA, **compared apixaban 2.5 mg twice daily with enoxaparin 30 mg twice daily**.[209] The rate of the primary efficacy outcome (a composite of asymptomatic and symptomatic DVT, nonfatal PE, and death from any cause during treatment) was 9.0% with apixaban and 8.8% with enoxaparin (RR: 1.02, 95% CI: 0.78 to 1.32). The composite incidence of major bleeding and clinically relevant nonmajor bleeding was 2.9% with apixaban and 4.3% with enoxaparin (P=0.03).

The second study which involved 3057 patients demonstrated superiority of **apixaban 2.5 mg twice daily against enoxaparin 40 mg once daily for 14 days**. The primary efficacy composite outcome of asymptomatic and symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death during treatment was 15% with apixaban and 24% with enoxaparin (RR: 0.62, 95% CI: 0.51 to 0.74; P<0.0001) without any significant difference in bleeding between the two groups.[210]

Edoxaban

In a double-blind, double-dummy RCT, patients received **oral edoxaban 30 mg once daily beginning 6 to 24 hours after surgery or enoxaparin 20 mg subcutaneously twice daily beginning 24 to 36 hours after surgery for 11 to 14 days**.[211] Of 716 patients enrolled, the composite outcomes of asymptomatic or symptomatic DVT and symptomatic PE was reported in 7.4% and 13.9% of the patients in the edoxaban and enoxaparin groups, respectively, indicating non-inferiority (P<0.001) and superiority (P=0.010) of edoxaban *vs.* enoxaparin. In the edoxaban and enoxaparin groups, major bleeding occurred in 1.1% *vs.* 0.3% of the patients (P=0.373); major or CRNM bleed-

ing occurred in 6.2% and 3.7% of the patients (P=0.129), respectively. In summary, edoxaban 30 mg once daily was more effective for thromboprophylaxis than subcutaneous enoxaparin 20 mg twice daily following TKA and demonstrated a similar incidence of bleeding events.

Betrixaban

Another direct oral inhibitor of factor Xa, betrixaban has been evaluated in an exploratory RCT in the US and Canada.[212] In this study, 215 patients undergoing TKA in a 2:2:1 ratio to receive **post-operative betrixaban 15 mg or 40 mg twice daily. or enoxaparin 30 mg twice daily, respectively, for 10-14 days**. The incidence of VTE was 20% (95% CI: 11% to 31%) for betrixaban 15 mg, 15% (95% CI: 8% to 27%) for betrixaban 40 mg, and 10% (95% CI: 3% to 24%) for enoxaparin. No bleeds were reported for betrixaban 15 mg, 2 (2.4%) CRNM bleeding events with betrixaban 40 mg, and one (2.3%) major and two (4.6%) clinically significant non-major bleeds with enoxaparin. A dose- and concentration-dependent effect of betrixaban on inhibition of thrombin generation and anti-Xa levels was observed. Betrixaban was withdrawn from the market in 2020.

Dabigatran

Dabigatran is a direct oral inhibitor of thrombin. Two double blind non-inferiority RCTs evaluated the efficacy and safety of dabigatran in patients having elective TKA.

In the first study (RE-MODEL), which involved 2076 patients, there were three groups of patients receiving dabigatran 150 mg, 220 mg twice daily or enoxaparin 40 mg daily for 6-10 days when bilateral venography was performed. The primary composite endpoint of **total VTE and all-cause mortality occurred in 40.5%, 36.4% and 37.7% of the groups, respectively** (P=0.0003 and 0.017 for non-inferiority of each group respectively *vs.* enoxaparin).[213]

In the second study (RE-MOBILIZE), which involved 1896 patients, there were also three groups of patients receiving dabigatran 150 mg once daily, dabigatran 220 mg once daily or enoxaparin 30 mg twice daily administered for 12-15 days (median 13 days).[214] Non-inferiority of either dabigatran dose was not confirmed. **The primary endpoint of total VTE and all-cause mortality occurred in 33.7%, 31.1% and 25.3% of the three groups respectively**. Dabigatran 220 mg and 110 mg showed inferior efficacy to enoxaparin (P=0.02 and P<0.001 respectively). In all three treatment groups, the composite primary endpoint was driven primarily by the occurrence of distal DVT whereas no significant difference was observed in mortality rates. There was no significant difference in major bleeding events between the various groups in either study.

Combined modalities

Three RCTs compared combined modalities with LMWH.

In the first study which included 131 patients having THA and TKA, the combination of LMWH plus IPC was more effective than LMWH plus GEC stockings.[182] In the subgroup of patients having TKA, **the incidence of VTE was 0% in the combined modalities group and 40% in the LMWH group using compression ultrasonography**.

In the second study involving 277 patients the combination of LMWH plus IPC was more effective than LMWH alone **(DVT incidence 6.6% *vs.* 19.5%; P=0.018)**.[183]

In the third study involving 1803 patients having various orthopedic operations the combination of LMWH plus IPC was also more effective than LMWH alone (symptomatic DVT incidence 0.4% *vs.* 1.7% using compression ultrasonography on the day of discharge). In the subgroup of 133 patients having TKA, **the incidence of DVT was 3.8% in the combined modalities group and 7.4% in the LMWH group (P<0.038)**[184] (see Section 12 on combined modalities).

Systematic review and meta-analysis on duration of prophylaxis

A systematic review involving nine studies (eight with LMWH and one with LDUH) published in 2001 indicated that extended duration prophylaxis for 30-42 days significantly reduced the frequency of symptomatic VTE (1.3% *vs.* 3.3%; OR: 0.38; 95% CI: 0.24 to 0.61; NNT=50). There was a greater risk reduction in patients undergoing THA (1.4% *vs.* 4.3%; OR: 0.33, 95% CI: 0.19 to 0.56; NNT=34) compared with TKA (1.0% *vs.* 1.4%; OR: 0.74, 0.26 to 2.15; NNT=250). A significant reduction in asymptomatic venographically-detected DVT was also observed (9.6% *vs.* 19.6%; OR: 0.48, 95% CI: 0.36 to 0.63; NNT=10). There was no increase in major bleeding, but extended-duration prophylaxis was associated with excess minor bleeding (3.7% *vs.* 2.5%; OR: 1.56, 95% CI: 1.08 to 2.26; NNH=83).[215]

Recommendations

In patients undergoing elective knee replacement, LMWH (initiated and dosed according to the manufacturer's recommendations) **(Level of evidence high, recommendation strong)**, **rivaroxaban (Level of evidence high, recommendation strong), apixaban (Level of**

evidence high, recommendation strong) fondaparinux (Level of evidence high, recommendation strong) and VKAs (although less effective) **(Level of evidence high, recommendation weak) are recommended**.

Aspirin may be considered for extended prophylaxis (**Level of evidence high for reduction in mortality and PE, but low for DVT prevention** and by inference reduction in PTS, **recommendation weak)** (see section B above on elective hip arthroplasty and D below on hip fracture).

IPC is an alternative option (**Level of evidence moderate** due to small study size, **recommendation moderate)**.

LMWH combined with IPC is more effective than LMWH prophylactic modality used alone and should be considered **(Level of evidence high, recommendation strong)**.

D. Hip fracture surgery

The risk

Patients having hip fracture surgery have the highest rates of DVT (46-60%)[90, 216, 217] and fatal PE (2.5-7.5%).[135, 217, 218] (Table 7.I,[51-118] 7.III, 7.IV). The VTE risk period lasts for 2-3 months after hip fracture surgery in spite of common short-term prophylaxis[27, 126] and the 90-day risk of overall death is 13%.[219] After hip fracture, the risk is greater than elective hip replacement, the majority dying of vascular events even though most patients receive some form of short-term prophylaxis.[47, 133]

Prophylactic methods and recommendations

General considerations

Because the risks of DVT and PE including fatal PE are high in patients with hip fracture (Table 7.I,[51-118] Table 7.III,[121, 123] Table 7.IV[124, 125]), prophylaxis should start as soon as possible after diagnosis and should be the same as that recommended for elective hip surgery.

IPC

Reduction in asymptomatic DVT has been demonstrated by **IPC** (RR: 0.2, 95% CI: 0.07 to 0.55)[142] and **FIT** in combination with **GEC stockings**[154] (RR: 0.32, 95% CI: 0.32 to 0.67) (Table 7.VIII).[9, 78, 139, 148-154] In a third study,[155] the combined endpoint of PE and proximal DVT using duplex ultrasound was reduced from 12% in the group without prophylaxis to 4% in the IPC group. More studies are needed.

Antiplatelet therapy

Aspirin *vs.* placebo

A meta-analysis[123] published in 1994 demonstrated that **antiplatelet therapy** in traumatic orthopedic surgery is only slightly effective for protection against DVT (RR: 0.86, 95% CI: 0.73 to 1) (Table 7.VI)[25, 129-132] but the observed reduction in the risk of PE was substantial (RR: 0.40, 95% CI: 0.22 to 0.71) (Table 7.VII,[123] Table 7.X[123]).

In a randomized, placebo-controlled trial of patients undergoing surgery for hip fracture (13,356 patients) or for elective hip or knee arthroplasty (4088 patients), aspirin at a dose of 160 mg daily started preoperatively was used as the primary prophylactic agent for 35 days.[174] The primary endpoint of the study was total mortality and the study failed to detect any difference between the placebo and aspirin groups. However, in the subgroup analysis of the patients with hip fracture, aspirin reduced the incidence of symptomatic DVT by 29% (95% CI: 3% to 48%; P=0.03) and PE by 43% (95% CI: 18% to 60%; P=0.002). PE or DVT was confirmed in 105 (1.6%) of 6,679 patients assigned aspirin compared with 165 (2.5%) of 6,677 patients assigned to placebo, which represents an absolute reduction of 9 per 1000 and a proportional reduction of 36% (95% CI: 19% to 50%; P=0.0003). However, the complication rate (transfusion requirements and bleeding) offset much of the reduction in symptomatic VTE.

Aspirin *vs.* LMWH

Two recent RCTs compared aspirin with LMWH in adult patients with fractures.[220, 221]

The ADAPT RCT, published in 2020 included adult patients with extremity fractures proximal to carpals or metacarpals or hip or acetabular fractures requiring VTE prophylaxis.[220] Of the 329 eligible patients **164 were assigned to LMWH and 165 to aspirin**. The primary outcome was a composite that included bleeding complications, VTE,

Table 7.X.—*Effect of antiplatelet therapy (e.g. aspirin) in the prevention of PE in randomized controlled studies (Antiplatelet Trialists' Collaboration, 1994).*[123]

Type of patient	Control groups			Antiplatelet groups			
	Number of trials with data	Number of patients	PE	Number of patients	PE	RR	95% CI
Orthopedic							
Traumatic	11	494	34 (6.9%)	504	14 (2.8%)	0.40	0.22 to 0.71
Elective	16	537	29 (5.4%)	529	14 (2.6%)	0.49	0.26 to 0.92

deep surgical infection, and death within 90 days after injury. **There were 12 (7.3%) VTE events in the aspirin group and 14 (8.5%) VTE events in the LMWH group (P=0.73)**. In terms of the composite endpoint there was no evidence of superiority between LMWH or aspirin.

The METRC RCT which involved **12,211 patients with fractures (12% had fractures other than lower limb) treated operatively, compared LMWH (enoxaparin 30 mg b.d.) with aspirin (81 mg b.d.) for 28 days**.[221] The primary outcome was death from any cause at 90 days. Secondary outcomes were nonfatal PE, DVT, and bleeding complications. **Death occurred in 47 (0.78%) patients in the aspirin group and in 45 (0.73%) patients in the in the LMWH group (P<0.001 for a noninferiority margin of 0.75 percentage points). PE occurred in 90 (1.49%) patients in each group. DVT occurred in 151 (2.47%) out of 6101patients in the aspirin group and 103 (1.68%) out of 6,110 patients in the LMWH group (RR: 0.68, 95% CI: 0.53 to 0.87; P=0.0022) favoring LMWH**. The authors concluded that aspirin was noninferior to LMWH in preventing death and was associated with a low incidence of DVT and PE and low 90-day mortality. In their conclusion, they did not refer to the significant reduction in DVT by LMWH compared with aspirin.

Although most of the patients that were included in these trials were comprised of lower extremity fracture patients, the injuries were not homogeneous and included patients with additional injuries such as head, chest or abdominal injuries.

A meta-analysis of the ADAPT and METRC RCTs shows that compared with aspirin, prophylaxis with **LMWH is associated with a lower rate of VTE** (RR: 0.67, 95% CI: 0.53 to 0.86; P=0.0014) (Figure 7.4).[220, 221] **This is driven by the lower rate of symptomatic DVT in the LMWH group of patients in the METRC RCT**.[221]

It is now established that local damage to the venous valves with the development of reflux as a result of DVT produces skin changes and symptoms of persistent pain and edema in 10-23% of patients leading to chronic venous insufficiency (CEAP C4-C6 clinical classes) and a DVT recurrence rate of up to 14%.[222-224] In addition, a recent meta-analysis has shown that PTS develops in 18% of patients with untreated asymptomatic isolated distal DVTs.[225] The incidence of such **distal asymptomatic DVTs after surgery or trauma in studies where routine venography was performed was approximately eight times higher than symptomatic DVT**.[226] Thus, despite the equivalence between aspirin and LMWH in terms of mortality and PE, based on the current knowledge the risk of PTS is likely to be much higher in patients on aspirin.

LDUH

Several studies performed in the 1970s demonstrated that **LDUH** was effective in reducing asymptomatic DVT, as reported in an overview[124] (RR: 0.51, 95% CI: 0.42 to 0.62). Although a significant reduction in total PE was not demonstrated, there was a significant reduction in fatal PE.

LMWH *vs.* LDUH, DANAPAROID AND FONDAPARINUX

LMWH has been assessed against placebo,[62, 227] LDUH,[228] danaparoid,[229] high dose LMWH (40mg enoxaparin)[203] and fondaparinux.[226] LMWH has been found to be equally effective as LDUH without increase in hemorrhagic complications.[230]

VKAs

Three RCTs demonstrated that **VKAs** were effective in preventing asymptomatic DVT with a 61% RR: reduction for DVT and 66% for proximal DVT, compared with no prophylaxis.[90, 231, 232] The increase in hemorrhagic complications reported varied from 0% to 47% without any increased bleeding in the most recent trial.[90]

FONDAPARINUX

Fondaparinux given for 11 days was more effective when compared with LMWH in reducing VTE from 19.1% to 8.3% (RR: 0.46, 95% CI: 0.32 to 0.59) and proximal DVT from 4.3% to 0.9% (RR: 0.22, 95% CI: 0.09 to 0.53).[226] There was no difference in major bleed-

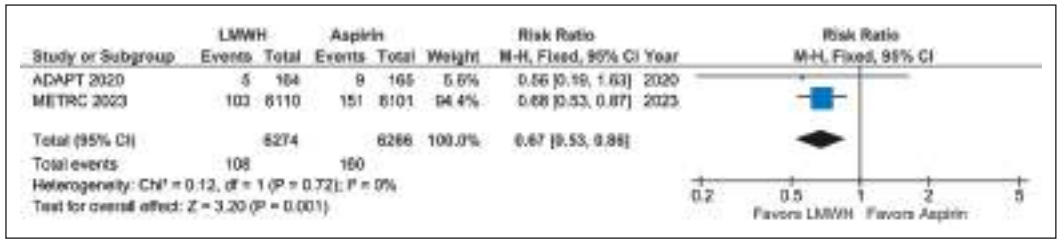

Figure 7.4.—Effect of aspirin versus low molecular weight heparin (LMWH) in the prevention of symptomatic DVT in patients with fractures.[220, 221]

ing, but minor bleeding was increased from 2.1% in the enoxaparin group to 4.1% in the fondaparinux group (P=0.02).

In a second study, patients who received **fondaparinux for seven days were randomized to continuation with fondaparinux or placebo for a further three weeks**.[233] The incidence of **venographic DVT was 1.4% in the extended prophylaxis group and 35% in the placebo group** (RR: 0.04, 95% CI: 0.01 to 0.13). Symptomatic VTE was 0.3% and 2.7% respectively (RR: 0.11, 95% CI: 0.01 to 0.88). There was no difference in hemorrhagic complications.

Delayed admission to hospital or delayed surgery following hip fractures is associated with a high incidence of DVT developing prior to surgery.[234-237] The incidence of pre-operative DVT as shown by venography can be as high as 62% for all DVTs and 14% for proximal DVT when the delay is 48 hours or more.[237] Thus, it is strongly recommended that prophylaxis is commenced as close to the time of fracture as possible. Prophylaxis should be restarted once postoperative hemostasis has been achieved.

Edoxaban

The scientific evidence regarding oral direct anti-Xa inhibitors in the prevention of VTE after hip fracture surgery is scant. A multicenter, open-label, RCT, evaluated the safety and efficacy of **edoxaban** compared with LMWH (enoxaparin) in Japanese patients undergoing hip fracture surgery.[238] In this study, 92 patients were randomized 2:1 to receive edoxaban 30 mg once daily (N.=62) or enoxaparin 20 mg twice daily (N.=30) for 11 to 14 days. In the edoxaban and enoxaparin treatment groups, the incidence of major or CRNM bleeding was 3.4% and 6.9%, respectively. The incidence of VTE was 6.5% in the edoxaban group and 3.7% in the enoxaparin group (P>0.05). All events were asymptomatic DVTs.

Rivaroxaban

An RCT, investigated the efficacy, safety, patient compliance, and cost-effectiveness of LMWH with sequential rivaroxaban anticoagulant therapy in patients with a hip fracture, following internal fixation.[239] A total of 287 patients were randomized into three groups: rivaroxaban alone, enoxaparin alone, and enoxaparin followed by rivaroxaban. The incidence of VTE was 5.21%, 14.74%, and 10.42% in the rivaroxaban, LMWH, and sequential therapy groups, respectively. The VTE related mortality rates were 0%, 1.05%, and 1.04%. The average hospital stay was 12±8, 15±7, and 11±5 d, whereas the compliance rates of the three groups were 82.3%, 71.6%, and 88.5%, respectively. The effects and the incidence of postoperative bleeding in the treatment of LMWH followed by rivaroxaban did not differ significantly from that of rivaroxaban alone.

Systematic review and meta-analysis of DOACs *vs.* LMWH

A recent meta-analysis published in 2022 evaluated the effectiveness of DOACs and LMWH for thromboprophylaxis in trauma patients with surgically treated hip fracture.[240] Meta-analysis was performed to compare the odds of VTE and secondary outcomes between DOACs and LMWH. Five studies matched inclusion criteria. Two of them were the RCTs mentioned above and three were retrospective cohort studies comparing apixaban, dabigatran and rivaroxaban with LMWH. A total of 4,748 hip fracture patients were analysed (DOACs: 2,276 patients, LMWH: 2,472 patients). The pooled risk of VTE for DOAC use compared with LMWH was not significantly different (OR: 0.52, 95% CI: 0.25 to 1.11; P=0.09). **No statistically significant differences between DOAC and LMWH were found for asymptomatic VTE, symptomatic DVT, PE, major or CRNM bleeding, and minor bleeding**. The authors of this meta-analysis concluded that DOACs are associated with equivalent effectiveness and safety compared with LMWH.

Recommendations

LMWH (initiated and dosed according to the manufacturer's recommendations) **(Level of evidence high, recommendation strong), fondaparinux (Level of evidence high, recommendation strong), adjusted dose VKA (INR range 2-3) (Level of evidence high, recommendation moderate) or LDUH (Level of evidence high, recommendation moderate)**.

Rivaroxaban may be considered **(Level of evidence moderate, recommendation moderate)**.

IPC or **FIT combined with GEC stockings** should be used when there are contraindications for pharmacological prophylaxis **(Level of evidence low, recommendation weak)**.

If surgery is likely to be delayed, prophylaxis should be initiated with LMWH or IPC or FIT plus GEC stockings as close to the fracture as possible (Level of evidence low, recommendation strong). Prophylaxis should be provided **for 4-5 weeks after surgery (Level of evidence high, recommendation strong)**.

In view of the relatively small reduction in DVT by aspirin and the increased risk of PTS in patients with asymp-

tomatic DVT[225] **aspirin should not be the first choice for VTE prevention if more effective methods are available (Level of evidence moderate, recommendation moderate)**.

E. Knee arthroscopy

The risk

Knee arthroscopy is a very common procedure which varies from a simple diagnostic technique to an extensive repair of injured soft tissues. The use of a tourniquet, manipulation of the leg and distension of the joint with fluid may all associate this procedure with a risk of VTE. However, symptomatic VTE is very rare. This poses a dilemma: rare events in a common procedure will lead to quite a high number of events even though the proportional risk is very low. However, universal prophylaxis would be very expensive, with uncertain cost benefit and risk benefit ratios.

The frequency of DVT in patients undergoing arthroscopic procedures in the absence of prophylaxis varies greatly between studies; symptomatic DVT occurs in perhaps 0.6%.[27] Meta-analysis of six studies[113, 114, 116-118, 241] by Ilahi in 2005 shows that asymptomatic DVT occurs in approximately 9.9%; however there is a large range: ultrasound demonstrates rates from 6%[241] to 16%[118] and venography from 3.1%[242] to 17.9%.[113]

Prophylactic methods and recommendations

General considerations

LMWH *vs.* GEC

A RCT (KANT) involving 1,317 patients compared LMWH with GEC stockings.[243] The three-month cumulative incidence of asymptomatic proximal DVT, symptomatic VTE, and all-cause mortality was 3.2% (21 of 660 patients) in the GEC group and 0.9% (6 of 657 patients) in the seven-day LMWH group (RR: 0.29, 95% CI: 0.12 to 0.71). The cumulative incidence of major or NMCR bleeding events was 0.3% in the stockings group, 0.9% in the seven-day LMWH group (not significant).

Systematic reviews and meta-analyses of studies using LMWH

In a meta-analysis of four RCTs where different **LMWHs** were given for 5-7 days,[244] the RR: of thrombotic events was 0.16 (95% CI: 0.05-0.52) compared with placebo (0.76% *vs.* 8.2%). All thrombotic events but one PE in the LMWH group, were distal. Adverse effects were more frequent in the intervention group (RR: 2.04, 95% CI: 1.21 to 3.44) (9.5% *vs.* 4.5%). The NNH was 20 for adverse effects.

An updated meta-analysis which included eight studies evaluated the efficacy and safety of interventions – whether mechanical, pharmacological, or a combination of both – for thromboprophylaxis in adult patients undergoing knee arthroscopy.[245] When compared with no prophylaxis, LMWH resulted in little to no difference in the incidence of PE in patients undergoing knee arthroscopy (RR: 1.81, 95% CI: 0.49 to 6.65). LMWH made little or no difference to the incidence of symptomatic DVT (RR: 0.61, 95% CI: 0.18 to 2.03). **LMWH reduced the risk of asymptomatic DVT (RR: 0.14, 95% CI: 0.03 to 0.61)**. LMWH probably made little or no difference to the risk of all adverse effects combined (RR: 1.85, 95% CI: 0.95 to 3.59), major bleeding (RR: 0.98, 95% CI: 0.06 to 15.72), or minor bleeding (RR: 1.79, 95% CI: 0.84 to 3.84). There was one study with 234 participants in which oral rivaroxaban 10 mg was compared with placebo.[245] There were no cases of PE reported. Rivaroxaban was associated with a non-significant reduction in symptomatic DVT (RR: 0.16, 95% CI: 0.02 to 1.29). and asymptomatic DVT (RR: 0.95, 95% CI: 0.06 to 15.01). No major bleeds occurred in either group, and rivaroxaban probably made little or no difference to minor bleeding (RR: 0.63, 95% CI: 0.18 to 2.19). One study compared aspirin with no prophylaxis. There was no PE, DVT or asymptomatic events detected in either group. There were no bleeding events reported. One study with 1317 participants compared LMWH with compression stockings. **LMWH led to little or no difference in the risk of PE compared to compression stockings (RR: 1.00, 95% CI: 0.14 to 7.05), but it reduced the risk of symptomatic DVT (RR: 0.17, 95% CI: 0.04 to 0.75)**. It was uncertain whether LMWH had any effect on asymptomatic DVT (RR: 0.47, 95% CI: 0.21 to 1.09). The results suggested LMWH probably leads to little or no difference in major bleeding (RR: 3.01, 95% CI: 0.61 to 14.88), or minor bleeding (RR: 1.16, 95% CI: 0.64 to 2.08).

Thus, although clinical VTE is uncommon and fatalities are rare, the huge number of patients undergoing knee arthroscopy surgery makes VTE complications potentially relatively frequent. There is a clear correlation between age and degree of trauma with VTE.[76] This justifies prophylaxis in patients with additional risk factors or when extensive surgery beyond a simple diagnostic procedure is performed.

Recommendations

Recommendation for simple diagnostic arthroscopy

A careful risk assessment should be undertaken. Routine prophylaxis is not recommended unless other risk factors are present **(Level of evidence moderate, recommendation moderate)**.

Recommendation for arthroscopic surgery (*e.g.*, ligament reconstructions)

LMWH starting before or after surgery **(Level of evidence moderate, recommendation moderate)** or **IPC** in the presence of contraindications to LMWH are recommended **(Level of evidence low, recommendation weak)** until full ambulation.

F. Isolated below knee injuries and plaster casts

The risk

Patients with below knee injuries and immobilization have a DVT incidence in the range of 10-35% depending on the type and severity of injury (Table 7.I)[51-118] and carry a risk of clinical PE in the range of 0.4-2.1%.[219] An ultrasound study following Achilles tendon injury showed a 29% DVT prevalence and no PE in 49 patients treated surgically, but a 39% DVT prevalence and 3 PE in 46 treated non-operatively.[246] The frequency of symptomatic events is unknown.

Prophylactic methods and recommendations

General considerations

This group is so heterogeneous that studies and recommendations are difficult to devise. A clinical risk assessment is mandatory and for those with risk factors, safe prophylaxis should be instituted. The risk of compartment syndrome, exacerbated by pharmacological thromboprophylaxis, must be considered in tibial fractures.

LMWH

In one RCT of 253 patients with plaster casts of which the majority had soft tissue injuries, ultrasound incidence of DVT at cast removal was reduced from 17% in the control group to 5% in the **LMWH** group.[105]

It was reduced from 4% in the control group to zero in the **LMWH** group in another study of 339 patients.[106] Considering both studies the RR: was 0.21 (95% CI: 0.09 to 0.49)

In patients with lower limb fractures, the five week incidence of venographically-detected DVT was reduced from 18% in the control group to 10% in the **LMWH** group in one study (N.=293),[107] from 13% to 11% in another (N.=150)[99] and from 13% to 9% in a third study (N.=238).[110] In none of the three studies was the effect of LMWH on DVT significant. However, in the subgroups of patients having Achilles tendon repair the incidence of DVT was reduced from 21% to 6% in the first study[107] and from 29% to 10% in the second.[108] However, in a more recent study[109] involving 93 patients LMWH was ineffective (28% *vs.* 21%). More effective methods are needed in well-defined groups of patients.

A multicenter, RCT evaluated the prevalence of VTE in patients with isolated foot and ankle fractures to determine whether routine prophylaxis is necessary in these patients.[247] After randomization, **patients received either thromboprophylaxis with LMWH or placebo for a period of 2 weeks.** All patients underwent **routine ultrasonography 1 day preoperatively, 1 week postoperatively, and 1 month postoperatively**. Of the 814 patients included in the study, 2.3% (95% CI: 0% to 31.9%) were found to have objectively confirmed VTE, but none of the patients were symptomatic. Of the 411 patients in the LMWH group, 2 developed VTEs preoperatively and 4 postoperatively; of the 403 patients in the placebo group, 5 developed VTEs preoperatively and 8 postoperatively. The overall incidence of asymptomatic postoperative DVT was 0.98% (95% CI: 0% to 20.3%) in the LMWH group and 2.01% (95% CI: 0% to 29.5%) in the placebo group without significant difference. No fatal pulmonary emboli or major bleeding complication occurred in either group.

Another multicenter single-blind RCT (PROTECT), evaluated the **efficacy and safety of nadroparin and fondaparinux** to determine the role of chemical thromboprophylaxis in patients immobilized in a below-knee plaster cast.[248] The patients were randomly assigned (1:1:1) **to a control group of no thromboprophylaxis or to one of the intervention groups**: once daily subcutaneous self-injection of either **nadroparin** (2850 IU anti-Xa) **or fondaparinux** (2.5 mg). Of 467 patients enrolled and assigned to either the nadroparin group (N.=154), the fondaparinux group (N.=157), or the control group (N.=156), a total of 273 patients (92, 92, and 94 patients, respectively) were analyzed. **A venous duplex sonography was performed after the removal of the cast or earlier if thrombosis was suspected**. The incidence of asymptomatic DVT in the nadroparin group was 2.2% compared with 11.7% in the control group (RR: 5.4, 95% CI: 1.2 to 23.6; P=0.011). The incidence of DVT in the

fondaparinux group was 1.1% compared with 11.7% in the control group (RR: 10.8, 95% CI: 1.4 to 80.7; P=0.003). No major complications occurred in any group. The authors concluded that thromboprophylaxis with **nadroparin or fondaparinux significantly reduced the risk of DVT** in patients with an ankle or foot fracture who were treated in a below-knee cast without any major adverse events.

A multicenter, open-label RCT (POT-KAST and POT-CAST) evaluated the role of thromboprophylaxis after knee arthroscopy and lower-leg casting.[249] Patients were assigned to receive **either a prophylactic dose of LMWH for the 8 days after arthroscopy in the POT-KAST trial or during the full period of immobilization due to casting in the POT-CAST trial or no anticoagulant therapy**. In the POT-KAST trial, symptomatic VTE occurred in 0.7% in the treatment group and in 0.4% in the control group (RR: 1.6; 95% CI, 0.4 to 6.8; absolute difference in risk, 0.3 percentage points; 95% CI, −0.6 to 1.2). Major bleeding occurred in 0.1% in the treatment group and in 0.1% in the control group (absolute difference in risk, 0 percentage points; 95% CI, −0.6 to 0.7). In the POT-CAST trial, VTE occurred in 1.4% in the treatment group and in 1.8% in the control group (relative risk, 0.8; 95% CI, 0.3 to 1.7; absolute difference in risk, −0.4 percentage points; 95% CI, −1.8 to 1.0). No major bleeding events occurred. The authors concluded that prophylaxis with LMWH for the 8 days after knee arthroscopy or during the full period of immobilization due to casting was **not effective for prevention of symptomatic venous thromboembolism**.

Rivaroxaban *vs.* enoxaparin

The number of RCTs regarding the direct oral anti-Xa inhibitors in the prevention of VTE after isolated below the knee injuries and plaster casts is limited.

A double-blind RCT (PRONOMOS) involving 3,604 patients evaluated the effect **of rivaroxaban compared with enoxaparin** in the **prevention of major VTE** after lower limb non-major orthopedic surgery.[250] Major VTE was a composite of symptomatic distal or proximal DVT, PE, or VTE–related death during the treatment period or asymptomatic proximal DVT at the end of treatment. Systematic compression ultrasonography was performed at the end of immobilization (*i.e.*, between 15 days and 3 months after randomization) in order to detect asymptomatic proximal DVT. **Major VTE occurred in 0.2% in the rivaroxaban group and in 1.1% in the enoxaparin group (RR: 0.25, 95% CI: 0.09 to 0.75; P< 0.001 for noninferiority; P=0.01 for superiority)**. The incidence of bleeding did not differ significantly between the rivaroxaban group and the enoxaparin group (1.1% and 1.0%, respectively, for major bleeding or nonmajor clinically relevant bleeding; 0.6% and 0.7%, respectively, for major bleeding). Thus, **rivaroxaban was found to be more effective than enoxaparin** in the prevention of venous thromboembolic events during a period of immobilization after nonmajor orthopedic surgery of the lower limbs.

Systematic reviews and meta-analyses

A Cochrane review of 8 RCT involving 3,680 patients, published in 2017 and **comparing LMWH with placebo or no prophylaxis** demonstrated **superiority for LMWH**. For all symptomatic and asymptomatic DVT (seven studies, 1676 patients screened with ultrasound) (OR: 0.49, 95% CI: 0.34 to 0.72) was reported, which supports a significant risk reduction for patients immobilized in plaster.[251] Furthermore, symptomatic VTE (six studies, 2517 patients) was also significantly reduced (OR: 0.40, 95% CI: 0.21 to 0.76). No clear differences were found between the LMWH and control groups for PE (OR: 0.50, 95% CI: 0.17 to 1.47). Complications were not increased in the LMWH group.

A subsequent **network meta-analysis of 13 RCTs, published in 2020 investigated the effectiveness of LMWH and fondaparinux to prevent VTE** in patients with temporary lower limb immobilization after injury.[252] The results of this meta-analysis have shown that **compared with no treatment, LMWH reduced the risk of any VTE** (OR: 0.52, 95% CrI: 0.37 to 0.71), **clinically detected DVT** (OR: 0.39, 95% CrI: 0.12 to 0.94) **and PE** (OR: 0.16, 95% CrI 0.01 to 0.74), whereas **fondaparinux reduced the risk of any VTE** (OR: 0.13, 95% CrI: 0.05 to 0.30) **and clinically detected DVT** (OR: 0.10, 95% CrI: 0.01 to 0.86), **with inconclusive results for PE** (OR: 0.40, 95% CrI: 0.01 to 7.53). The authors concluded that thromboprophylaxis with either fondaparinux or LMWH appears to reduce the odds of both asymptomatic and clinically detected VTE in people with temporary lower limb immobilization following an injury.

The most recent **network meta-analysis of 14 studies involving 8198 patients** with lower leg immobilization after trauma, published in 2022, evaluated the clinical efficacy and the safety of different thromboprophylactic treatments.[253] Compared with the control group, **rivaroxaban, fondaparinux, and LMWH were associated with a significant risk reduction of major VTE** (OR: 0.02, 95% CI: 0.00 to 0.19), (0.22, 95% CI: 0.06 to 0.65), and

0.32 (95% CI: 0.15 to 0.56), **respectively**. No increase of the major bleeding risk was observed with either treatment. **Rivaroxaban had the highest likelihood of being ranked top in terms of efficacy and net clinical benefit**. The authors concluded that their study confirms the favorable benefit/risk ratio of thromboprophylaxis for patients with leg immobilization after trauma.

Recommendations

Currently available data based on a mixture of different types of injury suggest that **routine LWMW, fondaparinux or DOAC (rivaroxaban) prophylaxis** should be considered for isolated lower limb trauma in the absence of contraindications, especially in cases of limited patient mobility or limb immobilization **(Level of evidence: moderate, recommendation moderate)**. The drug will need to be administered in the outpatient setting until the patient is weight bearing.

To-date, none of the direct oral anti-Xa inhibitors have been approved for this indication.

G. Multiple trauma

The risk

The incidence of DVT in patients who have sustained major trauma is in excess of 50%[69, 70, 254-257] (Table 7.I)[51-118] and PE is the third leading cause of death in those who survive beyond the first day.[69, 258-260] The risk is particularly high in patients with spinal cord injury, pelvic fracture and those needing surgery.[69, 70, 261-263]

Prophylactic methods and recommendations

General considerations

Patients with multiple injuries have a particularly high risk for VTE. The release of tissue factor by multiple injuries is potentiated by the likely surgical intervention and the subsequent prolonged immobility[261] which produces marked venous stasis. Routine venography has shown a DVT frequency of 58% in these patients.[69]

LMWH *vs.* LDUH

Well-designed studies in this area are few and thromboprophylaxis must be assessed according to the risk of bleeding. However, in the absence of intracranial bleeding and when bleeding is under control, **LMWH** (enoxaparin 30 mg twice daily) started within 36 hours of injury has been shown in a RCT to be **more effective than LDUH (5000 IU twice daily)**.[254] The incidence of venographically-detected DVT was reduced from 44% in the LDUH to 31% in the LMWH group (RR: 0.70, 95% CI: 0.51 to 0.97).

The superiority of LMWH to LDUH has been confirmed by a subsequent study and a meta-analysis.[256, 264]

A study comparing nadroparin fixed daily dose *vs.* a weight-adjusted dose did not demonstrate any significant difference (0% *vs.* 3% DVT).[265]

IPC

Five RCTs have tested the efficacy of **IPC**. The first was in 304 patients with pelvic fractures but the study was small and underpowered so that the asymptomatic DVT reduction from 11% in the control group to 6% in the IPC group was not significant (P>0.05).[155]

In the second study, which involved 149 patients, IPC was compared with FIT with an incidence of asymptomatic DVT of 6% and 21% respectively (P<0.02).[266]

IPC or FIT were compared with enoxaparin 30 mg twice daily in the third study involving 372 patients with an incidence of symptomatic DVT of 0.8% in the enoxaparin group, 2.5% in the IPC group and 5.7% in the FIT.[267]

The two most recent studies compared LMWH with IPC in 442 and 120 trauma patients.[268, 269] In these studies the incidence of DVT was 0.5% and 6.6% in the LMWH group with 2.7% and 3.3% in the IPC group respectively. Thus, mechanical methods are attractive if chemical prophylaxis is contraindicated.

Aspirin *vs.* LMWH

Clinical studies evaluating the efficacy of aspirin for VTE thromboprophylaxis in the general trauma population are limited. An open label RCT (ADAPT) **compared aspirin with LMWH for VTE prevention** in 329 adult patients admitted to an academic trauma centre with an operative extremity fracture, or a pelvic or acetabular fracture.[220] Patients were randomized to receive LMWH (enoxaparin 30-mg) twice daily (N.=164) or aspirin 81-mg twice daily (N.=165). The composite primary outcome included bleeding complications, VTE, deep surgical infections and death occurring within 90 days from injury. VTE events included PE and symptomatic DVT. **Screening of patients for asymptomatic DVT was not performed.** The findings of the Global Rank test suggested no evidence of superiority between LMWH or aspirin for VTE prevention in fracture patients.

A recent pragmatic, multi-center, RCT (PREVENT CLOT) evaluated **whether aspirin would be noninferior to LMWH i**n the prevention of VTE in patients who had a fracture of an extremity (anywhere from hip to midfoot

or shoulder to wrist) that had been treated operatively or who had any pelvic or acetabular fracture.[270] Among a total of 12,211 patients randomly assigned, death occurred in 0.78% of the patients in aspirin group and 0.73% of the patients in the LMWH group (difference, 0.05 percentage points; 96.2% confidence interval, −0.27 to 0.38; P<0.001 for a noninferiority margin of 0.75 percentage points). **Symptomatic DVT occurred in 151 (2.5%) out of 6,101 patients in the aspirin group and 103 (1.7%) out of 6110 patients in the LMWH group (RR: 0.68, 95% CI: 0.53 to 0.87) (P=0.0024) (intention-to-treat population)**. **The incidence of PE was 1.49% in each group**. Bleeding complications, and other serious adverse events were also similar in both groups. The authors concluded that the patients with extremity fractures that had been treated operatively or with any pelvic or acetabular fracture, thromboprophylaxis with aspirin is noninferior to LMWH in preventing death and was associated with low incidences of DVT and PE and low 90-day mortality. However, these results and those of another RCT (CRISTAL)[198] (see section B above) which demonstrated failure of aspirin to prevent symptomatic DVT as effectively as LMWH should induce caution in interpreting the conclusions of this trial.

Systematic review and meta-analysis of thromboprophylaxis in trauma patients

A recent meta-analysis of sixteen studies, published in 2023, investigated the effects of thromboprophylaxis in trauma patients on mortality and the incidence of DVT and PE.[271] The results have shown that prophylaxis reduced the risk of DVT in people with trauma (RR: 0.52, 95% CI: 0.32 to 0.84).

Mechanical prophylaxis also reduced the risk of DVT (RR: 0.43, 95% CI: 0.25 to 0.73) compared with no prophylaxis.

Pharmacological prophylaxis with LMWH or LDUH was more effective than mechanical methods at reducing the risk of DVT (RR: 0.48, 95% CI: 0.25 to 0.95).

LMWH appeared to reduce the risk of DVT compared with LDUH (RR: 0.68, 95% CI: 0.50 to 0.94).

Patients who received both mechanical and pharmacological prophylaxis had a lower risk of DVT (RR: 0.34, 95% CI: 0.19 to 0.60) than either method on its own.

IVC filters

Scientific evidence regarding the use of IVC filters to prevent PE in trauma patients in the absence of DVT is as follows.

A systematic review of seven observational studies revealed an associated 2% to 6% incidence of complications (IVC occlusion, filter migration and thrombosis at the insertion site).[272]

A multicenter RCT involving 240 **severely injured patients with contraindications to anticoagulation** evaluated if the placement of an IVC filter reduces the risk of PE or death in severely injured patients who have a contraindication to prophylactic anticoagulation.[273] Early placement of a vena cava filter **did not result in a significantly lower incidence of symptomatic PE or death than no placement of a filter** (13.9% in the vena cava filter group and 14.4% in the control group (HR 0.99, 95% CI: 0.51 to 1.94; P=0.98).

Systematic reviews and meta-analyses

The meta-analysis of 2013

A meta-analysis of eight controlled studies (only one was RCT) published in 2013 compared the effecacy of standard prophylaxis plus IVC filter *vs.* standard prophylaxis alone on PE, fatal PE, DVT, and/or mortality in trauma patients.[274] The results have shown a **reduction of PE (RR: 0.20, 95% CI: 0.06 to 0.70)** (6 studies involving 1,064 patients) **and fatal PE (RR: 0.09, 95% CI: 0.01 to 0.81**) (4 studies involving 570 patients) **with IVC filter placement**. There was no significant difference in the incidence of DVT (RR: 1.76, 95% CI: 0.50 to 6.19; P=0.38) or mortality (RR: 0.70, 95% CI: 0.40 to 1.23). The number needed to treat to prevent 1 additional PE was estimated to range between 109 and 962, depending on the baseline risk of PE. The authors concluded that the strength of evidence was low but supported the association of IVC filter placement with a lower incidence of PE and fatal PE in trauma patients. Which patients experience benefit enough to outweigh the harms associated with IVC filter placement remains unclear. Additional well-designed observational or prospective cohort studies may be informative.

The meta-analysis of 2023

A meta-analysis of 10 controlled studies (3 RCTs involving 310 patients and 7 observational studies involving 46,830 patients) was published in 2023. **IVC filters demonstrated no significant reduction in PE and fatal PE** (RR: 0.27, 95% CI: 0.06 to 1.28 and RR: 0.32, 95% CI: 0.01 to 7.84, respectively) **by pooling RCTs with low certainty**.[275] However, it demonstrated a significant reduction in the risk of PE and fatal PE (RR: 0.25, 95% CI: 0.12 to 0.55 and RR: 0.09, 95% CI: 0.011 to 0.81, respectively) by pooling observational studies with very low certainty.

IVC filter did not improve mortality in both RCTs and observational studies (RR: 1.44, 95% CI: 0.86 to 2.43 and RR: 0.63, 95% CI: 0.3 to 1.31, respectively). The authors concluded that in trauma patients, **moderate risk reduction of PE and fatal PE was demonstrated among observational data but not RCTs**. The desirable effect is not robust enough to outweigh the undesirable effects associated with IVC filter complications. Current evidence suggests against routinely using prophylactic IVC filters.

Recommendations

LMWH starting as soon as bleeding risk is acceptable **(Level of evidence high, recommendation strong)** or **IPC** in the presence of contraindications to LMWH **(Level of evidence high, recommendation strong)** and continued until full ambulation.

Electrical stimulation of the calf muscles may be considered in patients in whom pharmacological prophylaxis is contraindicated because of multiple injuries and IPC cannot be applied because of external fixation to a leg fracture. This is by extrapolation from studies in general surgery **(Level of evidence low, recommendation weak)**.

The routine use of **IVC filter** for primary prevention of PE when LMWH or IPC are contraindicated and is not recommended **(Level of evidence moderate, recommendation moderate)**.

Aspirin should not be used in place of LMWH to prevent VTE complications in patients with multiple trauma **(Level of evidence moderate, recommendation moderate)**.

H. Elective spine surgery

The risk

Elective spine surgery consists of a mixture of types of surgical procedures ranging from simple laminectomy to complicated multilevel fusion. The procedures can be performed with a posterior, anterior or combined approach. Data are very limited in elective spine surgery, both for efficacy and safety of different prophylactic methods. The incidence of DVT detected by routine venography in the absence of prophylaxis has been found to be 18%[112, 276] (Table 7.I).[51-118] A review of studies on complications in patients having spinal fusion reported a 3.7% incidence for symptomatic DVT and 2.2% for PE.[277]

The major risk of pharmacological prophylaxis after spine surgery is epidural hematoma and potential neurologic damage. Regarding this, a systematic review evaluated the effect of pharmacological thromboprophylaxis on the risk of epidural hematoma.[278] Of 16 studies, 6 included pharmacological prophylaxis consisting of LMWH or UFH, while 10 studies did not implement any kind of pharmacological prophylaxis. There was no difference in the observed incidence of epidural hematoma between these 2 groups. The range of reported incidence of epidural hematoma was 0% to 0.7% in studies where patients received pharmacological anticoagulation and 0% to 1% in all of the included studies.

A retrospective cohort study evaluated the impact of early (<48 hr) versus late (≥48 hr) initiation of pharmacological VTE prophylaxis on outcomes and complications among trauma patients undergoing operative fixation of spine fractures.[279] Of 206 patients included in this study, 48 (23.3%) received early prophylaxis and 158 (76.7%) received late prophylaxis. No patient developed an epidural hematoma or postoperative bleeding necessitating intervention in either group. Thirteen patients (6.2%) developed VTE, of which 12 occurred in the late VTE prophylaxis group. Age (≥45 years) and traumatic brain injury were associated with an increased risk of VTE events. The authors concluded that initiation of VTE prophylaxis within 48 hours of operative fixation was not associated with increased risk of bleeding or neurologic complications.

A systematic review and meta-analysis of 4 studies assessed the impact of continuing aspirin administration on the bleeding and cardiovascular events during the perispinal surgery period.[280] The continuation of aspirin did not increase the risk of blood loss during the spinal surgery (95% CI: -111.7 to -0.59; P=0.05). There was also no increase in the operative time (95% CI: -33.29 to -3.89; P=0.01) and postoperative blood transfusion (95% CI: 0.00 to 0.27; P=0.05). There were not enough samples to make an accurate decision about the cardiovascular risks without aspirin continuation and mean hospital length of stay with aspirin continuation. The authors concluded that the patients undergoing spinal surgery with continued aspirin therapy do not have an increased risk for bleeding or increase in the operation time and postoperative blood transfusion.

However, due to the risk of postoperative epidural hematoma in patients undergoing spinal surgery, additional large studies evaluating the safety of antiplatelet agents as pharmacological prophylaxis are necessary.

Prophylactic methods and recommendations

General considerations

The number of RCTs investigating the efficacy or harm of different methods of VTE prophylaxis is limited. How-

ever, useful information may be obtained from some observational studies presented below.

GEC *vs.* GEC with IPC *vs.* GEC with VKA

A RCT determined the incidence of DVT after major adult spinal surgery.[281] In this study, 110 patients were randomized to three groups: a) GEC; b) IPC with GEC and c) warfarin with GEC. They were compared with a fourth group of 219 nonrandomized patients having GEC with IPC. All patients were scanned with ultrasound between the fifth and seventh postoperative day. None of the randomized group had symptoms of DVT, and no DVT was found on screening. One of the nonrandomized patients had DVT (overall incidence of 0.3%). Two patients in the warfarin group had major blood loss of more than 800 ml. The authors concluded that mechanical prophylaxis with GEC and IPC is preferable to anticoagulation therapy.

LDUH

Three retrospective studies evaluated the efficacy and safety of LDUH.

The first one was a retrospective cohort study which evaluated the impact of preoperative DVT prophylaxis administration on the rate of postoperative DVT, PE, and spinal epidural hematoma after elective spinal surgery.[282] Of 3870 patients included in the study, a total of 1428 patients received prophylaxis in the form of 5000 U heparin twice daily. Nineteen patients developed symptomatic DVT and/or PE. Nine of these had received preoperative prophylaxis. Sixteen patients developed a spinal epidural hematoma, and 7 of these received preoperative chemoprophylaxis. There was no significant difference in the incidence of VTE and epidural hematoma rates between treatment groups.

The second retrospective study evaluated a departmental protocol implemented for early VTE prophylaxis consisting **of combined IPC with LDUH initiated either preoperatively or on the same day of surgery**.[283] The authors compared the incidence of VTE in spine surgery patients before and after implementing this protocol. Before the protocol, VTE prophylaxis was variable and provider dependent without any uniformity. The new protocol consisted of LDUH 5000 administered three times daily, except in patients older than 75 years or weighing less than 50 kg, who received this dose twice daily. **All patients also received IPC (SCD)**. Of the 941 patients in the before the protocol group, 25 developed DVT (2.7%), six developed PE (0.6%), and six developed postoperative epidural hematoma (0.6%). Of 992 patients in the after the protocol initiation group, 10 had DVT (1.0%), 5 had PE (0.5%), and 4 had postoperative epidural hematoma (0.4%). The reduction in DVT after the protocol's implementation was statistically significant (P=0.009). Despite early aggressive prophylaxis, the incidence of postoperative epidural hematoma did not increase and compared favorably to the published literature.

The third retrospective cohort study evaluated the incidence and risk factors for VTE and the association of pharmacologic prophylaxis with VTE and bleeding complications after elective spine surgery.[284] In this study a national cohort (National Surgical Quality Improvement Program Database) comprised of 109,609 patients and an institutional cohort comprised of 2855 patients at the authors' institution were analyzed. The main method of pharmacological thromboprophylaxis was LDUH (>90%), but LMWH and warfarin were also used. Pharmacologic prophylaxis did not significantly influence the rate of VTE but was associated with a significant increase in hematoma requiring reoperation (RR: 7.37; P=0.048). The authors concluded that pharmacologic prophylaxis, primarily with LDUH, after elective spine surgery was not associated with a significant reduction in VTE. However, there was a significant increase in postoperative hematoma requiring reoperation among patients undergoing prophylaxis.

LMWH

Two retrospective studies investigated the safety and efficacy of prophylactic LMWH.

The first retrospective study investigated the safety and efficacy of prophylactic LMWH started 24 to 36 hours after degenerative spine surgery.[285] Of 367 patients included in the study, mechanical prophylaxis was used throughout hospitalization, and prophylactic LMWH was started on the first postoperative day. No patients receiving LMWH 24 to 36 hours after surgery developed postoperative hemorrhage (95% CI: 0 to 0.8%). Nearly half of the study population underwent lower extremity ultrasonography or chest computed tomography, and acute VTE was diagnosed in 14 patients. The authors concluded that LMWH prophylaxis seems to carry a very low hemorrhagic risk when started 24 to 36 hours after spine surgery. Larger, prospective studies are needed to assess the safety of early delayed LMWH administration more definitively.[286]

The second retrospective study evaluated the efficacy and safety of LMWH in the prevention of thromboembolic complications after spine surgery.[287] In this study, 947 patients who received a therapeutic dose of LMWH daily after surgery (therapeutic group) were compared with 814

patients not given any heparin treatment (control group). The therapeutic group showed a lower rate of symptomatic thromboembolic complications after surgery compared with the control group (0.21% *vs.* 1.6%; P=0.002). The overall rate of bleeding complications was higher in the therapeutic group compared with the control group, but this difference was not significant (1.8% *vs.* 0.74%; P=0.051). The authors concluded that the use of LMWH significantly decreases the incidence of thrombosis and thromboembolic complications after spine surgery, but increases the incision bleeding, leading to an elevated risk of symptomatic spinal epidural hematoma.

Argatroban *vs.* LMWH

A retrospective study evaluated the safety and efficacy of the direct thrombin inhibitor **argatroban** for the prevention of VTE in 556 patients who underwent posterior lumbar decompressive surgery for trauma and degenerative diseases.[288] The patients were divided into two groups: the argatroban group (N.=274), and LMWH group (N.=282). The frequency of postoperative VTE and complications including hemorrhage and allergic reaction was compared between the two groups. Postoperative VTE was reported in seven patients. No PE occurred in any patient. Thrombosis was reported in three cases (1.0%) and bleeding in 1 case (0.04%) in argatroban group *vs.* 4 (1.4%) and 4 (1.4%) in LMWH group, showing no significant difference between the two groups (P>0.05). The authors concluded that argatroban can be equally effective as LWMH for anticoagulation therapy. Both drugs exhibited a similar preventive effect against postoperative VTE after posterior lumbar spine surgery, without increasing the risk of postoperative bleeding.

Rivaroxaban and Apixaban

A retrospective study compared the efficacy and safety of apixaban and rivaroxaban after lumbar spine surgery.[287] A total of 480 patients were included, with 240 patients allocated to the apixaban group (2.5 mg orally twice daily for 14 days) and 240 patients in the rivaroxaban group (10 mg once daily for 14 days). All patients were also provided with graduated compression stockings for six weeks and intermittent pneumatic compression devices while in-hospital. Bilateral lower limb ultrasonography was performed between postoperative days three and seven. The primary outcomes were VTE events and bleeding complications. There were 12 VTE events (5%) in the apixaban group, consisting of 4 PEs (2 fatal, 2 nonfatal) and 8 DVTs (2 symptomatic and 6 identified by ultrasonography). There were 9 VTE events (3.75%) in the rivaroxaban group consisting of 3 PE (1 fatal, 2 nonfatal) and 6 DVTs (1 symptomatic and 5 identified by ultrasonography). There was no significant difference in the incidence of VTE between the groups (P>0.05). Compared with rivaroxaban there was significantly less bleeding in the apixaban group (P=0.03).

Rivaroxaban *vs.* LMWH

A prospective RCT involving 665 patients, evaluated the efficacy and safety of rivaroxaban 10 mg once daily compared with LMWH (parnaparin 40 mg once daily) for preventing VTE in patients having lumbar spine surgery.[289] Both prophylactic methods started 6-8 hours after the operation and continued for 14 days. The primary endpoint was symptomatic DVT and asymptomatic DVT using ultrasound screening on the 2nd, 7th and 14th postoperative days. **There were 6 thrombotic events (1.7%), in the rivaroxaban group. There were 10 thrombotic events (3.1%), in the LMWH group**. The bleeding event rates, including severe and non-severe bleeding, were not significantly different in both groups. **The authors concluded that rivaroxaban is equally effective as LMWH for prevention of postoperative VTE after lumbar spine surgery, without increasing the risk of bleeding complications**.

IVC filters

A retrospective study evaluated the safety and efficacy for prophylactic IVC filter placement in patients at high risk for VTE following major spinal reconstruction.[290] In this study, 74 spine surgery patients with a contraindication to anticoagulation received prophylactic IVC filters. Patients were considered high risk for VTE events if they demonstrated a history of VTE, malignancy, thrombophilia, staged procedures, and anesthesia duration over 8 hours. The outcome measures were IVC filter complications, DVT and PE. There were 27 DVTs (31%), of which 18 (24.3%) were proximal and one PE (1.3%) during weekly ultrasonography of the lower limbs. There was only one complication related to failed IVC filter deployment. The authors concluded that despite a high incidence of DVT following high-risk spinal surgery, prophylactic IVC filter placement appears to protect patients from PE.

Another retrospective study evaluated the role of preoperative prophylactic IVC filter placement in 219 patients considered at high risk for major spinal reconstructive surgery.[291] In this study, the incidence of DVT was 18.7%

(41/219) and PE was 3.7% (82/219), and paradoxical embolus rate was 0.5% (1/219). Prophylactic IVC filter reduced the odds ratio of PE development (OR: 3.7, P<0.05) compared with population controls. The authors concluded that prophylactic IVC filter placement significantly lowers VTE events and can be considered for high-risk patients having spinal surgery.

Systematic review and meta-analysis

A systematic review of 28 studies evaluated the frequency of DVT and PE in spinal surgery patients receiving no thromboprophylaxis, mechanical thromboprophylaxis, and chemoprophylaxis.[292] The mean incidence of DVT and PE was higher in the mechanical thromboprophylaxis group (DVT: 1%, PE: 0.81%) compared with the chemoprophylaxis group (DVT: 0.85%, PE: 0.58%), but this was not statistically significant. Six percent of PE were fatal; the rate of epidural hematomas was 0.3%. The incidence of DVT was higher in prospective studies (1.4%) compared with retrospective studies (0.61%). **The authors concluded that the overall incidence of DVT and PE was relatively low regardless of prophylaxis type chosen**; however, it was difficult to draw meaningful conclusions due to the heterogenous nature of the studies included. However, PE in these patients has been associated with a relatively high rate of mortality, which suggests a role for chemoprophylaxis in select patients who have undergone spine surgery.

Recommendations

Mechanical method: IPC (Level of evidence: moderate, recommendation moderate) by extrapolation from studies in other orthopedic operations.

LMWH (Level of evidence moderate, recommendation moderate) by extrapolation from studies in other orthopedic operations.

Rivaroxaban started after the operation can also be considered **(Level of evidence moderate, recommendation moderate)** when it becomes registered for this indication.

Initiation: before operation for IPC or 24 hours after operation for LMWH; duration: during hospitalization **(Level of evidence moderate, recommendation moderate)**.

The routine use of **IVC filter** placement for prevention of PE when LMWH or IPC are contraindicated and is not recommended **(Level of evidence moderate, recommendation moderate)**. The IVC filter placement may be considered in high-risk patients for spinal surgery when LMWH or IPC are contraindicated **(Level of evidence low, recommendation weak)**.

I. Spinal cord injury

The risk

In the absence of prophylaxis, the incidence of asymptomatic DVT is in the order of 35% (Table 7.I).[51-118] In this group of patients, PE is the third leading cause of death.[293, 294] In a series of 1,649 patients undergoing rehabilitation, symptomatic DVT occurred in 10% and PE in 3%.[295]

Prophylactic methods and recommendations

General considerations

LDUH *vs.* placebo

Three studies have compared **LDUH** with placebo.[99, 100, 296] Compared with controls, LDUH was associated with a non-statistically significant reduction in DVT (20.0% *vs.* 29.4%; OR: 0.55, 95% CI: 0.11 to 2.64; P=0.46).[297]

LDUH fixed doses *vs.* adjusted doses

A small RCT involving 75 patients evaluated the efficacy and safety of LDUH in either fixed doses of 5000 IU twice daily or in doses adjusted to prolong the APTT to approximately 1.5 times the control.[298] Patients were monitored with daily clinical examinations, serial impedance plethysmography, and Doppler flow studies. The primary outcome was symptomatic or asymptomatic VTE events which were confirmed by venography, ventilation\perfusion scans, or pulmonary angiography. VTE occurred in 31% of the patients in the fixed-dose regimen and 7% of the patients in the adjusted-dose regimen (P=0.02). None of the patients who received the adjusted dose and whose APTT reached the target level had DVT, but bleeding occurred in seven patients. No patient on the fixed-dose regimen bled. The authors concluded that patients with spinal cord injury who can be maintained on doses of heparin sufficient to prolong their APTT to 1.5 times the control values can be prevented from VTE complications, but they are at high risk of bleeding, especially if they have trauma to other tissues in addition to their spinal cord injury.

LMWH *vs.* LDUH

Four studies have compared LDUH with **LMWH**.[299-302] A meta-analysis comparing LDUH with LMWH published in 2008 reported that although LMWH was associated with a non-statistically significant reduction in the rate of all VTE (24.4% *vs.* 22.7%; OR: 0.78, 95% CI: 0.24 to 2.53; P=0.60), it was associated with a significant reduc-

tion in the rate of total PE (3.1% *vs.* 9.2%; OR: 0.29, 95% CI: 0.09 to 0.95; P=0.04).[297] Also, compared with LDUH, LMWH was associated with a nearly significant reduction in major bleeding (2.4% *vs.* 5.2%; OR: 0.50, 95% CI: 0.24 to 1.04 P=0.07).

LDUH plus Electrical calf muscle stimulation (ECMS) *vs.* LDUH

A RCT evaluated the efficacy of LDUH, alone or in combination with electrical calf muscle stimulation, in the prevention of DVT in 48 patients with spinal cord injury.[100] Patients were assigned to saline placebo (N.=17), LDUH (5,000 IU three times a day) (N.=16), and LDUH plus electrical calf muscle stimulation (23 hours per day) (N.=15) for 28 days. Surveillance for DVT was evaluated by daily ^{125}I fibrinogen scanning. Venography was performed to confirm a positive test for two consecutive days and at the completion of the study. The incidence of DVT was 8 of 17 (47%) in the placebo group, 8 of 16 (50%) in the LDUH group, and 1 of 15 (6.6%) in the electrical stimulation plus low-dose heparin group. The use of electrical stimulation plus low-dose heparin significantly decreased the incidence of DVT compared with the other treatments (P=0.02).

LMWH plus GEC *vs.* GEC

A RCT evaluated the incidence of DVT in acute spinal cord injury patients having LMWH plus GEC or GEC alone. Occurrence of DVT was monitored through daily clinical assessment and ultrasonography at 2 weeks.[303] Of 74 patients included, 37 patients (group I) received no prophylaxis except for GEC and 37 patients (group II) received LMWH and GEC. DVT occurred in 21.6%of the patients in group I and 5.4% in group II. The difference was significant (P=0.041). There was no significant difference in the incidence of DVT-related complications including PE in any of the subjects.

Enoxaparin *vs.* Dalteparin

A multicenter RCT involving 95 patients with spinal cord injury, compared the safety and efficacy of dalteparin with enoxaparin.[304] Patients were randomized to receive LMWH (enoxaparin 30 mg twice a day) or LMWH (dalteparin 5000 IU once daily). Prophylaxis was continued for 3 months for motor-complete and 2 months for motor-incomplete patients. DVT occurred in 6% of the patients in the enoxaparin group and in 4% in the dalteparin group (P=0.51). Four percent developed bleeding while receiving dalteparin and 2% while receiving enoxaparin (P=0.72). No differences were noted in compliance, health status, or most of the satisfaction measures. The authors concluded that similar compliance, health status, DVT and bleeding rates were found between dalteparin and enoxaparin.

LDUH plus IPC *vs.* LMWH

A RCT involving 107 patients compared LDUH plus IPC with LMWH (enoxaparin) as thromboprophylaxis after spinal cord injury.[305] The incidence of VTE was 63.3% with LDUH-IPC *vs.* 65.5% with enoxaparin (P=0.81). The incidence of PE was 18.4% with LDUH-IPC *vs.* 5.2% with enoxaparin (P=0.03). Among all randomized patients, the incidence of major bleeding was 5.3% with LDUH-IPC *vs.* 2.6% with enoxaparin (P=0.14). The authors concluded that safety and efficacy of LDUH-IPC and enoxaparin were generally similar.

The meta-analysis of 2013

A systematic review and meta-analysis of 18 studies involving 2,578 patients published in 2013 attempted to estimate the effect of heparin for thromboprophylaxis in patients with acute spinal cord injury.[306] The incidence of VTE and major bleeding complication were recorded as the endpoints. Of the 18 selected studies, 7 studies were RCTs, one was quasi-RCT and the remaining 10 used observational study method (cohorts, case-control and cross-sectional studies).

Four studies evaluated the effects of LDUH compared with placebo or untreated patients. No significant differences were observed for VTE (RR: 0.66, 95% CI: 0.36 to 1.12).

Only one RCT compared fixed-dose LDUH with adjusted-dose LDUH, which showed lower VTE incidence but higher bleeding incidence for adjusted dose.

Nine trials compared LDUH with LMWH. No significant differences were observed for VTE (RR: 1.63, 95% CI: 0.82 to 3.24). **However, major bleeding was lower with LMWH (RR: 2.03, 95% CI: 1.02 to 4.06)**.

Three studies compared different LMWHs, which included one for enoxaparin *vs.* tinzaparin and two for enoxaparin *vs.* dalteparin. No significant differences were observed for VTE (RR: 0.69, 95% CI: 0.34 to 1.43).

Three studies compared different doses of LMWH. No differences were observed. The authors concluded that in patients with acute SCI, LDUH has no thromboprophylactic effect compared with placebo or untreated patients; LMWH seems to reduce bleeding incidence, but not risk of thromboembolism compared with LDUH. Because good quality studies do not exist in this setting, well-designed RCTs are urgently needed.

The meta-analysis of 2017

A systematic review and meta-analysis of 9 studies (8 RCTs and one prospective, non-randomized comparative study) evaluated the efficacy, safety, and timing of anticoagulant thromboprophylaxis for the prevention of VTE in patients with acute spinal cord injury.[307] There was a trend toward a lower risk of DVT in patients treated with LMWH (enoxaparin). There were no significant differences in rates of DVT, PE, bleeding, and mortality between patients treated with different types of LMWH or between LMWH and UFH. Combined anticoagulant and mechanical prophylaxis initiated within 72 hours of spinal cord injury resulted in lower risk of DVT than treatment commenced after 72 hours of injury. The authors concluded that thromboprophylaxis can be used to lower the risk of VTE events in patients with acute spinal cord injury, without significant increase in risk of bleeding and mortality and should be initiated within 72 hours.

IVC FILTERS

A retrospective observational study evaluated whether the prophylactic placement of an IVC filter after acute spinal cord injury causes an increased incidence of DVT.[308] Of 112 patients, 54 (47%) had prophylactic IVC filters placed. Of those with filters, 11 (20.4%) experienced a DVT during their rehabilitation stay. Of the 58 without filters, only three (5.2%) experienced a DVT during rehabilitation (P=0.021). Only one individual experienced pulmonary embolism during rehabilitation hospitalization, and that was in a person with a prophylactic IVC filter. The authors concluded that the presence of prophylactic IVC filters in acute SCI: patients may increase the risk of DVT.

Recommendations

LMWH **(Level of evidence: moderate, recommendation moderate)** and LMWH plus IPC **(Level of evidence low, recommendation weak)**.

In the presence of contraindications to pharmacological prophylaxis IPC and GEC on admission and LMWH when bleeding risk is acceptable **(Level of evidence low, recommendation strong)**.

Duration: LMWH and IPC for 3 months and continuation with GEC indefinitely **(Level of evidence low, recommendation weak)**.

The routine use of **IVC filter** placement for prevention of PE is not recommended **(Level of evidence moderate, recommendation moderate)**. IVC filter placement may be considered in high-risk patients for spinal surgery when LMWH or IPC are contraindicated **(Level of evidence low, recommendation weak)**.

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SECTION 8

Prevention in patients with burns

The risk

There is a spectrum from mild to severe risk of VTE in patients with burns. All ages are represented although the risk is higher after the age of 50 and in females.[1] Some patients have additional injuries to other organs or co-morbid diseases requiring a multidisciplinary approach and intensive care.

The incidence of DVT using routine screening with duplex scanning in the absence of prophylaxis varies between 6% and 27% (Table 8.I).[2-6] Symptomatic VTE occurs in 0.2% to 7.0% of patients.[2, 7, 8]

A review of large observational studies in 2016 reported that the incidence of symptomatic DVT ranged from 0.25% to 2.4% in patients with burns who were on some form of prophylaxis; it ranged from 0.9% to 5.92% in the absence of prophylaxis.[5]

An analysis of 33,637 thermally injured patients between 1995 and 2007 indicated that the overall rate of symptomatic DVT was 0.48%, PE was 0.18%, and VTE was 0.61%.[9] Among those with total body surface area (TBSA) burnt by more than 10%, the incidence of DVT was 0.92%, PE was 0.38%, and VTE was 1.22%. After controlling for age, gender, presence of inhalation injury, central venous catheter insertion, and ventilator days, three factors – TBSA burned, ICU days, and number of operations – were independently associated with increased VTE risk.

Risk stratification using the Caprini Risk Score (CRS) in a prospective study of 1,939 patients with burns found that the incidence of symptomatic VTE was 0.18% for CRS of 0-2, 0.69% for CRS of 3-4, 0.78% for CRS of 5-6, 3.66% for CRS of 7-8 and 8.82% for CRS >8.[10] In this study, prophylaxis was not administrated to those with a CRS of 0-2. Prophylactic LMWH was administered in those with CRS of 3 or more starting on the day of admission and continued until ambulation. Among the 792 patients who received LMWH one patient (0.13%) developed HIT and 2 patients (0.25%) developed major bleeding. In addition to the CRS, age, abbreviated burn severity index score, overall and full thickness TBSA, central venous catheters, day of ambulation and hospital stay were significantly higher in patients with VTE than in those without VTE (P<0.05).

TABLE 8.I.—*The frequency of all DVT in trauma, surgery, and medical patients in the absence of prophylaxis (diagnosed by surveillance with objective methods: phlebography, FUT or DUS). The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.*

Patient groups	Number of studies	Patients N.	DVT incidence (weighted mean)	95% CI
Burns				
Wait *et al.* 1990[2]	71	14		
Wahl *et al.* 2002[3]	30	7		
Wibbenmeyer *et al.* 2003[4]	148	9		
Ajuja *et al.* 2016[5]	100	4		
Total	4	349	34 (9.7%)	7.6% to 13%

Prophylactic methods

LMWH

An RCT involving 100 patients with a 30-60% TBSA burnt compared LMWH (enoxaparin 0.5 mg/kg twice daily with a maximum dose of 60 mg/day) throughout the hospital stay in 50 patients, with no prophylaxis in the control group. Duplex scanning identified DVT in four (8%) out of 50 patients in the control group and none in the LMWH group (P=0.021). Only one patient in the enoxaparin group developed mild epistaxis which resolved

spontaneously. Patients with DVT had significantly higher TBSA burns, prolonged immobility and longer duration of hospital stay compared with patients without DVT in the control group.[11]

In a prospective study of 30 patients with severe burns (TBSA 43% ± SD 17%) receiving LMWH, peak anti-factor Xa (anti-Xa) activity on days 5, 10 and 14 was decreased and associated with increased nucleosome levels due to DNA release.[12] In this study 23 (77%) of the 30 patients were affected by heparin resistance defined as anti-Xa activity <0.2 IU/mL. The authors suggested that monitoring anti-Xa activity with appropriate therapy escalation should be used in patients with severe burns.

The development of VTE despite pharmacological prophylaxis with LMWH has stimulated the decision to use a combination of IPC and LMWH and investigate the anti-Xa activity whose goal for effective prophylaxis should be 0.2-0.4, four hours after the third dose of enoxaparin.[13] In several studies the anti-Xa level was subtherapeutic in 42-76% of patients.[12, 14-16] As a result of these findings an adjusted LMWH dose is recommended by some teams.[13]

A survey of VTE prophylaxis practice addressing the incidence of VTE in 3,799 adult patients with burns and its association with outcomes in burn units in Australia and New Zealand was published in 2021. Use of VTE prophylaxis ranged from 48.6% to 94.8% of patients. In-hospital death was recorded in 33 (0.87%) patients. After adjusting for confounders, receipt of VTE prophylaxis was associated with a decrease in the adjusted odds ratio of in-hospital mortality (OR: 0.21, 95% CI: 0.07 to 0.63; P=0.006).[17]

RCTs are needed to establish the true efficacy of DOACs in patients with burns.

Recommendations

These recommendations are based on the evidence presented above and on extrapolation from studies on trauma patients (see Section 7).

LMWH (Level of evidence moderate, recommendation strong) initiated as soon as it is considered safe to do so and continued for as long as the patient remains at risk **(Level of evidence low, recommendation strong)**.

Adjusted dose of LMWH according to weight (*e.g.*, enoxaparin 30 mg twice daily for patients <90 kg or 40 mg twice daily for patients >90 Kg) may be considered **(Level of evidence low, recommendation moderate)** or according to anti-Xa activity for patients in the ICU **(Level of evidence low, recommendation strong)**.

For moderate to high-risk patients, combined LMWH with IPC should be used **(Level of evidence moderate, recommendation strong)**.

For patients at high risk of bleeding, mechanical thromboprophylaxis with GEC and IPC is recommended **(Level of evidence low, recommendation strong)** if the burns do not involve the lower limbs.

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SECTION 9

Prevention in neurosurgical patients

The risk

In patients undergoing neurosurgical procedures, in the absence of prophylaxis, the incidence of asymptomatic DVT in the 1970s and 1980s detected by the fibrinogen uptake test (FUT), venography or ultrasound was approximately 23%, with proximal thrombosis found in 5%[1-9] (Table 9.I).[1, 3-5, 8, 9] The incidence of asymptomatic DVT after neurosurgery was high (13.5%), even when GEC was used.[10] The VTE risk was particularly high (21-32%) in patients with glioma,[11-16] and persisted for a year or more.[11] In more recent studies the incidence of asymptomatic DVT has ranged from 10% to 26%.[17-20]

Brain parenchyma is rich in thromboplastin which together with tissue factor are released in the circulation because of injury. Thromboplastin combines with factor VII activating the extrinsic coagulation pathway.[21, 22] Patients with brain tumors or metastases are particularly prone to activation of the coagulation pathway.[23, 24] Additional risk factors are the duration of the neurosurgical operation which often exceeds three hours[25, 26] and venous stasis due to the dependency of the lower limbs during surgery.[27]

A publication in 2015, based on a series of 4844 patients who underwent craniotomy, indicated that the incidence of postoperative symptomatic VTE was 3.5% (PE: 1.4%, DVT 2.6%).[28] The authors indicated that 61% of the patients with PE did not have an associated diagnosis of DVT, confirming similar findings from other studies and suggesting that the majority of PE arise from asymptomatic DVT. Multivariable logistic regression analysis identified several independent predictors which could be used in a model to predict the risk of VTE. These were craniotomy for managing malignancy, transfer from acute care hospital, age ≥60, dependent functional status, tumor involving CNS, sepsis, emergency surgery, operating time ≥ 4 hours, postoperative urinary tract infection, postoperative pneumonia, on ventilation for ≥48 hours and return to the operating room for exploration. The risk of VTE increased with increasing numbers of risk factors.[28] It was 0.5% for score 0, 1.2% for score 1, 2.1% for score 2, 4.1% for score 3, 7.6% for score 4 and 14.7% for score 5 or greater.

This scoring system applicable to patients having craniotomy needs to be validated by prospective studies.

Prophylactic methods

IPC *vs.* no prophylaxis

In the early 1970s two RCTs investigated the efficacy of IPC on the reduction of postoperative DVT in patients

TABLE 9.I.—*The frequency of all DVT in neurosurgery in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS). The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.*

Patient groups	Number of studies	Patients N.	DVT incidence (weighted mean)	95% CI
Neurosurgery				
Skillman *et al.* 1978[1]		48	11	
Cerrato *et al.* 1978[9]		50	16	
Turpie *et al.* 1977[3]		63	12	
Turpie *et al.* 1985[5]		68	12	
Turpie *et al.* 1989[4]		81	16	
Zelikovski *et al.* 1981[8]		20	10	
Total	6	330	77 (23%)	19% to 28%

having neurosurgery. The first study involved 161 patients undergoing craniotomy. **IPC reduced the incidence of asymptomatic DVT from 23.5% in the control group receiving no prophylaxis to 1.5% in the test group (RR: 0.07, 95% CI: 0.009 to 0.49)**.[3] The second study involved 95 patients having either craniotomy or spinal surgery. In this study the incidence of **asymptomatic DVT was reduced from 25% to 8.3% (RR: 0.33, 95% CI: 0.11 to 0.94)**.[1]

A systematic review and meta-analysis (direct meta-analysis and network meta-analysis) demonstrated that by 2019 there had been nine RCTs involving 1024 patients comparing prophylaxis using IPC with no prophylaxis. In six of these trials, patients had craniotomy while in the remaining three trials, patients had craniotomy or spinal surgery.[29] Direct meta-analysis of these nine studies demonstrated that **IPC produced a significant decrease in the incidence of postoperative DVT (RR: 0.43, 95% CI: 0.30 to 0.62)**.

GEC *vs.* GEC plus IPC

In a RCT involving 239 patients having craniotomy or spinal surgery, **IPC combined with GEC** reduced the incidence of asymptomatic DVT from 20% in the **GEC group** to 9% in the combined group (RR: 0.45, 95% CI: 0.20 to 1.04).[4] In a subsequent RCT[30] involving 150 patients, the efficacy of calf compression using **IPC combined with GEC** reduced the incidence of asymptomatic DVT from 18.7% in the GEC group to 4% in the combined group (RR: 0.21, 95% CI: 0.05 to 0.75).

LDUH or LMWH *vs.* no prophylaxis

A RCT involving 100 patients performed in the late 1970s compared **LDUH** with no prophylaxis.[9] The incidence of DVT was reduced from 34% in the control group to 6% in the heparin group (RR: 0.18, 95% CI: 0.05 to 0.56). There was no increase in hemorrhagic complications. A second similar RCT failed to show efficacy but confirmed the safety shown by the first study.[31] A meta-analysis performed in 2000 included four RCTs involving a total of 827 patients. **LMWH** was used in three of these studies and **LDUH** in one. There was a reduction in the incidence of all DVT from 29.0% in the no prophylaxis group to 15.6% in the heparin group (RR: 0.54, 95% CI: 0.41 to 0.70) and a reduction in proximal DVT (2 studies; 616 patients) from 12.5% to 6.25% (RR: 0.50, 95% CI: 0.30 to 0.84).[32] The incidence of major hemorrhage increased from 2.5% to 3.1% (RR: 1.23, 95% CI: 0.60 to 2.53). Overall bleeding significantly increased from 2.9% to 5.9% (RR: 2.0, 95% CI: 1.09 to 3.67). Thus, the number needed to treat for VTE was 7.7 and the number needed to harm was 102.

Systematic reviews and meta-analyses of heparin (LDUH or LMWH)

A meta-analysis performed in 2011 reported results of six RCT involving 1170 patients undergoing elective craniotomy.[33] The pooled RR was 0.58 (95% CI: 0.45 to 0.75). Intracranial hemorrhage was more common in those receiving heparin, but this was not statistically significant. For every 1000 patients who received heparin prophylaxis, 91 VTE events were prevented of which, approximately 35 were proximal DVT or PE and 9-18 were symptomatic, whereas seven intracranial hemorrhages and 28 more minor bleeds occurred. The authors concluded that heparin prophylaxis for patients undergoing elective craniotomy reduces the risk of VTE but may also increase bleeding risks with a ratio of serious or symptomatic VTE relative to serious bleeding that is only slightly favorable.

Another systematic literature review and meta-analysis, published in 2016, identified nine RCTs involving 1450 patients in which heparin was used (LDUH in three and LMWH in six).[34] The control groups did not receive any prophylaxis in five studies and GEC was used in four. The results showed a significant benefit with heparin (OR: 0.51, 95% CI: 0.37 to 0.71; P<0.0001). There was no significant increase in major intracranial hemorrhage (P=0.60), major extracranial hemorrhage (P=0.98) or minor bleeding complications (P=0.60).

The most recent systematic review and meta-analysis (direct meta-analysis and network meta-analysis by Wang *et al.* published in 2021)[29] demonstrated that by 2019 there had been five RCTs involving 1,114 patients comparing prophylaxis with LMWH *vs.* no prophylaxis. In two of these trials, patients had craniotomy, in two patients had craniotomy or spinal operation and in one, patients had exclusively spinal operation. Direct meta-analysis of these nine studies demonstrated that LMWH produced a significant decrease in the incidence of postoperative DVT (RR: 0.59, 95% CI: 0.44 to 0.80). There was no evidence of a significant increase in major intracranial hemorrhage (RR: 1.27, 95% CI: 0.51 to 3.15), major extracranial hemorrhage (RR: 1.56, 95% CI: 0.30 to 7.97) or minor bleeding (RR: 1.89, 95% CI: 0.87 to 4.08).

LMWH combined with GEC *vs.* GEC

Two large multicenter RCTs investigated the efficacy and safety of **adding LMWH** to **GEC**.[35, 36]

In the first trial which involved 345 evaluable patients, LMWH (nadroparin) initiated postoperatively combined with GEC was more effective than GEC alone in reducing VTE (venographic DVT or PE) (18.7% *vs.* 26.3%) (RRR: 28.9%; P=0.047) at 10 days; it also reduced proximal DVT or PE (6.9% *vs.* 11.5%) (RRR: 40.2%; P=0.065). The incidence of major hemorrhage was 2.5% in the LMWH plus GEC group and 0.8% in the GEC group (P=0.87).[35]

In the second trial which included 259 evaluable patients, LMWH (enoxaparin) initiated within 24 hours after surgery or placebo was given for at least 7 days.[36] Both groups had GEC. The incidence of venographic DVT was 32% in the placebo group and 17% in the LMWH group (RR: 0.52, 95% CI: 0.33 to 0.82). Proximal DVT was found in 13% of patients in the placebo group and 5% in the LMWH group (RR: 0.41, 95% CI: 0.17 to 0.95). The incidence of intracranial hemorrhage was 3% in each group.

LMWH compared with LDUH

In a prospective double-blind RCT performed in 2002, 150 patients undergoing craniotomy for brain tumour were randomized to **LDUH** or **LMWH** (enoxaparin) **in addition to GEC and IPC** in both groups. Symptomatic VTE did not occur. On screening with ultrasound there was a 9.3% overall incidence of asymptomatic DVT, equal in both groups. Ten of the 14 patients with DVT had thrombus limited to the deep veins of the calf.[37] The authors concluded that the low rate of DVT was the result of multimodal prophylaxis.

Systematic reviews of IPC compared with LMWH

A systematic review and meta-analysis published in 2008 identified 18 RCTs. The results showed that LMWH or IPC compared with no prophylaxis were effective in reducing the rate of DVT (LMWH-RR: 0.60, 95% CI: 0.44 to 0.81; IPC: RR: 0.41, 95% CI: 0.21 to 0.78). In head-to-head trials, there was no statistical difference in the rate of intracranial hemorrhage between therapy with LMWH and IPC (RR: 1.97, 95% CI: 0.64 to 6.09).).[38] However, the pooled rates of intracranial hemorrhage and minor bleeding were higher in the heparin group (2.1% with heparin *vs.* 1.1% with mechanical methods).

The most recent systematic review and meta-analysis[29] (direct meta-analysis and network meta-analysis) published in 2021 reported that by 2019 there had been two RCTs involving 186 patients comparing LMWH with IPC. In one of these trials, patients had craniotomy and in the other they had craniotomy or spinal operation. Direct meta-analysis of these two studies demonstrated that there was no significant difference in efficacy between IPC and LMWH prophylaxis (RR: 1.69, 95% CI: 0.50 to 5.65). There was no evidence that IPC compared with LMWH plus IPC was associated with a smaller risk of major intracranial hemorrhage (RR: 0.44, 95% CI: 0.06 to 3.22), major extracranial hemorrhage (RR: 0.33, 95% CI: 0.01 to 8.02) or minor bleeding (RR: 1.75. 95% CI: 0.54 to 5.67).

Results of network meta-analysis

In the most recent systematic review and meta-analysis (direct meta-analysis and network meta-analysis) published in 2021, network meta-analysis was based on the nine RCT of IPC *vs.* no prophylaxis, the five RCT of LMWH *vs.* no prophylaxis and the two RCT of IPC *vs.* LMWH.[29]

This network meta-analysis demonstrated that compared with no prophylaxis, both IPC (RR: 0.41, 95% CrI: 0.26 to 0.60) and LMWH (RR: 0.48, 95% CrI: 0.28 to 0.68) reduced the risk of DVT. A difference between IPC and LMWH was not found (RR: 0.86, 95% CrI: 0.50 to 1.50). IPC prophylaxis had the highest probability of being the most effective treatment in reducing the incidence of DVT, followed by LMWH.

This network meta-analysis also demonstrated that both IPC and LMWH reduced PE (RR: 0.10, 95% CrI: 0.01 to 0.60 and RR: 0.31, 95% CrI: 0.05 to 1.00, respectively).

The same network meta-analysis demonstrated that there was no significant difference between IPC and LMWH in terms of the risk of major intracranial hemorrhage (RR: 0.71, 95% CrI: 0.10 to 4.80), major extracranial hemorrhage (RR: 1.00, 95% CrI: 0.02 to 48.00) and minor bleeding complications (RR: 2.10, 95% CrI: 0.38 to 13.00).

Initiation, regimen and duration of heparin prophylaxis

A systematic review identified three single-center retrospective studies in which patients received LMWH or LDUH for VTE prophylaxis in elective cranial surgery and compared any of the following: time of initiation, regimen or duration of prophylaxis with reports of outcomes including objectively identified VTE, or intracranial hemorrhage.[39-42]

Two of these studies showed an association between later initiation of heparin prophylaxis and VTE rates.[40, 41] Patients who developed VTE were significantly more likely to have received their first postoperative dose later (mean: 144 *vs.* 29 hours, P=0.04). One study found that longer duration of prophylaxis was associated with a higher rate

of intracranial hemorrhage without significant change in VTE rate.[42] Shorter duration of prophylaxis (<7 days) was associated with significantly lower intracranial hemorrhage rates (P=0.03) compared with longer courses (>21 days).

RCTs that directly compare timing of first dose and duration of prophylaxis with LDUH or LMWH, and a possible association with bleeding are needed.

Recommendations

IPC is recommended in all patients having craniotomy or spinal surgery with or without GEC stockings. Prophylaxis should start at the time of operation and be continued until the patient is fully ambulant **(Level of evidence high, recommendation strong)**.

LMWH is an alternative method provided it is commenced 24 hours after surgery or when there is no increased risk of bleeding **(Level of evidence high, recommendation moderate)**.

LMWH should be preferred to **LDUH because it involves only one injection per day and has a lower incidence of HIT** (see Section 20) **(Level of evidence: moderate, recommendation moderate)**.

Addition of **LMWH to IPC** is associated with increased efficacy. This is based on extrapolation from studies in different populations (see section 12 on combined modalities). Thus, patients with previous DVT or PE should be considered for combined prophylaxis **(Level of evidence moderate, recommendation moderate)**. However, the use of, and timing of LMWH administration should be individualized because of increased risk of bleeding.

In the absence of RCTs extended prophylaxis should be individualized depending on perceived risk for each patient **(Level of evidence low, recommendation weak)**.

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SECTION 10

Prevention of VTE in medical patients

The risk

Thrombotic risk

The majority of hospital-acquired VTE events occur in acute medically ill patients, who have more severe forms of VTE and have a higher number of VTE-related deaths than surgical patients.[1, 2] In three large RCTs involving acutely ill medical patients, the frequency of symptomatic VTE ranged from 3.4% to 6.6%.[3-5] The frequency of asymptomatic DVT in medical patients in the absence of prophylaxis diagnosed by surveillance using phlebography, fibrinogen uptake test or ultrasound in early studies was found to vary between 9% and 56% depending on the type of disease (Table 10.I).[3, 6-19, 21-26] The highest frequencies were found in patients with myocardial infarction (22%), patients in ICU (25%) and patients with stroke (56%). In three recent RCTs of hospitalized medical patients, proximal DVT found by screening methods has consistently been shown to be associated with a higher mortality rate compared with those who have isolated calf or no DVT and thus continues to remain a relevant endpoint in clinical trials of thromboprophylaxis.[27-29]

Fatal PE is the leading cause of sudden death in hospitalized medical patients. Autopsy studies show that approximately 75% of patients dying from PE in general hospitals were immobilized patients with medical illnesses.[30] Overall mortality in medical patients admitted to general hospitals is about 10%, and about one in 10 hospital deaths is due to PE.[30, 31] A population-based case-cohort study estimated that in the absence of appropriate VTE prophylaxis, one in 20 hospitalized medical patients may suffer a fatal PE.[32] In addition to in-hospital VTE, a substantial proportion (50-60%) of VTE occurs in the immediate postdischarge period,[33-35] where the rate of symptomatic VTE more than doubles in the first 21 days and is associated with a five-fold increase of fatal PE within 45-day postdischarge.[33] Lastly, approximately 40% of community-acquired VTE is associated with a recent medical hospitalization.[36]

Both disease-specific (extrinsic) risk factors as well as patient-related (intrinsic) risk factors for VTE should be considered to determine the overall thrombotic risk in medical inpatients.[37] Acute medical conditions such as stroke, congestive heart failure (especially NYHA Stage III or IV), malignancy, respiratory disease, acute infections, and stay in an intensive care unit (ICU) are associated with a high risk of VTE (Table 10.II).[38, 39] Patient-related risk factors that predict high risk of VTE in medically ill patients include a prior history of VTE, advanced age, immobility, history of thrombophilia, and obesity.[37-41] More recently, an elevated D-dimer during hospitalization (more than twice the upper limit of local laboratory normal) has also been associated with high VTE risk in medically ill patients, including those with congestive heart failure (Table 10.II).[42, 43] There are two well-validated VTE risk assessment models in this population, the Padua and IMPROVE VTE models, using established cut-offs based on weighted and scored clinical risk factors (Table 10.III, IV).[33, 41] The more recent IMPROVE-DD VTE model represents a refinement of the original IMPROVE VTE model by incorporating elevated D-dimer to improve original model discrimination (Table 10.IV).[44]

Bleeding risk

Individual disease- and patient-specific bleeding risk factors that predict high risk of major bleeding in hospitalized medical patients include active cancer, dual antiplatelet therapy at baseline, a history of any bleeding or active gastroduodenal ulcer within three months of hospitalization,

TABLE 10.I.—*The frequency of all DVT in medical patients in the absence of prophylaxis (diagnosed by surveillance with objective methods: phlebography, FUT or DUS). The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.*

Patient groups	Number of studies	Patients N.	DVT incidence (weighted mean)	95% CI
Stroke				
Czechanowski *et al.* 1981[6]		41	23	
Dahan *et al.* 1986[7]		27	3	
Elias *et al.* 1990[8]		15	12	
McCarthy *et al.* 1977[9]		16	12	
McCarthy *et al.* 1986[10]		161	117	
Prins *et al.* 1989[11]		30	15	
Sandset *et al.* 1990[12]		50	17	
Turpie *et al.* 1987[13]		25	7	
Warlow *et al.* 1972[14]		30	18	
Total	8	395	224 (56%)	51% to 61%
Patients in ICU				
Moser *et al*. 1981 (FUT)[15]		33	4	
Cade 1982 (FUT)[16]		60	17	
Fraisse *et al*. 2000 (Venography)[17]		85	24	
Total	3	178	45 (25%)	19% to 32%
Myocardial infarction				
Emerson *et al*. 1977[18]		41	14	
Handley 1972[19]		24	7	
Nicolaides *et al*. 1971[20]		51	8	
Warlow *et al*. 1973[21]		64	11	
Total	4	180	0 (22%)	16% to 28%
General medical				
Gallus *et al*. 1973[22]		15	7	
Belch *et al*. 1981[23]		50	13	
Prescott *et al*. 1981[24]		45	4	
Cade 1982[16]		67	7	
Dahan *et al*. 1986[7]		131	12	
Schönhofer *et al*. 1998[25]		196	21	
Samama *et al*. 1999[3]		288	43	
Oger *et al*. 2002[26]		234	14	
Total	8	1026	121 (12%)	10% to 14%
Geriatric (>65 years)				
Dahan *et al.* 1986[7]	1	131	12 (9%)	5% to 15%

TABLE 10.II—*Individual disease-specific and patient-specific high VTE risk factors in hospitalized medical patients.*

Individual disease-specific and patient-specific high VTE risk factors
History of VTE*
Family history of VTE
Acute infection
Malignancy*
Age >75 years*
CHF
Obesity
Stroke
Immobility >4 days
Pregnancy/postpartum
Acute/chronic lung disease
Acute inflammatory disease
Shock/ICU stay
Elevated Dd (>2X ULN)**

*APEX criteria; **novel biomarker.

TABLE 10.III—*Padua Prediction Score (high risk of VTE: ≥4).*

Baseline features	Score
1. Active cancer*	3
2. Previous VTE (with the exclusion of superficial vein thrombosis)	3
3. Reduced mobility#	3
4. Already known thrombophilic condition^	3
5. Recent (≤1 month) trauma and/or surgery	2
6. Elderly age (≥70 years)	1
7. Heart and/or respiratory failure	1
8. Acute myocardial infarction or ischemic stroke	1
9. Acute infection and/or rheumatologic disorder	1
10. Obesity (BMI≥30)	1
11. Ongoing hormonal treatment	1

*Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous six months; #bedrest with bathroom privileges (either due to patient limitations or on physicians order) for at least three days; ^carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

TABLE 10.IV.—*Risk score points assigned to each independent VTE risk factor in hospitalized acutely ill medical patients – the IMPROVE VTE RAM.**

VTE risk factor	Points for the Risk Score
Previous VTE	3
Thrombophilia**	2
Lower limb paralysis	2
Cancer***	2
Immobilization****	1
ICU/CCU stay	1
Age >60 years	1

ICU: Intensive Care Unit; CCU: Coronary Care Unit.
*For the IMPROVE-DD VTE score = D-dimer >twice the upper limit of local laboratory normal is 2 points. For both IMPROVE-VTE and IMPROVE-DD VTE = a score of 0-1 constitutes low VTE risk, a score of 2-3 constitutes moderate VTE risk, and a score of 4 or more constitutes high VTE risk; **a known congenital or acquired condition leading to an excess risk of thrombosis; ***may include active cancer (excluding non-melanoma skin cancer) or a history of cancer within 5 years; modified definition is a history of cancer; ****strict definition is complete immobilization confined to bed or chair ≥7 days; modified definition is complete immobilization ≥1 day.

TABLE 10.VI.—*Bleeding Risk Score Points Assigned to Each Independent Factor: the IMPROVE Bleed Score.**

Bleeding Risk Factors	Points
Renal failure GFR 30-59 *vs.* ≥60 mL/min/m^2	1
Male *vs.* female	1
Age 40-80 *vs.* <40 years	1.5
Current cancer	2
Rheumatic disease	2
CV catheter	2
ICU/CCU	2.5
Renal failure GFR<30 *vs.* ≥60 mL/min/m^2	2.5
Hepatic failure (INR>1.5)	2.5
Age ≥85 *vs.* <40 years	3.5
Platelets <50 × 10^9 cells/L	4
Bleeding in 3 months before admission	4
Active gastroduodenal ulcer	4.5

ICU: Intensive Care Unit; CCU: Critical Care Unit; CV: central venous; GFR: glomerular filtration rate; INR: international normalized ratio.
*A score of 7 or more constitutes high bleed risk.

bronchiectasis or pulmonary cavitation, severe chronic kidney disease with CrCl<30 mL/min, and severe thrombocytopenia (platelet counts <50 × 10^9 cells/L)[37] (Table 10.V). The IMPROVE Bleed score is a validated bleeding risk model in hospitalized medical patients that predicts major bleeding risk using established score cut-offs[45, 46] (Table 10.VI).

Effect of VTE prophylaxis on atherosclerotic cardiovascular events

VTE and atherothrombosis share a common pathophysiology and shared mechanisms of thrombosis.[47, 48] The novel paradigm is that VTE is part of a pan-vascular syndrome that includes coronary artery disease, peripheral arterial disease, and cerebrovascular disease. VTE and atherosclerosis share common risk factors such as cigarette smoking, hypertension, diabetes, and obesity, which are often modifiable, in addition to shared pathophysiologic mechanisms of inflammation, hypercoagulability, and endothelial injury from fibrin and erythrocyte deposition and platelet activation, although to varying degrees.[48] Multiple studies suggest that markers of inflammation or coagulation such as C-reactive protein or D-dimer may be useful biomarkers for both disease states.[42, 43] Based on the above, it is not surprising that extended thromboprophylaxis in medical ill patients with direct oral anticoagulants (DOACs) has been shown to decrease major and fatal vascular events that include arterial thromboembolic events such as stroke, TIA, and myocardial infarction in addition to VTE.[49-56]

TABLE 10.V.—*Risk factors for bleeding in hospitalized medical patients.*

Disease-specific	Patient-specific
History of pulmonary cavitation/ bronchiectasis*	Severe chronic kidney disease (CrCL<30 mL/min) *
Recent history of bleed (within 3 months of hospitalization) *	Severe thrombocytopenia (platelet counts <50 × 10^9 cells/L*
Hepatic failure	Advanced age >85 years
Rheumatic disease	Dual antiplatelet therapy*
Active gastroduodenal ulcer (within 3 months of hospitalization)*	Male sex
Prior stroke	
Active malignancy*	
ICU/CCU stay	

*Key bleed risk factors (including MAGELLAN sub-population).

Prophylactic methods

A. Acutely ill medical patients

LDUH

Three RCTs performed in the 1970s and early 1980s demonstrated that **LDUH** was effective in preventing asymptomatic DVT when compared with no prophylaxis.[16, 22, 23] It reduced DVT from 21% in the control groups to 5.5% in the treatment groups (RR: 0.25, 95% CI: 0.14 to 0.47). However, significant differences in mortality in hospitalized medical patients using LDUH were not shown.[57, 58]

LMWH

Subsequently, two RCTs demonstrated that **LMWH** was effective in preventing asymptomatic DVT when compared with no prophylaxis.[3, 7] It reduced the incidence of DVT from 13% to 4.7% (RR: 0.36, 95% CI: 0.22 to 0.59). There was no increased bleeding in any of the studies. A third RCT using a composite outcome (combination of

symptomatic DVT, symptomatic PE, asymptomatic proximal DVT and sudden death) assessed the efficacy and safety of LMWH (dalteparin) for 14 days *vs.* placebo in acutely ill medical patients (N.=3706).[4] By day 21, the incidence of VTE was reduced from 4.96% in the placebo group to 2.77% in the LMWH group (RR: 0.55, 95% CI: 0.38 to 0.80).

A double blind, placebo controlled, multicenter RCT attempted to estimate the efficacy of LMWH on symptomatic VTE (distal, or proximal DVT, fatal or non-fatal PE) at 30 days in patients over the age of 70, hospitalized for acute medical conditions.[59] Patients were randomized to receive LMWH (enoxaparin 40 mg daily) or placebo for 6-14 days. The trial was prematurely discontinued because of drug supply issues. By the time of trial discontinuation, 2559 patients had been randomly assigned instead of 4634 based on power calculations. The primary efficacy outcome occurred in 22 (1.8%) out of 1278 patients in the enoxaparin group and in 27 (2.2%) out of 1263 patients in the placebo group (P=0.46). The incidence of major bleeding was 0.9% in the enoxaparin group and 1.0% in the placebo group. At 90 days there were 14 symptomatic pulmonary emboli in the enoxaparin group and 25 in the placebo group (OR: 0.55, 95% CI: 0.28 to 1.06; P=0.074); all 39 pulmonary embolism events resulted in hospital readmission and/or death, with 5 deaths from pulmonary embolism in the enoxaparin group and 11 deaths in the placebo group. The authors concluded that this trial did not demonstrate that enoxaparin reduced the risk of symptomatic VTE after 1 month. Because the trial was prematurely discontinued, larger trials were needed to definitively address this question.

LMWH vs. *LDUH*

Four RCTs performed in the years 1996-2003, compared **one daily dose of LMWH with 12 or 8 hourly LDUH**.[60-63] Although none of the studies showed any advantage for LMWH for asymptomatic DVT on its own, an advantage was apparent when the results were combined (4.24% *vs.* 5.77%) (RR: 0.73, 95% CI: 0.56 to 0.97).

Fondaparinux

In a double-blind RCT in 849 acutely ill medical patients over the age of 60, **fondaparinux** administered for 6-14 days reduced the incidence of VTE (venographic asymptomatic DVT and symptomatic VTE) from 10.5% in the placebo group to 5.6% in the fondaparinux group (RR: 0.50, 95% CI: 0.28 to 0.91).[5] Symptomatic VTE occurred in five patients in the placebo group and none in the fondaparinux group (P=0.029). There was no PE in the fondaparinux group compared with five PE cases in the placebo group, all of which were fatal. Major bleeding occurred in one patient (0.2%) in each group. At the end of follow-up, 14 patients in the fondaparinux group (3.3%) and 25 in the placebo group (6.0%) had died (P=0.073).

LMWH plus GEC vs. *placebo*

The LIFENOX study was a large (8,307 patients) multicenter RCT that compared **enoxaparin plus GEC with placebo plus GEC**. Overall mortality from any cause was the endpoint. Pharmacological prophylaxis did not reduce the mortality rate and did not improve survival. The rate of death from any cause at day 30 was 4.9% in the enoxaparin plus GEC group and 4.8% in the placebo plus GEC group (RR: 1.0; 95% CI: 0.8 to 1.2). The rate of major bleeding was 0.4% in the enoxaparin group and 0.3% in the control group (RR: 1.4, 95% CI: 0.7 to 3.1).[64]

Systematic reviews and meta-analyses

Meta-analysis of 2000

A meta-analysis of seven trials performed in 2000, comparing prophylactic heparin treatment with a control (15,095 patients) demonstrated a **significant decrease in DVT and PE with risk reductions of 56% and 58% respectively and without any significant difference in the incidence of major bleeding or death**.[65] In the same study, nine trials comparing LMWH with LDUH were also included and although there was no significant difference regarding DVT, PE or mortality, **there was a 52% lower incidence of major hemorrhage using LMWH (P=0.049)**.

Meta-analysis of 2007

A meta-analysis of nine RCT (N.=19,958) comparing the effects of anticoagulation prophylaxis with no prophylaxis in hospitalized medical patients was performed in 2007.[66] **There was a reduction in any PE from 0.49% to 0.20%** (RR: 0.43, 95% CI: 0.26 to 0.71) **and fatal PE from 0.41% to 0.15%** (RR: 0.38, 95% CI: 0.21 to 0.69),a non-significant trend for reduction in symptomatic DVT (3 RCTs) from 0.97% to 0.46% (RR: 0.47, 95% CI: 0.22 to 1.00) and a non-significant increase in major bleeding from 0.45% to 0.59% (RR: 1.32, 95% CI: 0.73 to 2.37). Anticoagulant prophylaxis had no effect on all-cause mortality.

Meta-analysis of 2011

A systematic review of VTE prophylaxis in hospitalized medical patients and those with stroke (18 trials; 36,122 patients) performed in 2011 investigated the effect of hep-

arin prophylaxis (LDUH, LMWH) and fondaparinux on PE and total mortality.[67] The authors reported that heparin prophylaxis did not reduce total mortality, but **reduced PE from 1.10% to 0.83% (RR: 0.74, 95% CI: 0.60 to 0.92)**. In medical patients (10 trials; 20,717 patients), PE was reduced from 1.24% to 0.84% (RR: 0.68, 95% CI: 0.52 to 0.89) and major bleeding increased from 0.25% to 0.40% (RR: 1.23, 95% CI: 1.02 to 1.49). In patients with stroke (5 trials; 14,862 patients), PE was reduced from 0.96% to 0.78% (RR: 0.86, 95% CI: 0.66 to 1.23) and major bleeding increased from 0.88% to 1.50% (RR: 1.38, 95% CI: 1.02 to 1.17 to 1.62). No statistically significant differences in efficacy or major bleeding were observed in the 14 trials that compared LDUH with LMWH.

Meta-analysis of 2014

This systematic review and meta-analysis included 16 trials with a combined total of 34,369 participants with an acute medical illness.[68] Ten studies compared heparin with placebo, or no treatment and six studies compared LMWH to LDUH. Heparin reduced the incidence of DVT (OR: 0.38, 95% CI: 0.29 to 0.51; P<0.00001). The estimated reductions in symptomatic non-fatal PE (OR: 0.46, 95% CI: 0.19 to 1.10; P=0.08), fatal PE (OR: 0.71, 95% CI: 0.43 to 1.15; P=0.16) and in combined non-fatal PE and fatal PE (OR: 0.65; 95% CI: 0.42 to 1.00; P=0.05) associated with heparin were imprecise. Heparin resulted in an increase in major hemorrhage (OR: 1.81, 95% CI: 1.10 to 2.98; P=0.02). There was no clear evidence that heparin had an effect on all-cause mortality. Compared with UFH, LMWH reduced the risk of DVT (OR: 0.77, 95% CI: 0.62 to 0.96; P=0.02) and major bleeding (OR: 0.43, 95% CI: 0.22 to 0.83; P=0.01). There was no clear evidence that the effects of LMWH and UFH differed for the PE outcomes and all-cause mortality.

B. Acute myocardial infarction

Traditionally, patients with acute myocardial infarction are among the highest-risk medical patients for VTE. However, in the presence of the currently aggressive antithrombotic and thrombolytic therapies for myocardial infarction, specific prophylactic regimens are not routinely required.

C. Acute ischemic stroke

LDUH and LMWH

LDUH was effective in reducing asymptomatic DVT from 75% to 12.5% when compared with no prophylaxis in one study (RR: 0.30, 95% CI: 0.22 to 0.41).[10] A **low molecular weight heparinoid** (danaparoid) was also effective (30.4% *vs.* 2.3%) (RR: 0.14, 95% CI: 0.03 to 0.64).[13] **LMWH** was effective in reducing asymptomatic DVT when compared with no prophylaxis in two small RCTs[8, 11] but not in a third one,[12] all performed between 1989 and 1990.

A systematic review of 10 LMWH trials published in 2000 reported that low dosage (<100 IU per kg) did not reduce the incidence of DVT compared with the placebo groups. However, higher doses reduced the incidence of symptomatic DVT from 5.5% to 2.7% (RR: 0.51, 95% CI: 0.35 to 0.75) and symptomatic PE from 1.9% to 0.6% (RR: 0.34, 95% CI: 0.16 to 0.72) although there was an increased risk of major intracranial hemorrhage from 1.1% to 2.6% (RR: 1.33,95% CI: 1.13 to 1.55).[69]

LMWH vs. LDUH

Two trials have compared **danaparoid**[70, 71] and one **LMWH** (enoxaparin)[72] with **LDUH.** A meta-analysis calculated a reduction of asymptomatic DVT from 22% in the LDUH groups to 13% in the danaparoid or enoxaparin groups (RR: 0.59, 95% CI: 0.43 to 0.82).[73]

In the PREVAIL trial, 1762 patients with acute ischemic stroke who were unable to walk unassisted were randomly assigned within 48 hours of symptom onset to receive either **enoxaparin 40 mg subcutaneously once daily or LDUH 5000 U subcutaneously12-hourly for 10 days**.[74] The primary efficacy endpoint was a composite of symptomatic or asymptomatic DVT, symptomatic PE, or fatal PE. Enoxaparin reduced the risk of VTE by 43% compared with LDUH (10% *vs.* 18%) (RR: 0.57, 95% CI: 0.44 to 0.76). Bleeding rates were the same (8%) with enoxaparin or unfractionated heparin (P=0.83). The frequency of a composite of symptomatic intracranial and major extracranial hemorrhage was small (1%) and similar between groups.

Graduated elastic compression stockings (GEC)

Two RCTs investigated the effect of **GEC** on the incidence of DVT in immobile medical patients with stroke. In the first study (**CLOTS trial 1**),[75] 2518 patients who were admitted to the hospital within one week of an acute stroke and who were immobile were randomized to routine care plus thigh-length GCS (N.=1256) or to routine care without GCS (N.=1262). **The incidence of symptomatic or asymptomatic DVT on ultrasound was 10.0% in the GCS group and 10.5% in the group without stockings (RR: 1.03, 95% CI: 0.81 to 1.29)**. Skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients allocated to GCS than in those allocated to avoid their use (16% *vs.* 5%) (RR: 4.05, 95% CI: 2.35-6.97).

In the second study (**CLOTS trial 2**),[76] 1,552 patients were randomized to thigh-length stockings and 1,562 patients to below-knee stockings to wear while in the hospital. A duplex scan in 1,406 patients (96% of survivors) in each treatment group between seven and 10 days after enrolment was performed. **The incidence of symptomatic or asymptomatic DVT on ultrasound was 6.3% in the thigh length group and 8.8% in the knee length stockings (RR: 0.71; 95% CI: 0.55 to 0.91)**. Skin breaks occurred in 61 patients (3.9%) who received thigh-length stockings and 45 (2.9%) who received below-knee stockings.

Results from the CLOTS trials 1 and 2 are, at first sight, difficult to reconcile with the relatively high efficacy of GES in preventing DVT in moderate risk general surgical patients (see Section 3). It is also difficult to explain the differences between the two CLOTS studies. First, it appears that GEC is less effective in medical than surgical patients. Second, one should not assume that the mechanism of DVT is the same in medical and surgical patients. There is evidence that under general anesthesia, veins in the limbs dilate producing tears in the endothelium with exposure of underlying collagen to circulating blood.[77] This endothelial damage, combined with venous stasis and the hypercoagulable state because of the surgical trauma produces DVT. GEC prevents both vein dilatation and stasis. The mechanism of DVT in medical patients is more likely to be the result of the combination of venous stasis and hypercoagulability without endothelial damage. Further basic research is needed in this area.

IPC

A multicenter RCT involving 2876 patients with stroke in 94 UK hospitals compared the effect of IPC to no compression (CLOTS 3).[78] The primary outcome was DVT in popliteal or femoral veins, detected by ultrasound or any symptomatic DVT in proximal veins confirmed by imaging within 30 days of randomization. **The primary outcome occurred in 122 (8.5%) of 1438 patients allocated to IPC and 174 (12.1%) of 1438 patients allocated to no IPC, giving an absolute reduction in risk of 3.6% (95% CI: 1.4% to 5.8%) (RR: 0.69, 95% CI: 0.55 to 0.86)**. After excluding 323 patients who died prior to any primary outcome and 41 who had no screening with ultrasound, the primary outcome occurred in 122 (9.6%) of 1267 IPC participants compared with 174 (14.0%) of 1245 no-IPC: participants, giving an adjusted odds ratio of 0.65 (95% CI: 0.51 to 0.84; P=0.001). In patients treated with IPC, there was a statistically significant improvement in survival to 6 months (HR: 0.86, 95% CI: 0.73 to 0.99; P=0.042).

D. Acute hemorrhagic stroke

LMWH vs. *no prophylaxis*

Three small, underpowered RCTs involving a total of 194 patients with acute hemorrhagic stroke have tested the value of LMWH in the prevention of in-hospital DVT.[79-81] LMWH was administered after documentation of cessation of bleeding. A meta-analysis of these trials demonstrated a non-significant reduction in PE (OR: 0.38, 95% CI: 0.14 to 1.05) and a non-significant reduction in VTE (OR: 0.77, 95% CI: 0.38 to 1.57). No differences in any hematoma enlargement and mortality between the groups were observed. It should be emphasized that patients included in these studies were highly selected and one study was stopped prematurely due to slow recruitment.[81] Exclusion criteria were intracranial hemorrhage due to vascular malformation, subarachnoid hemorrhage, subdural hematoma, bleeding disorders, renal failure, severe hepatic failure, known neoplastic disease, pregnancy, necessity of therapeutic anticoagulant or antiplatelet agents for concomitant disease, or patient refusal to consent.

IPC + GEC vs. *GEC*

Another study randomized 133 patients with documented intracerebral hemorrhage to **GEC** alone or **GEC combined with IPC**. The incidence of ultrasound detected **asymptomatic DVT on day 10 was reduced from 15.9% in the GEC group to 4.7% in the GEC combined with IPC group (RR: 0.29, 95% CI: 0.08 to 1.00)**.[82]

IPC

In the CLOTS 3 RCT (see above under acute stroke), which found IPC to be an effective method of reducing the risk of proximal DVT, 322 of the patients had hemorrhagic stroke.[78, 81] **In this subgroup the relative risk of the primary outcome was reduced from 17% in the no-IPC group to 6.7% in the IPC group (OR: 0.36, 95% CI: 0.17 to 0.75)**.

E. Congestive cardiac failure

LMWH vs. *placebo*

Several RCTs that included patients with congestive heart failure (NYHA Stage III or IV) showed a decrease of total VTE with either **LMWH** (enoxaparin 40mg once daily, dalteparin 5000IU once daily) or **fondaparinux** (2.5 mg once daily) *vs.* placebo without excess major bleeding.[3-5] In addition, a sub-study of the PRINCE trial in patients with chronic cardiac failure revealed improved efficacy of enoxaparin 40 mg once daily *vs.* UFH 5000 IU twice daily with a 40% RRR (P=0.014).[63]

In the PRE-VENT RCT[83] which tested dalteparin 5000 U once daily *vs.* placebo in acutely ill hospitalized medical patients, 43% of the study cohort consisted of patients in decompensated heart failure. During hospitalization, **dalteparin was associated with a 27% reduction in VTE**. Most of the VTE reduction occurred in patients with asymptomatic proximal leg DVT, diagnosed by screening with ultrasound.

Patients admitted to hospital with acute heart failure consisted of 32% of the patients in the MAGELLAN and 40% in the MARINER RCTs on extended thromboprophylaxis (see below).

F. Intensive care patients

LMWH and LDUH

Three RCTs with LMWH or UFH and one systematic review investigated treatment effects of heparin thromboprophylaxis in critically ill patients.[61, 84-86] **Pharmacological thromboprophylaxis reduced mortality, PE, and DVT, with no significant excess major bleeding**. The PROTECT trial compared LMWH (dalteparin 5000 U once daily) with UFH 5000U twice daily and found that **PE was significantly lower with dalteparin compared with UFH (HR: 0.51, 95% CI: 0.30 to 0.88; P=0.01)** and with less HIT (HR: 0.27, 95% CI: 0.08 to 0.98; P=0.046).[87]

A systematic review and meta-analysis published in 2013 included 7 RCTs involving 7,226 patients investigated the efficacy and safety of heparin thromboprophylaxis in medical-surgical patients in the ICU.[88] **Any heparin thromboprophylaxis compared with placebo reduced the rate of DVT (RR: 0.51, 95% CI: 0.41 to 0.63; P<0.0001) and PE (RR: 0.52, 95% CI: 0.28 to 0.97; P=0.04)** but not symptomatic DVT (RR: 0.86, 95% CI: 0.59 to 1.25; P=0.43). There was no significant difference in major bleeding (RR: 0.82, 95% CI: 0.56 to 1.21; P=0.32) and mortality (RR: 0.89, 95% CI: 0.78 to1.02; P=0.09) rates. **Compared with LDUH, LMWH reduced the rates of PE (RR: 0.62, 95% CI: 0.39 to 1.00; P=0.05) but not DVT (RR: 0.90, 95% CI: 0.74 to 1.08; P=0.26),** symptomatic DVT (RR: 0.87, 95% CI: 0.60 to 1.25; P=0.44), major bleeding (RR: 0.97, 95% CI: 0.75 to 1.26; P=0.83), or mortality (RR: 0.93, 95% CI: 0.82 to 1.04; P=0.20).

Systematic review and meta-analysis of IPC vs. *no prophylaxis or other modalities*

The systematic review and meta-analysis of 10 studies (6 RCT and 4 observational studies) involving 4759 patients published in 2020 compared IPC with no prophylaxis or a different modality.[89] Four studies that compared **IPC with no prophylaxis demonstrated a significant reduction in VTE incidence (6.0% for IPC *vs.* 16.3% without prophylaxis) (RR: 0.35, 95% CI: 0.018 to 0.68; P=0.002)**.

Three studies that compared IPC with GCS demonstrated a lower VTE incidence in the IPC group (4.2% *vs.* 9.1%) (RR: 0.47, 95% CI: 0.24 to 0.91; P=0.03).

Three studies which compared IPC with LMWH did not demonstrate any significant difference between the groups (6.6% *vs.* 6.0%, RR: 1.26, 95% CI: 0.72 to 2.22, P=0.41).

Four studies used IPC as an adjunct treatment, and no significant difference for VTE was observed between groups (8.8% *vs.* 9.7%; RR: 0.55, 95% CI: 0.24 to 1.27; P=0.16) (for combined modalities see Section 12).

Systematic review and meta-analysis of 2022

A recent review and network meta-analysis, which included 13 RCTs (9619 patients) and evaluated the efficacy of thromboprophylaxis in critically ill patients demonstrated that **the incidence of DVT was reduced by LMWH (OR: 0.59, 95% CI: 0.33 to 0.90) but not significantly by LDUH (OR: 0.82, 95% CI: 0.47 to 1.37)**.[90]

When LMWH was compared with LDUH it reduced the incidence of DVT further (OR: 0.72, 95% CI: 0.46 to 0.98). In this meta-analysis, IPC or GEC were treated as one modality with a weak effect found on reduction in VTE. Other studies and meta-analyses have demonstrated that the efficacy of IPC outweighs the efficacy of GEC (see above).

Extended posthospital discharge thromboprophylaxis

With shortening hospital length of stays for medically ill patients in advanced health systems (which is approximately 4-5 days in the United States) most thrombotic events in medical inpatients now occur in the immediate posthospital discharge period.[37] A review of 1,897 VTE episodes occurring in the Worcester (MA, USA) healthcare system showed that a large proportion of patients with VTE (37%) had been hospitalized during the three months prior to developing acute VTE.[36] Consistent longitudinal data reveal that in the immediate postdischarge period, the rate of symptomatic VTE more than doubles in the first 21 days and is associated with a five-fold increase of fatal PE within 45 days postdischarge in medically-ill patients.[33-35] These shortening hospital length-of-stays, coupled with the fact that less than 4% of patients receive any type of post-discharge thromboprophylaxis, leads to an inability to reduce the burden of hospital-acquired VTE by focusing efforts only in in-hospital thromboprophylaxis.[37, 91] A

recent large quality improvement program in 35 Michigan health systems in the United States showed no difference in VTE-free survival in hospitalized medical patients based on in-hospital only VTE prophylaxis performance even though the absolute rates of pharmacological thromboprophylaxis between the lowest and highest performing hospitals differed absolutely by more than 30%.[92] The median hospital length-of-stay was 4.5 days.

Trials of extended thromboprophylaxis with either LMWH or DOACs when compared with standard in-patient LMWH followed by placebo in medically ill patients had mixed results. In the EXCLAIM trial, extended duration VTE prophylaxis was tested after hospital discharge in high-risk medical patients with heart failure, respiratory insufficiency, infection, or reduced mobility.[93] There was a reduction in symptomatic VTE among those patients receiving extended post discharge prophylaxis (28 days) with enoxaparin 40 mg daily. However, a methodological problem with EXCLAIM was a change in enrolment eligibility midway through the study to make the definition of "immobility" stricter, thereby recruiting extremely immobile patients with a higher VTE risk, after interim analyses suggested lower-than-expected VTE rates.[94] Overall, in EXCLAIM, **extended-duration enoxaparin significantly reduced VTE at 28 days from 4.0% in the placebo group to 2.5% (P=0.0011) in the enoxaparin group (RR: 0.62, 95% CI: 0.47 to 0.83)**. The significant reduction in risk of VTE events persisted out to 90 days and the rates for placebo and extended prophylaxis were 5.2% and 3.0%, respectively (P=0.0015). Major hemorrhage was more frequent in extended-duration enoxaparin treated patients (0.8% *vs.* 0.3%) (RR: 2.68, 95% CI: 1.25 to 5.75). Benefits from extended-duration enoxaparin seemed to be restricted to women, patients older than 75 years and those with severe immobility.

In the ADOPT RCT involving 4,495 evaluable acutely ill medical patients, **apixaban 2.5 mg twice daily administered orally for 30 days was compared with enoxaparin 40 mg daily administered for six to 14 days**.[95] **The primary efficacy outcome** (asymptomatic proximal DVT detected by ultrasound, symptomatic DVT or PE and VTE related death**) at 30 days was 2.7% in the apixaban group and 3.1% in the enoxaparin group (RR: 0.87, 95% CI: 0.62 to 1.23) (P=0.44)**. Major bleeding was more frequent in the apixaban group (0.47% *vs.* 0.19%) (RR: 2.58, 95% CI: 1.02 to 7.24; P=0.04).

In the MAGELLAN RCT involving 8,101 acutely ill medical patients,[92] **extended duration of prophylaxis with rivaroxaban for 35 days was tested against enoxaparin for 10 days followed by placebo**.[96] The primary efficacy outcome (asymptomatic proximal DVT detected by ultrasound, symptomatic DVT or PE and VTE related death) at 10 days was 2.7% in both groups (RR: 0.97, 95% CI: 0.71 to 1.33) (P=0.0025 for non-inferiority). **At 35 days there was a reduction in the primary efficacy outcome from 5.7% in the placebo group to 4.4% in the group receiving extended prophylaxis with rivaroxaban (RR: 0.62, 95% CI: 0.77 to 0.96) (P=0.021 for superiority)**. At 10 days, clinically relevant bleeding was increased from 1.2% in the enoxaparin/placebo group to 2.8% in the rivaroxaban group (RR: 2.21, 95% CI: 1.58 to 3.08). Major hemorrhage was more frequent in rivaroxaban treated patients (0.6% *vs.* 0.3%) (RR: 2.18, 95% CI: 1.07 to 4.45). At 35 days, clinically relevant bleeding was increased from 1.7% in the placebo group to 4.1% in the extended prophylaxis group (RR: 2.4, 95% CI: 1.83 to 3.20). Major hemorrhage was more frequent in the extended-duration rivaroxaban treated patients (1.1% *vs.* 0.4%) (RR: 2.87, 95% CI: 1.60 to 5.16).

In the APEX RCT which involved 7,513 medically ill patients, a relatively novel DOAC betrixaban at a dose of 80 mg daily for 35-42 days when compared with enoxaparin 40mg daily for six to 14 days **just missed statistical significance in reducing total VTE in the overall intention-to-treat population (RR: 0.81, 95% CI: 0.65 to 1.00; P=0.054)**.[97] However, there was significant benefit in the safety population who took at least one dose of study medication (RRR: 24%, P=0.006). Major bleeding occurred in 0.7% of the betrixaban group and 0.6% of the enoxaparin group (RR: 1.19, 95% CI: 0.67 to 2.12; P=0.55). However, betrixaban is no longer available for clinical use.

In the largest of the extended DOAC thromboprophylaxis trial – MARINER – a total of 12,024 hospitalized medical patients were randomized at discharge to rivaroxaban 10 mg once daily for patients with a CrCl of at least 50 mL/min (reduced to 7.5mg daily for a CrCl of 30-49 mL/min) *vs.* placebo for 45 days post-discharge.[98] Patients were selected based on the IMPROVE score of 4 or more or a score of 2-3 with D-dimer >twice upper limit of normal. The primary efficacy outcome of symptomatic VTE or VTE-related death occurred in 0.83% on rivaroxaban and 1.10% on placebo (HR: 0.76, 95% CI: 0.52 to 1.09; P=0.14). **Pre specified secondary outcomes showed that rivaroxaban reduced symptomatic nonfatal VTE (HR: 0.44, 95% CI: 0.22 to 0.89) and the composite of symptomatic VTE and all-cause mortality (HR: 0.73, 95% CI: 0.54 to 0.97)**. Major bleeding was rare and did not

differ amongst groups: 0.28% in the rivaroxaban group and 0.15% in the placebo group (HR: 1.88, 95% CI: 0.84 to 4.23).

Meta-analyses of extended thromboprophylaxis RCTs

A meta-analysis of 5 RCTs of extended thromboprophylaxis using different agents (enoxaparin, apixaban, rivaroxaban or betrixaban) of unselected hospitalized medically ill populations **revealed a 40% reduction in symptomatic VTE and VTE-related death (RR 0.61, 95% CI 0.44 to 0.83; P=0.002)** at a cost of an over two-fold increase in major and fatal bleeding (RR 2.04, 95% CI 1.42 to 2.91, P<0.001), (trade off: 82 fewer events at the cost of 64 major bleeds).[99]

Another meta-analysis suggested a four-fold difference with extended thromboprophylaxis in preventing the most patient-important outcomes of thrombosis *vs.* incurring those similar weighted outcomes with bleeding (absolute risk reduction 0.25% of symptomatic non-fatal PE or VTE-related death, NNT=403 *vs.* absolute risk increase 0.056% of fatal or critical-site bleeding, NNH=1785).[100]

Post-hoc analyses of the trials with rivaroxaban and betrixaban identified subgroups of medically ill patients at low bleed risk and high thrombotic risk that benefited from extended post-discharge thromboprophylaxis.[101-103]

A group of five key bleeding risk factors (active cancer, dual antiplatelet therapy at baseline, a history of any bleeding or active gastroduodenal ulcer within 3 months of hospitalization, and bronchiectasis or pulmonary cavitation) excluded approximately 20% of the overall MAGELLAN population. In the remaining subpopulation the rate of major bleeding and fatal bleeding both in-hospital and in the extended post-discharge phase of the trial was reduced by approximately 50% and there were no longer statistically significant (RR 1.48, 95% CI 0.77 to 2.84) key reductions in fatal bleeding.[101] In this low bleed risk MAGELLAN subpopulation, **an IMPROVE score of 4 or more or a score of 2-3 with elevated D-dimer >twice upper limit of normal predicted a nearly three-fold higher VTE risk population that benefited from extended thromboprophylaxis (RR 0.68, 95% CI 0.51 to 0.91; P=0.008)**.[102] A further subgroup analysis of the same **low bleed risk MAGELLAN subpopulation of patients with congestive heart failure (NYHA Stage III or IV) revealed a 36% reduction in total VTE (RR 0.64, 95% CI 0.44 to 0.93; P=0.018),** without an increase in major bleeding (RR 1.67, 95% CI 0.61 to 4.56; P=0.316).[85]

Individual high VTE risk factors such as age ≥75 years, a prior history of VTE or cancer, and elevated D-dimer >twice upper limit of normal, all predict high risk of VTE with net clinical benefit of extended thromboprophylaxis.[84, 103]

Additional benefits

Based on shared pathophysiologic mechanisms of thrombosis for VTE and atherothrombosis – especially against a background of antiplatelet therapy in many medically ill patients that may potentiate dual antithrombotic pathway inhibition[86, 104] extended thromboprophylaxis with a DOAC has been shown to reduce major and fatal thromboembolic events that include both arterial thromboembolism as well as VTE.[50-53]

Extended duration **betrixaban reduced all-cause stroke and TIA by 41% (RR: 0.59, 95% CI: 0.35 to 0.97; P=0.034)** while extended **duration rivaroxaban in a pre specified analysis of the MARINER trial reduced a composite of symptomatic VTE, MI, stroke, and CV death by 28% (HR: 0.72, 95% CI: 0.52 to 1.00; P=0.049)**.[50, 52]

The health implications of a strategy of extended post-discharge thromboprophylaxis in low bleeding risk medical inpatients implies that we can prevent 20 to 63 major and fatal thromboembolic events per 10,000 patients at a cost of 0 to 8 major and fatal bleeds, and that these treatment effects are more robust the longer one administers extended thromboprophylaxis.[53] Such a strategy may prevent in the US and EU alone 12,000 major and fatal thrombotic events at a cost of one half to one-fourth of that number in major and fatal bleeds.[101]

Health-system wide implementation of thromboprophylaxis

Despite evidence supporting pharmacologic thromboprophylaxis, prophylaxis is underutilized in medical patients compared with surgical patients.[38, 105-108] The exact reasons why VTE prophylaxis is so frequently withheld in high-risk patients are not clear. In the ENDORSE study, which was a global cross-sectional study[109, 110] patients were enrolled from 358 hospitals in 32 countries across six continents. Of these patients, about half were judged to be at moderate to high risk for developing VTE. Although VTE prophylaxis rates were low, surgical patients received guideline recommended VTE prophylaxis more often than medical patients (58% *vs.* 40%).[109] Among the 9257 U.S. patients from 81 hospitals enrolled in ENDORSE, there was wide variation in VTE prophylaxis practices.[110] Even when VTE pharmacological prophylaxis is ordered for hospitalized patients, these orders are not necessarily carried out. In one study, patient refusal was the most

common reason for lack of injectable VTE anticoagulant medication adherence.[111] This high refusal rate for the use of parenteral thromboprophylaxis was confirmed in subsequent studies of medically ill patients.[111, 112]

All hospitalized medical patients should be assessed for risk of VTE, and those with high individual VTE risk factors or those that meet score thresholds using validated VTE risk models such as Padua and IMPROVE VTE should receive pharmacologic thromboprophylaxis.[38, 113]

There are diverse approaches to improve clinical effectiveness of VTE prophylaxis among hospitalized medical patients.[114] One approach is that of a multipronged quality improvement initiative at a health system or national level utilizing formalized VTE risk assessment, supporting resources, and audit feedback that has shown to improve rates of pharmacological thromboprophylaxis and at least in one national initiative – the UK prevention program – reduced fatal PE.[92, 115] Hospital staff can screen for at risk patients not on prophylaxis and alert the responsible physician with a telephone call or page.[116] Pharmacist-led multifaceted intervention management programs have been shown to substantially reduce preventable VTE from 18.6 to 4.9 per 1000 patient discharges, *i.e.*, by 74% (95% CI: 44 to 88%).[117] However, these efforts are labor intensive and costly.

Advanced health informatics with clinical decision support incorporated into clinician workflow has the potential to improve rates of thromboprophylaxis by adopting evidence-based practice and ultimately improve outcomes.[118] Computerized decision support with a single screen electronic alert can remind the responsible physician to order VTE prophylaxis.[119] A RCT showed that this approach had reduced the symptomatic VTE rate by more than 40%.[108] Multi-screen alerts may be more effective than single screen alerts[120] and maintain their effectiveness over time.[117] A recent large cluster RCT utilizing an agnostic electronic health record clinical decision support tool that incorporated the IMPROVE-DD VTE score revealed high adoption rates (77.8%) that significantly improved rates of in-hospital thromboprophylaxis by 52%, at discharge extended thromboprophylaxis by 93%, and reduced major thromboembolism by 29% without an increase in major bleeding, although all-cause mortality was increased in the intervention group that included more patients with COVID-19.[121]

Recommendations

Acutely ill medical patients

All acutely ill medical patients in ward and critical care settings. with acute congestive heart failure NYHA class III/IV, respiratory disease (respiratory failure with or without ventilation or exacerbation of respiratory disease), active cancer requiring therapy, acute infective disease including severe infection and sepsis, rheumatic and inflammatory disease, ischemic stroke, or acute myocardial infarction **should have formalized VTE risk assessment on admission and considered for in-patient thromboprophylaxis (Level of evidence high, recommendation strong)**.

For acutely ill medical patients with high individual risk factors for VTE (*i.e.*, prior history of VTE, acute infection, malignancy, advanced age >75 years, congestive heart failure, stroke, immobility, history of thrombophilia, obesity, ICU stay, lower limb paralysis, reduced mobility or D-dimer twice the upper limit of local laboratory normal) **or with minimum score thresholds utilizing validated VTE RAMs** (*i.e.*, PADUA VTE score of 4 or more; IMPROVE or IMPROVE-DD VTE score of 2 or more), in-hospital prophylaxis with **LMWH (enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) (Level of evidence high, recommendation strong)** is recommended, provided that patients do not have high bleed risk based on individual bleed risk factors or utilizing a validated Bleed RAM (*i.e.*, IMPROVE Bleed score <7). **If LMWH is not available, LDUH 5000 IU twice daily or three times a day for 6-14 days** is recommended. Single daily doses of 2.5 mg of fondaparinux or 10 mg of rivaroxaban are an alternative **(Level of evidence moderate, recommendation moderate)**. LMWH is preferable to LDUH because it requires one injection per day, is associated with less hemorrhagic complications and less HIT. Fondaparinux is also given as one injection per day and is associated with less HIT than LDUH. Rivaroxaban is orally administered.

Formalized VTE risk assessment should be considered at discharge as well, especially in health systems with a reduced hospital length of stay for medically ill patients **(Level of evidence high, recommendation strong)**. **Extended duration of thromboprophylaxis with LMWH (enoxaparin 40 mg once daily) or rivaroxaban 10 mg daily for approximately 30 days** may be considered on an individual basis **(Level of evidence moderate, recommendation moderate)** provided that patients do not have high bleed risk factors and that they are at high thrombotic risk, either utilizing individual high VTE risk factors (*i.e.*, age ≥75 years, a prior history of VTE or cancer, and elevated D-dimer > twice upper limit of normal) or minimum high risk score thresholds utilizing validated VTE RAMs (*i.e.*, IMPROVE or IMPROVE-DD VTE scores of 4 or more) (note: at the time of writing, September 2023,

rivaroxaban had been approved for this indication by the FDA in the US but not approved by EMA in EU).

Health informatics technology in the form of electronic alerts or clinical decision support tools may be considered to identify these key populations that may benefit from in-hospital and extended pharmacologic thromboprophylaxis (**Level of evidence moderate, recommendation moderate**).

Patients with hemorrhagic stroke

In patients with suspected or proven hemorrhagic stroke and in those with ischemic stroke in whom the risks of prophylactic anticoagulant therapy are perceived to outweigh the benefits, **IPC combined with GEC** is recommended **(Level of evidence moderate, recommendation strong)**. This recommendation is based on extrapolation of data from trials in neurosurgical patients,[122-125] and surgical patients,[126, 127] one randomized controlled study in patients with ischemic hemorrhagic stroke,[82] and one in patients with both ischemic and hemorrhagic stroke.[78]

Critically ill patients

In critically ill patients **LMWH** (*i.e.*, dalteparin as per label) is recommended **(Level of evidence high, recommendation strong)**.

For patients with contraindications to pharmacologic prophylaxis, the use of **GEC stockings with IPC** is an alternative **(Level of evidence moderate, recommendation strong)**.

For patients with contraindications to any thromboprophylaxis, **surveillance with duplex scanning is** indicated **(Level of evidence low, recommendation weak)**.

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SECTION 11

Prevention in patients with cancer

The risk

Thrombotic risk

Venous thromboembolism (VTE) is a clinically important and potentially fatal complication in patients with cancer, who have a sevenfold increased risk of VTE compared with patients without malignancy.[1] The results of a record-linkage study of 66,329 patients showed an overall cumulative incidence of VTE of 1.23% in the first six months after cancer diagnosis with a risk of recurrence within six months of the first thrombotic event of 1.84% compared with 0.39% in cancer patients without a prior thrombotic event.[2] The risk of VTE varies with the type of malignancy. Six months after diagnosis of cancer, the highest rates reported were in patients with bone (37.7 per 1000), ovarian (32.6 per 1000), brain (32.1 per 1000), and pancreatic tumors (22.7 per 1000).[2] The risk for developing VTE in cancer patients undergoing surgery is approximately twice that for patients without cancer,[3-5] and PE has been cited as the most common cause of death among patients undergoing general, urologic or gynecologic surgery for cancer.[6] For patients with solid tumors, the risk of VTE is greater in the presence of metastatic disease compared with patients with only local disease.[1, 2, 7]

Studies consistently show a higher risk of VTE during the first six months of cancer diagnosis, decreasing rapidly thereafter.[1, 7, 8] This early risk is likely to be related to the use of cancer treatments, especially chemotherapy and hormonal therapy.[1, 2, 9, 10] In a breast cancer prevention trial where women at high risk for the development of cancer were randomized to placebo or hormone therapy with tamoxifen, the rate of DVT was 0.84 per 1000 for women receiving placebo compared with 1.34 per 1000 in those receiving tamoxifen (RR: 1.6, 95% CI: 0.91 to 2.86).[11] Corresponding rates for PE were 0.23 per 1000 and 0.69 per 1000 (RR: 3.0, 95% CI: 1.15 to 9.27). Increasing disease burden in breast cancer is associated with an increased risk of therapy-associated thrombosis, with rates ranging from 1% in node-negative disease to 17% for advanced disseminated malignancy.[12-17] Rates for other tumor stages or types are summarized in Table 11.I,[12-14, 16-18] Table 11.II.[7, 8, 10, 19-23]

The Stockholm surgical studies evaluated potential benefits or harms from preoperative radiotherapy to reduce local recurrence in patients with rectal cancer undergoing operative intervention. Patients who received radiotherapy (RT) had a higher frequency of VTE within three months

TABLE 11.I.—*Incidence of thrombosis in early-stage breast cancer.*

Study	Treatment	Number of patients	Patients with thrombosis %
Node negative			
Fisher 1990[14]	T	1318	0.9
	Placebo	1326	0.15
	CMFT	768	4.2
	T	771	0.8
Node positive			
Levine 1988[13]	CMFVP	102	8.8
	CMFVP + AT	103	4.9
Pritchard 1996[17]	CMF + T	353	9.6
	T	352	1.4
Clahsen 1994[16]	Perioperative FAC	1292	2.1
Rivkin 1994[18]	No Rx	1332	0.8
	CMFVP + T	303	3.6
	CMFVP	300	1.3
Fisher 1990[14]	T	295	0
	ACT	383	3.1
Weiss 1981[12]	T	367	1.6
	CMFVP	143	6.3
	CMF	144	3.5

A: Adriamycin; C: cyclophosphamide; F: fluorouracil; M: methotrexate; P: prednisone; T: tamoxifen; V: vincristine.

TABLE 11.II.—*Incidence of venous thrombosis in patients with different tumors.*

Study	Tumor type	Patients (N.)	Cumulative incidence of VTE (%)	Follow-up
Alcalay *et al.* 2006[8]	Colorectal	68 142	3.1	2 years
Caruso *et al.* 2010[10]	Lymphoma	18 018	5.3	1-3 years
	Non-Hodgkin	997	6.5	1-3 years
	Hodgkin	2505	4.7	1-3 years
Tateo *et al.* 2005[19]	Ovarian	253	16.6 (6.4% during chemotherapy)	12 years
Brandes *et al.* 1997[20]	Malignant glioma	77	26	
Weijl *et al.* 2000[21]	Germ cell	179	8.4	
Chew *et al.* 2006[7]	Prostate (localized)	33 383	1.0	2 years
	Prostate (regional)	7041	1.3	2 years
	Prostate (remote)	3515	1.2	2 years
	Breast (localized)	27 014	0.8	2 years
	Breast (regional)	13 629	1.3	2 years
	Breast (remote)	2029	2.6	2 years
	Uterus (localized)	6437	1.2	2 years
	Uterus (regional)	1302	2.2	2 years
	Uterus (remote)	598	4.8	2 years
	Lung (localized)	6558	1.3	2 years
	Lung (regional)	8775	2.2	2 years
	Lung (remote)	22 486	2.4	2 years
Jacobson *et al.* 2009[22]	Cervical cancer	436	11.7	7 years
Jacobson *et al.* 2005[23]	Invasive cervical cancer + chemoradiation	48	16.7	≥8 months

of therapy and surgery compared with those who did not (7.5% *vs.* 3.5%).[24] In a large cohort involving 66,329 patients with cancer, those who underwent chemotherapy as initial treatment were at increased risk of VTE compared with those who did not receive this therapy (RR: 2.2, 95% CI: 1.8 to 2.7), whereas there was no increased risk among patients undergoing radiotherapy (RR: 0.7, 95% CI: 0.6 to 0.9) or surgery (RR: 1.0, 95% CI: 0.8 to 1.2).[2]

Despite the use of venous thromboprophylaxis, patients with malignancy remain at risk of a thrombotic event. In a *post-hoc* analysis of a randomized study involving 23,078 patients undergoing surgery lasting more than 30 minutes who received heparin thromboprophylaxis, autopsy data showed that fatal PE was more common among patients with cancer compared with non-cancer patients (0.33% *vs.* 0.09%; P=0.0001) at 14 days post-prophylaxis.[25]

Risk assessment models and their performance

A VTE risk assessment model for ambulatory cancer patients requiring chemotherapy developed by Khorana *et al.* in 2008 has been validated in multiple outpatient cancer groups.[26] Five predictive variables were identified in a multivariable model namely site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet count of 350x10^9/L or more, hemoglobin less than 100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents, leukocyte count more than 11x10^9/L, and Body Mass Index of 35 kg/m^2 or more (1 point each). Rates of VTE in the derivation and validation cohorts respectively, were 0.8% and 0.3% in low-risk (score=0), 1.8% and 2% in intermediate-risk (score=1-2), and 7.1% and 6.7% in high-risk (score≥3) category over a median of 2.5 months (C-statistic=0.70 for both cohorts). This model can identify patients with a nearly 7% short-term risk of symptomatic VTE and may be used to select cancer outpatients who would benefit from thromboprophylaxis.

Although it is the most validated tool for VTE in cancer patients, the discriminatory performance of the Khorana Score is not equally reliable in all types of cancers. For this reason, new scores have been proposed such as the modified Khorana Score, the CATS Score, the ONKOTEV Score, the Thrombosis-Lymphoma Predictive Score, the SAVED Score, the IMPEDE VTE Score and the COMPASS-CAT Score which, were evaluated in several studies.[27-32]

In the Vienna Cancer and Thrombosis Study (CATS), the Khorana risk scoring model was expanded by incorporating 2 biomarkers: soluble P-selectin, and D-Dimer.[27] In this study, which included 819 patients, 61 (7.4%) patients experienced VTE during a median follow-up of 656 days. The cumulative VTE probability in the original risk model after 6 months was 17.7% in patients with the highest risk score ≥3, (N.=93), 9.6% in those with score 2 (N.=221), 3.8% in those with score 1 (N.=229), and 1.5% in those with score 0 (N.=276). In the expanded risk model, the cumulative VTE probability after 6 months in patients with

the highest score (≥5, N.=30) was 35.0% and 10.3% in those with an intermediate score (score 3, N.=130) as opposed to only 1.0% in patients with score 0 (N.=200); the Hazard Ratio (HR) of patients with the highest compared with those with the lowest score was 25.9, 95% CI: 8.0 to 84.6. Thus, the modification of the Khorana score by the addition of two biomarkers enabled better prediction of VTE and allowed better identification of cancer patients at high or low risk of VTE.

The ONKOTEV Study prospectively evaluated 843 patients with active cancers, collecting clinical and laboratory data.[28] All the patients were screened with duplex ultrasound of the upper and lower limbs to evaluate the incidence of DVT (both asymptomatic and symptomatic). The Khorana risk model for VTE was also explored in this study population. The presence of metastatic disease, compression of vascular/lymphatic structures by tumor, a history of previous VTE, and a Khorana Score >2 were the risk factors significantly associated with VTE on univariate analysis and further confirmed in the multivariable analysis. The time-dependent receiver operating characteristic (ROC) curve analysis showed a significant improvement in the area under the curve of the new score over the Khorana model at 3 months (71.9% *vs.* 57.9%; P=0.001), 6 months (75.4% *vs.* 58.6%, P<0.001), and 12 months (69.8% *vs.* 58.3%; P=0.014).

The Thrombosis-Lymphoma Predictive Score was developed in a study population of 1820 lymphoma patients.[29] The variables independently associated with increased risk for thromboembolism were: previous venous and/or arterial events, mediastinal involvement, BMI>30 kg/m^2, reduced mobility, extranodal localization, development of neutropenia and hemoglobin level <100 g/L. Based on the risk model score, the population was divided into three risk categories: low (score: 0-1), intermediate (score: 2-3), and high (score: >3). For patients classified at intermediate and high-risk, there was a negative predictive value of 98.5%, a positive predictive value of 25.1%, a sensitivity of 75.4%, and a specificity of 87.5%. A high-risk score had a positive predictive value of 65.2%. The authors concluded that the Thrombosis-Lymphoma Score was more specific for lymphoma patients than any other available score targeting thrombosis in cancer patients.

VTE is a common cause of morbidity and mortality among patients with multiple myeloma (MM). The International Myeloma Working Group (IMWG) developed guidelines recommending primary thromboprophylaxis, in those identified at high-risk of VTE by the presence of risk factors. The National Comprehensive Cancer Network (NCCN) has adopted these guidelines. A clinical study aimed to derive and validate a new risk assessment model for immunomodulatory drug (IMiD) associated VTE was then performed.[30] The final risk assessment model, named as the "SAVED" Score, included 5 clinical variables: prior surgery, Asian race, VTE history, age ≥80 years, and dexamethasone dose. The model stratified approximately 30% of patients as high-risk in both the derivation and the validation cohorts. Hazard ratios (HRs) were 1.85 (P<0.01) and 1.98 (P<0.01) for high- *vs.* low-risk groups in the derivation and validation cohorts, respectively. In contrast, the method of stratification recommended in the NCCN Guidelines for cancer-associated VTE, had HRs of 1.21 (P=0.17) and 1.41 (P=0.07) for the corresponding risk groups in the 2 datasets. The authors concluded that the SAVED Score outperformed the NCCN Guidelines score for risk-stratification of patients with MM receiving IMid therapy.

The IMPEDE VTE score (Immunomodulatory agent; Body Mass Index ≥25 kg/m^2; pelvic, hip or femur fracture; erythropoietin stimulating agent; dexamethasone/doxorubicin; Asian ethnicity/race; VTE history; tunneled line/central venous catheter; existing thromboprophylaxis) has shown a satisfactory discrimination in the derivation cohort comprised of 4446 patients within the Veterans Administration Central Cancer Registry, C-statistic =0.66.[31] Risk of VTE significantly increased as the score increased (HR: 1.20; P<0.0001). Within the external validation cohort comprised of Surveillance, Epidemiology, End Results (SEER)-Medicare database (N.=4256), IMPEDE VTE had a C-statistic of 0.64. For comparison, when evaluating the performance of the IMWG/NCCN guidelines, the C-statistic was 0.55. In summary, the IMPEDE VTE score outperformed the IMWG/NCCN guidelines score and was recommended as a new standard risk stratification for VTE.

The COMPASS-CAT Score was derived from a cohort of 1023 patients with cancer not receiving thromboprophylaxis.[32] Documented symptomatic VTE was the endpoint. It included patients with breast (61%), colorectal (17%), lung (13%), or ovarian cancer (8.6%) at localized (30%) or advanced stage (70%). Symptomatic VTE occurred in 8.5% of patients. The following variables were used: a) anthracycline or anti-hormonal therapy; b) time since cancer diagnosis; c) central venous catheter; d) stage of cancer; e) presence of cardiovascular risk factors; f) recent hospitalization for acute medical illness; g) personal history of VTE, and h) platelet count. At 6 months, patients stratified at low/intermediate and high-risk groups had VTE rates of

1.7% and 13.3%, respectively. The area under the curve of ROC analysis was 0.85. The sensitivity and specificity were 88% and 52%, respectively. The negative and positive predictive values of the RAM were 98% and 13% respectively. An external validation study included 3,814 patients with invasive breast, ovarian, lung or colorectal cancer in which 5.85% developed VTE at six months.[33] Patients stratified into low/intermediate- and high-risk groups had VTE rates of 2.27% and 6.31%, respectively. The sensitivity, specificity, and negative and positive predictive value of the RAM were 95%, 12%, 97.73%, and 6.31%, respectively. Diagnostic accuracy via ROC curve was calculated at 0.62 of the area under the curve.

Prophylactic methods

A. Prophylaxis in surgical patients with cancer

LDUH and LMWH

In surgical patients with malignancy, **LDUH** reduces the risk of DVT and fatal PE[15, 34-40] and **LMWH** is at least as effective as **LDUH**.[38-42] The intensity of peri-operative antithrombotic therapy in cancer patients has been assessed by several studies. In gynecologic oncology patients, **LDUH** twice a day demonstrated no benefit when compared with no prophylaxis,[43] whereas administration three times a day was effective (RR: 0.47, 95% CI: 0.22 to 0.98)[37] (see Section 5 on gynecologic surgery). In a study of 2,070 cancer patients, 65% of whom underwent laparotomy for malignant disease, two different doses of the LMWH (dalteparin sodium) were assessed.[44] The frequency of VTE was reduced from 14.9% in patients receiving 2,500 anti-Xa IU to 8.5% in patients receiving 5000 units once daily (RR: 0.52, 95% CI: 0.37 to 0.74) without any significant increase in peri-operative bleeding complications.

Fondaparinux *vs.* LMWH

In the PEGASUS RCT the efficacy of postoperative **fondaparinux was compared with LMWH** (dalteparin) started preoperatively in surgical patients with high prevalence of cancer (69%).[45] In the surgical patients the overall VTE rate in the fondaparinux group was 4.6% compared with 6.1% in the dalteparin group (Odds Ratio reduction =25.8%; P=0.14). In the cancer surgery subgroup, the prevalence of VTE was 4.7% in the patients receiving fondaparinux compared with 7.7% in the dalteparin group (major bleeding 3.4% in fondaparinux treated patients and 2.4% for dalteparin group).

Continuation of thromboprophylaxis for 4 weeks in surgical patients

In a double-blinded multicenter study involving 332 patients undergoing planned curative open surgery for abdominal or pelvic cancer received enoxaparin (40 mg daily) for 6 to 10 days and were then randomly assigned to receive either enoxaparin or placebo for another 21 days.[46] Bilateral venography was performed between days 25 and 31, or sooner if symptoms of venous thromboembolism occurred. The primary end point with respect to efficacy was the incidence of VTE between days 25 and 31. This approach has been shown to reduce the risk of asymptomatic DVT from 13.8% to 5.5% (RR: 0.36, 95% CI: 0.16 to 0.79) and VTE from 12.0% in the placebo group to 4.8% in the enoxaparin group (P=0.02). There were no significant differences in the rates of bleeding or other complications during the double-blind or follow-up periods.

In another randomized, double-blind study (CANBESURE), 625 patients admitted for abdominal or pelvic surgery for cancer received bemiparin once daily for eight days followed by either bemiparin or placebo for 20 days.[47] While extended thromboprophylaxis with bemiparin did not result in an improvement in the primary efficacy endpoint of venographically detected DVT, non-fatal PE and all-cause mortality, the incidence of major VTE (proximal DVT, non-fatal PE and VTE-related deaths) was decreased (0.80% *vs.* 4.6%; RRR: 82.4%, 95% CI: 21.5 to 96.1%; P=0.010) without any increase in major bleeding complications.

Another randomized study investigated the efficacy and safety of antithrombotic prophylaxis with LMWH given for one week or four weeks in patients undergoing laparoscopic surgery for colorectal cancer.[48] VTE occurred in 11 of 113 patients randomized to one week (9.7%) and in none of the 112 patients randomized to extended LMWH prophylaxis (P=0.001). The rate of bleeding was similar in the two treatment groups. Two patients died during the study period, one in each treatment group. This study showed that extended antithrombotic prophylaxis was safe and reduced the risk for VTE compared with prophylaxis after laparoscopic colorectal cancer surgery.

An open-label, multi-center RCT compared the safety and efficacy of **apixaban** (2.5 mg twice daily) **or enoxaparin** (40 mg once daily) for four weeks in 400 postoperative women with gynecologic cancer.[49] **There were no statistically significant differences between the apixaban and enoxaparin groups** in terms of rates of major bleeding events, clinically relevant non-major bleeding events, VTE events, adverse events, medication adher-

ence, or quality of life between the groups. Participant satisfaction was significantly greater in the apixaban group regarding ease of taking the medication and pain. This study suggested that oral apixaban is a potentially safe, less painful, and easier-to-take alternative to subcutaneous enoxaparin for thromboprophylaxis after surgery for gynecologic cancer.

In a double-blind placebo-controlled study (PROLAPS II), consecutive patients who had laparoscopic surgery for colorectal cancer were randomized to receive **rivaroxaban** (10 mg once daily) or a **placebo** to be started at 7±2 days after surgery and given for the subsequent three weeks.[50] All patients received LMWH from surgery to randomization. The primary study outcome was the composite of symptomatic objectively confirmed VTE, asymptomatic ultrasonography-detected deep vein thrombosis (DVT), or VTE-related death at 28±2 days after surgery. The primary safety outcome was major bleeding. The primary study outcome event occurred in 11(3.9%) of 282 patients in the placebo group compared with 3(1.0%) of 287 in the rivaroxaban group (OR 0.26, 95% CI: 0.07 to 0.94; log-rank P=0.032). Major bleeding occurred in none of the patients in the placebo group and two patients in the rivaroxaban group.

Rivaroxaban *vs.* LMWH

In a recent study (VALERIA), patients undergoing major gynecological cancer surgery who had thromboprophylaxis with LMWH during hospitalization were randomized at hospital discharge to receive rivaroxaban 10 mg once daily or enoxaparin 40 mg once daily for 30 days.[51] The primary efficacy outcome (combination of symptomatic VTE and VTE-related death or asymptomatic VTE at day 30) occurred in 3.51% of patients assigned to rivaroxaban and in 4.39% of patients assigned to enoxaparin (RR: 0.80, 95% CI: 0.22 to 2.90; P=0.7344). Patients assigned to rivaroxaban had no primary bleeding event, and 3 patients (2.63%) in the enoxaparin group had a major or CRNM bleeding event (HR: 0.14, 95% CI: 0.007 to 2.73; P=0.1963). Although, the power was limited due to not reaching the intended sample size of 440 patients, the authors concluded that the results supported the hypothesis that DOACs might be an attractive alternative strategy to LMWH to prevent VTE in this high-risk population.[49]

Systematic reviews and meta-analyses

A systematic review published in 2008 comparing the relative efficacy and safety of four weeks' therapy *vs.* in hospital LMWH thromboprophylaxis confirmed the **reduction in asymptomatic DVT in cancer patients undergoing major abdominal or pelvic surgery (RR: 0.21, 95% CI: 0.05 to 0.94)**. However, extended thromboprophylaxis was associated with increased bleeding at four weeks (RR: 2.94, 95% CI: 0.12 to 71.85) and failed to demonstrate a reduction in death at three months (RR: 0.49, 95% CI: 0.12 to 1.94).[52]

A systematic review and meta-analysis evaluating the efficacy and safety of extended and conventional thromboprophylaxis in 2018 revealed that **extended prophylaxis with LMWH after major abdominal and pelvic surgery decreased postoperative VTE, DVT, and proximal DVT rates without increased postoperative bleeding**.[53] The NNT to prevent VTE, overall DVT, and proximal DVT were 14, 14, and 44, respectively. Cases of postoperative symptomatic PE were rare, and the incidence was similar in both groups. In addition, the **extended prophylaxis with LMWH was associated with a decrease in asymptomatic VTE**. The evidence regarding the impact of extended thromboprophylaxis on PE was sparse because of the overall low incidence.

B. Prophylaxis in medical patients with cancer

VKA

In a prospective study of 311 ambulant cancer patients with metastatic breast cancer receiving chemotherapy, patients were randomized to **low dose warfarin** (INR between 1.3 and 1.9) **or placebo**.[54] The frequency of symptomatic VTE was reduced from 4.5% with placebo to 0.8% with warfarin (P=0.038, Fisher's Exact Test) (RR: 0.14, 95% CI: 0.02 to 1.18).

LMWH

In a double blind RCT in ambulatory patients with metastatic or locally advanced cancer, 1150 patients received either the **LMWH nadroparin** (3800 IU anti-Xa once daily) **or placebo**.[55] The rate of symptomatic venous or arterial events was halved in the LMWH group (2.0% for nadroparin *vs.* 3.9% for placebo; single-sided P=0.02) with similar reductions in events reported for VTE (1.4% *vs.* 2.9%, respectively). The rate of major bleeding events did not differ between treatment groups (0.7% *vs.* 0%, respectively; two-sided P=0.18).

A large study **compared subcutaneous semuloparin 20 mg once daily with placebo** for ambulatory cancer patients receiving chemotherapy.[56] The median treatment duration was 3.5 months. **VTE occurred in 20 (1.2%) of 1608 patients receiving semuloparin, compared with 55 (3.4%) of 1604 receiving placebo (RR: 0.36, 95% CI:**

0.21 to 0.60), with consistent efficacy among subgroups defined according to the origin and stage of cancer and the baseline risk of VTE. The incidence of clinically relevant bleeding was 2.8% and 2.0% in the semuloparin and placebo groups respectively (RR: 1.40; 95% CI: 0.89 to 2.21). Major bleeding occurred in 19 (1.2%) of 1589 patients receiving semuloparin and 18 (1.1%) of 1583 receiving placebo (RR: 1.05, 95% CI: 0.55 to 1.99).

In another prospective, open-label, randomized, multicenter study (CONKO-004 Trial), histologically proven advanced pancreatic cancer involving 312 patients were randomly assigned to **ambulant first-line chemotherapy and prophylactic use of enoxaparin or chemotherapy alone** to investigate potential reduction in symptomatic VTEs and impact on survival.[57] Within the first 3 months, **15 of 152 patients in the control group and two of 160 patients in the enoxaparin group developed symptomatic VTE (HR: 0.12, 95% CI: 0.03 to 0.52; P=0.001)**. Major bleeding events occurred in five of 152 patients in the observation arm and seven of 160 patients in the enoxaparin arm (HR: 1.4, 95% CI: 0.35 to 3.72; P=1.0). Overall cumulative incidence rates of symptomatic VTEs were 15.1% (observation) and 6.4% (HR: 0.40, 95% CI: 019 to 0.83; P=0.01).

In the FRAGEM study, 123 patients with advanced pancreatic cancer were randomized to receive either **gemcitabine alone or gemcitabine in combination with weight-adjusted dalteparin for 12 weeks. The incidence of all-type VTE** during the treatment period (<100 days from randomization) **was reduced from 23% in the control group to 3.4% in the dalteparin group (P=0.002)**, without an appreciable increase in the hemorrhagic risk.[58]

In the FRAGMATIC study, 2202 patients with newly diagnosed lung cancer of any stage and histology were randomized to receive standard treatment alone or associated with **prophylactic doses of enoxaparin and were followed-up for up to six months**.[59] While there was no evidence of a difference in overall or metastasis-free survival between the two arms (primary study endpoint), **there was a reduction in the incidence of VTE from 9.7% to 5.5% (P=0.001) in the LMWH arm**, with a statistically not significant increase in the composite of major and clinically relevant non-major bleeding.

Another randomized, double-blinded, phase 2 trial evaluated the **fixed-dose (40 mg daily) and weight-adjusted dose (1 mg/kg daily) of enoxaparin** in hospitalized patients with active cancer at high risk of developing VTE based on Padua risk score.[60] There were no major hemorrhages or symptomatic VTE in either arm. There was only 1 incidentally identified PE that occurred in the weight-adjusted arm. The cumulative incidence of DVT was 22% (90% CI: 0% to 51.3%). This phase 2 trial has shown that weight adjusted LMWH thromboprophylaxis was feasible and well-tolerated in high risk hospitalized cancer patients.

Apixaban

A placebo-controlled, double-blind RCT (AVERT) assessed the efficacy and safety of **apixaban (2.5 mg twice daily for 180 days)** for thromboprophylaxis in ambulatory patients with cancer who were at intermediate-to-high risk for VTE (Khorana score ≥2) and were starting chemotherapy.[61] **VTE occurred in 12 of 288 patients (4.2%) in the apixaban group and in 28 of 275 patients (10.2%) in the placebo group (HR 0.41, 95% CI: 0.26 to 0.65; P<0.001)**. In the modified intention-to-treat analysis, major bleeding occurred in 10 patients (3.5%) in the apixaban group and in 5 patients (1.8%) in the placebo group (HR: 2.00, 95% CI: 1.01 to 3.95, P=0.046). During the treatment period, major bleeding occurred in 6 patients (2.1%) in the apixaban group and in 3 patients (1.1%) in the placebo group (HR: 1.89, 95% CI: 0.39 to 9.24). Apixaban therapy resulted in a significantly lower rate of VTE than did placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy. The rate of major bleeding episodes was higher with apixaban than with placebo.

A *post-hoc* analysis of the AVERT trial assessed the efficacy and safety of using thromboprophylaxis with **apixaban (2,5 mg twice daily)** in patients with gastrointestinal cancer.[62] **At 180 days, VTE occurred in 3 (4.6%) patients in the apixaban group and 13 (20%) patients in the placebo group (HR: 0.27, 95% CI: 0.13 to 0.54; P=0.0002)**. Major bleeding occurred in 2 (3.1%) patients in the apixaban group and 1 (1.5%) patient in the placebo group (HR: 2.39, 95% CI: 0.29 to19.78, P=0.42). None of the major bleeding events occurred in patients with upper gastrointestinal or colorectal cancers. Primary thromboprophylaxis with apixaban therapy seems to be safe and effective in patients with gastrointestinal cancers. Major bleeding complications were uncommon in patients with gastrointestinal cancers.

Rivaroxaban

A double-blind, RCT (CASSINI) involved intermediate to high-risk 841 ambulatory patients with cancer (Khorana Score of ≥2) and randomly assigned patients without DVT at whole limb screening to receive **rivaroxaban 10 mg daily or placebo** for up to 180 days, with further screening

at 8 weeks, 16 weeks and 180 days.[63] Premature discontinuation of therapy occurred in 47% of patients. The primary end point of symptopmatic and asymptomatic VTE occurred in 25(6.0%) of 420 patients in the rivaroxaban group and in 37(8.8%) of 421 in the placebo group (HR: 0.66, 95% CI: 0.40 to 1.09; P=0.10) in the period up to day 180. In the prespecified intervention-period analysis (from start to end of therapy), **the primary end point occurred in 11 patients (2.6%) in the rivaroxaban group and in 27 (6.4%) in the placebo group (HR: 0.40, 95% CI: 0.20 to 0.80)**. Major bleeding occurred in 8 of 405 patients (2.0%) in the rivaroxaban group and in 4 of 404 (1.0%) in the placebo group (HR: 1.96, 95% CI: 0.59 to 6.49). In high-risk ambulatory patients with cancer, treatment with rivaroxaban did not result in a significantly lower incidence of VTE or death due to venous thromboembolism in the 180-day trial period. During the intervention period, rivaroxaban led to a substantially lower incidence of such events, with a low incidence of major bleeding.

A *post-hoc* analysis of the CASSINI trial evaluated the efficacy and safety of **rivaroxaban in patients with and without gastric/gastroesophageal junction (G/GEJ) tumors**.[64] In patients with G/GEJ tumors, the rates for the primary efficacy endpoint were 3.4% for rivaroxaban *vs.* 6.9% for placebo (HR: 0.45, 95% CI: 0.11 to 1.80). In patients with non-G/GEJ tumors, the rivaroxaban group had a lower risk of the primary end point (6.6% *vs.* 9.3%) (HR: 0.70, 95% CI: 0.40 to 1.21). Rates of major bleeding in patients with G/GEJ tumors were 4.6% (4/88) *vs.* 1.2% (1/85) for rivaroxaban and placebo; rates in patients with non-G/GEJ tumors were 1.3% (4/317) *vs.* 0.9% (3/319), respectively. Excluding patients with G/GEJ tumors resulted in a definable population of cancer patients who achieved an improved benefit-risk balance from rivaroxaban prophylaxis.

The RHESO observational study

In a prospective, observational study (RHESO Study) in 22 French palliative care units, the most common reason for palliative care was cancer (90.7%).[65] The cumulative incidence of clinically relevant bleeding was 9.8% (95% CI: 8.3 to 11.6). Symptomatic DVT occurred in six patients (cumulative incidence of 0.5%, 95% CI: 0.2 to 1.1). Cancer, recent bleeding, antithrombotic prophylaxis and antiplatelet therapy were independently associated with clinically relevant bleeding at 3 months. The authors concluded that the decisions regarding the use of thromboprophylaxis in palliative care patients should consider the high risk of bleeding in these patients.

ASA

An open-label, multicenter RCT **compared aspirin (ASA) or fixed low-dose warfarin with LMWH** for preventing thromboembolism in patients with myeloma treated with thalidomide-based regimens.[66] In this study, compared with LMWH, the absolute differences were +1.3% (95% CI: -3.0% to 5.7%; P=0.544) in the ASA group and +3.2% (95% CI, -1.5% to 7.8%; P=0.183) in the warfarin group, showing a similar efficacy in reducing serious thromboembolic events, acute cardiovascular events, and sudden deaths by LMWH, except in elderly patients where warfarin showed less efficacy than LMWH.

Another open-label, RCT compared the efficacy and safety of low-dose ASA compared with LMWH in patients with newly diagnosed MM, treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone-lenalidomide consolidation.[67] In this study, the incidence of VTE was 2.27% in the ASA group and 1.20% in the LMWH group. Compared with LMWH, the absolute difference in the proportion of VTE was 1.07% (95% CI: −1.69 to 3.83; P=0.452) in the ASA group. Pulmonary embolism was observed in 1.70% of patients in the ASA Group and none in the LMWH group. No arterial thrombosis, acute cardiovascular events, or sudden deaths were reported. No major hemorrhagic complications were reported. The authors concluded that ASA could be an effective and less-expensive alternative to LMWH thromboprophylaxis in previously untreated patients with MM receiving lenalidomide with a low thromboembolic risk.

Systematic reviews and meta-analyses

The LA MAITRE meta-analysis of 2009

In a meta-analysis of three RCTs of patients with lung cancer, concomitant treatment with **warfarin** was associated with an increased risk of bleeding (OR: 1.7, 95% CI: 1.2 to 2.6) whereas no such association was apparent for **LMWH**.[68]

The Di Nisio meta-analysis of 2016

This was a Cochrane systematic review and meta-analysis which involved 26 trials with a total of 12,352 patients. It reported that, **LMWH significantly reduced the incidence of symptomatic VTE (RR: 0.54, 95% CI: 0.38 to 0.75)** with a non-statistically significant 44% higher risk of major bleeding events (RR: 1.44, 95% CI: 0.98 to 2.11) when compared with no thromboprophylaxis.[69] **LMWH was associated with a significant reduction in symptomatic VTE compared with warfarin (RR: 0.33, 95%**

CI: 0.14 to 0.83) in patients with multiple myeloma, while the difference between LMWH and aspirin was not statistically significant (RR: 0.51, 95% CI: 0.22 to 1.17). Major bleeding was observed in none of the participants treated with LMWH or warfarin and in less than 1% of those treated with aspirin. Warfarin was associated with a non-statistically significant reduction of symptomatic VTE (RR: 0.15, 95% CI: 0.02 to 1.20) when compared with placebo.

The Rutjes meta-analysis of 2020

An updated Cochrane meta-analysis has shown that **thromboprophylaxis with DOACs** (apixaban and rivaroxaban) **demonstrated a non-significant trend for a lower incidence of symptomatic VTE (RR: 0.43, 95% CI: 0.18 to 1.06),** (3 studies, 1526 participants with advanced metastatic cancer).[70]

LMWH reduced the incidence of symptomatic VTE (RR: 0.62, 95% CI: 0.46 to 0.83) (11 studies, 3931 participants; high-certainty evidence) **and increased the risk of major bleeding events (RR: 1.63, 95% CI: 1.12 to 2.35** (15 studies, 7282 participants; moderate-certainty evidence) **when compared with no thromboprophylaxis**.

In patients with MM, **LMWH resulted in lower symptomatic VTE compared with the vitamin K antagonist warfarin (RR: 0.33, 95% CI: 0.14 to 0.83)** (1 study, 439 participants). **LMWH compared with aspirin did not produce a significant reduction in symptomatic VTE (RR: 0.51, 95% CI: 0.22 to 1.17**) 2 studies, 781 participants).

Major bleeding was observed in none of the participants with MM treated with LMWH or warfarin and in less than 1% of those treated with aspirin.

When compared with placebo or no thromboprophylaxis, warfarin did not reduce symptomatic VTE (RR: 0.15, 95% CI: 0.02 to 1.20), (1 study, 311 participants) and did not result in a significant increase in major bleeding (RR: 3.82, 95% CI: 0.97 to 15.04), (4 studies, 994 participants).

The Alsubaie meta-analysis of 2021

The most recent meta-analysis assessed the efficacy and safety of DOACs for prophylaxis in hospitalized and ambulatory patients with cancer.[71] It included four studies on primary prevention (MAGELLAN, APEX, CASSINI, AVERT) with enoxaparin in two and placebo in two as control, and four additional studies for prevention with dalteparin as control.

In primary prevention, there was no difference between DOACs and LMWH or placebo regarding the occurrence of VTE events (RR: 0.69, 95%CI: 0.48 to 1.00). **The use of DOACs was associated with a 42% reduction in symptomatic VTE events when compared with LMWH or placebo (RR: 0.58, 95% CI: 0.37 to 0.91; NNT=45)**. The use of DOACs was associated with an incremental risk of major bleeding or CRNMB when compared with LMWH or placebo (RR: 1.57, 95% CI: 1.10 to 2.26; NNH=56).

In secondary prevention, the use of **DOACs was associated with a 38% reduction in VTE recurrence as compared with LMWH (RR: 0.62, 95%CI: 0.44 to 0.87; NNT=29)**. There was no difference between the use of DOACs or LMWH regarding major bleeding or CRNMB (RR: 1.36, 95% CI: 0.94 to 1.97).

The authors concluded that DOACs were associated with a lower risk of symptomatic VTE, but the risk of bleeding remains a considerable concern. Clinical decisions should be made by assessing individual patients' risk of VTE and bleeding.

C. Prophylaxis in patients with central venous catheters

Historical data suggest that cancer patients with central venous catheters (CVC) have a high risk for developing VTE. More recent studies suggest a low incidence of symptomatic catheter-related thrombosis of 5% or less,[72-75] but reported rates of venographically detected upper limb DVT in the absence of thromboprophylaxis, while highly variable, remain high (18%).[73, 76]

LMWH

The use of **LMWH** (dalteparin sodium 2500 U once daily) in cancer patients with central venous catheters has been shown to be **effective in reducing venographic thrombosis from 62% to 6% (RR: 0.04, 95% CI: 0.01 to 0.42)**.[77]

VKA

W**arfarin** (1 mg/day) has been shown to be **effective in reducing the risk of all venographic thromboses, from 37% to 9.5% (RR: 0.17, 95% CI: 0.05 to 0.59)**.[78]

LMWH *vs.* VKA

However, subsequent clinical trials evaluating **low dose warfarin, fixed dose warfarin** or **LMWH**[72-74, 79-83] as well as several meta-analyses[76, 84-92] have shown inconclusive results for routine thromboprophylaxis in this situation. This may be due to changes in the way that newer generations of catheters are inserted or maintained and improvements in catheter biocompatibility.

DOACs

A prospective two-center pilot RCT evaluated the safety and efficacy of **rivaroxaban (10 mg daily)** to prevent VTE complications in patients with active cancer and a newly inserted CVC.[93] Among 105 patients enrolled, VTE occurred in two (3.9%, 95% CI: 0.5 to 13.2) and 3 (5.7%, 95% CI: 1.2 to 15.7) patients in the rivaroxaban and control group, respectively (HR: 0.66, 95% CI: 0.11 to 3.9). One patient (1.9%) receiving rivaroxaban had a major bleeding event.

Another study involving 217 patients evaluated the efficacy and safety of thromboprophylaxis with apixaban in the subpopulation of patients with cancer and a CVC in the AVERT trial.[94] **VTE occurred in 6 (4.8%) patients in the apixaban group and 17 (18.7%) patients in the placebo group (HR: 0.26, 95% CI: 0.14 to 0.47; P<0.0001)**. Major bleeding occurred in 2 (1.6%) patients in the apixaban group and 2 (2.2%) patients in the placebo group (HR: 0.69, 95% CI: 0.20 to 2.35; P=0.556). Thus, primary thromboprophylaxis with apixaban in patients with cancer and CVC was associated with a reduced risk of VTE in the AVERT study population, without an increased risk of bleeding.

Systematic review and meta-analysis

A recent meta-analysis, which included 12 RCTs (3545 patients) using warfarin, LMWH and DOACs revealed that the **total rates of VTE were significantly lower in patients receiving thromboprophylaxis compared with those not receiving primary prevention (7.6% *vs.* 13%) (OR: 0.51, 95% CI: 0.32 to 0.82; P<0.01)**.[95] The rates of major bleeding complications were not higher in patients receiving thromboprophylaxis (0.9% *vs.* 0.6%) (OR: 1.12, 95% CI: 0.29 to 4.40, P=0.87). Primary thromboprophylaxis significantly reduced the risk of VTE without increasing the risk of major bleeding complications in patients with cancer and CVC. Future studies are needed to confirm these findings.

Recommendations

In surgical patients with cancer, **LMWH** (initiated and dosed according to manufacturer's recommendations) (**Level of evidence high, recommendation strong**) should be used. An alternative is **LDUH** (5000 IU three times per day commenced prior to operation) **(Level of evidence high, recommendation moderate)**.

In the post-discharge period prolonged thromboprophylaxis with **LMWH** (enoxaparin or dalteparin) for up to 4 weeks after operation **should be considered** especially in patients who are at high risk for VTE **(Level of evidence moderate, recommendation moderate)**.

In ambulatory cancer patients receiving chemotherapy, thromboprophylaxis should be based on the risk for VTE determined by the acute medical condition and comorbidities. In high risk (Khorana Score ≥2) ambulatory cancer patients, thromboprophylaxis with prophylactic dose **LMWH (Level of evidence high, recommendation strong), apixaban (Level of evidence moderate, recommendation moderate) or rivaroxaban (Level of evidence moderate, recommendation moderate)** should be considered for up to 6 months or longer.

In cancer patients hospitalized with **acute medical illness, prophylaxis with LMWH as in the group of the high-risk medical patients should be provided (Level of evidence high, recommendation strong)**.

LDUH, fondaparinux, and rivaroxaban may also be considered as less preferred alternatives **(Level of evidence moderate, recommendation moderate)** (see Section 10).

For high-risk cancer patients with central venous catheters, thromboprophylaxis with **LMWH, apixaban or rivaroxaban** to prevent central venous catheter associated thrombosis should be considered **(Level of evidence moderate, recommendation moderate)**. There is no evidence in favor of routine pharmacological prophylaxis in cancer patients having a central venous catheter.

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SECTION 12

Combined modalities (IPC plus pharmacological prophylaxis) in surgical patients

General considerations

Despite contemporary developments in pharmacology and biomedical engineering, VTE is not fully preventable and thus remains a serious complication of trauma, surgery, and medical conditions. Current and previous guidelines recommend risk stratification to tailor implementation of prophylactic methods so that combined modalities are recommended based on supportive evidence in high-risk patients, although cost and potential adverse events make them less effective for low-risk groups. The reason for the increased efficacy of combined modalities is based on the multifactorial etiology of VTE as first described by Rudolph Virchow in the 19th century.[1] Physical methods reduce venous stasis while pharmacological methods affect hypercoagulopathy. The fact that combined modalities are more effective than single modalities was first shown by Borow in 1983 followed by several studies supporting this concept.[2] While elastic stockings are effective in reducing further VTE rates achieved by perioperative antithrombotic prophylactic pharmacotherapy, as indicated in several places in this document, several modern studies have evaluated the role of the combination of IPC with pharmacological methods, and this will be the focus of this section.

Prophylactic methods

A 2022 Cochrane review update evaluated the efficacy of combined modalities, **intermittent pneumatic compression** (**IPC**) **and pharmacological prophylaxis**: treatment group) **against single modalities alone** (control group) **to prevent PE and DVT in patients at high risk for VTE**.[3] Thirty-four studies that included 14,931 patients were identified, of which 25 were RCTs. The studies evaluated orthopedic patients (N.=14), urology patients (N.=3), and general surgery, cardiothoracic and other types of patients (N.=17). Compared with compression alone, combined modalities significantly reduced the incidence of both symptomatic PE (from 1.34% to 0.65%) (OR: 0.51, 95% CI: 0.29 to 0.91) and DVT (from 3.81% to 2.03%) (OR: 0.51, 95% CI: 0.36 to 0.72).

Compared with pharmacological prophylaxis alone, combined modalities significantly reduced the incidence of PE (from 1.84% to 0.91%) (OR: 0.46, 95% CI: 0.30 to 0.71). Compared with pharmacological prophylaxis alone, combined modalities significantly reduced the incidence of DVT (from 9.28% to 5.48%) (OR: 0.38, 95% CI: 0.21 to 0.70).

The comparison of compression plus pharmacological prophylaxis *vs.* compression plus aspirin showed a non-significant reduction in PE and DVT in favor of the former group. Repeat analysis restricted to the RCTs did not change the overall effect on either PE or DVT.

The additive role of mechanical and pharmacological modalities suggests that venous stasis and hypercoagulopathy are independent pathogenic risk factors. IPC reduces venous stasis by producing active flow enhancement[4, 5] and also increases tissue factor pathway inhibitor (TFPI) plasma levels.[6]

In a recent study 407 patients who underwent major surgery and had a Caprini Score of ≥11 were randomized to receive either IPC in addition to standard prophylaxis with antiembolic stockings and low-molecular-weight heparin (IPC group) or standard prophylaxis alone (control group).[7] The primary outcome was an asymptomatic venous thrombosis of the lower limbs, as detected by duplex ultrasound scan performed before inclusion and every 3-5 days after surgery. The primary outcome occurred in 1 (0.5%) patient in the IPC group and 34 (16.7%) patients

in the control group (RR: 0.03, 95% CI: 0.01 to 0.21). Pulmonary embolism occurred in none of the 204 patients in the IPC group and in 5 (2.5%) patients in the control group (RR: 0.09, 95% CI: 0.01 to 1.63). Postoperative death occurred in 6 (2.9%) patients in the IPC group and 10 (4.9%) in the control group (RR: 0.50, 95% CI: 0.50 to 1.60).

The results of the above meta-analyses and study endorse a recommendation that high-risk patients should receive multimodal prophylaxis. Although most patients that used combined modalities in the studies reviewed were at high risk for developing VTE, future studies on this topic should use the most recent and validated criteria, including the use of validated VTE risk models, to define the high-risk patient.

Recommendations

Combined modalities (IPC and pharmacological prophylaxis) should be considered in all high-risk surgical patients **(Level of evidence: high, recommendation strong)**. Individual recommendations for specific groups of patients appear in the relevant sections of this document.

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SECTION 13

Thrombophilia

General considerations

The term thrombophilia is conventionally used for describing a propensity condition for developing VTE due to the presence of either inherited or acquired prothrombotic abnormalities.[1, 2] The accurate planning of anticoagulant therapy necessitates a thoughtful comprehension of VTE pathogenesis that disturbs the balance of hemostasis towards hypercoagulability, leading to a first episode of VTE and increased risk of recurrence. Clinical thrombophilia is associated with recognized blood alterations in only around 50% of subjects (Table 13.I, Table 13.II[3-18]).

Hereditary thrombophilias

Congenital thrombophilias can be classified in two groups. 1. Loss of function of natural coagulation inhibitors such as antithrombin (AT), protein C (PC), and protein S (PS) deficiencies or 2. Gain of-function with mutations in clotting proteins such as Factor V Leiden (FVL) and prothrombin *G20210A* mutations.[19, 20]

The prevalence and odds ratio for VTE of the most common hereditary and acquired hematological alterations associated with clinical thrombophilia are summarized in Table 13.II.[3-18] The most common blood disorders associated with hereditary thrombophilia are the Factor V Leiden (FVL) mutation, and *G20210A* mutation in the prothrombin gene (FII *G20210A*) (PGM).

FVL mutation

FVL mutation related to activated protein C resistance (APCR) was identified as a cause of hereditary thrombophilia in 1994, transmitted as an autosomal dominant trait. The FVL variant abolishes a cleavage site for activated PC in FV increasing its procoagulant activity (Figure 13.1).[21] It is a low-risk thrombophilia.[20, 22] There is a positive gradient from southern to northern Europe for heterozygosity for FVL. It is present in about 5% to 7% of individuals of European descent but it is rare or absent in populations from sub-Saharan Africa, East Asia, South America, and Australia. Homozygosity for FVL occurs approximately

TABLE 13.I.—*Classification of blood disorders associated with the incidence of VTE incidence according to their origin.*

Hereditary thrombophilia	Acquired thrombophilia	Potential thrombophilia (see discussion)
Antithrombin deficiency	Acquired deficiency of natural inhibitors of coagulation (Liver dysfunction, nephrotic syndrome, disseminated intravascular coagulation (DIC), L-asparaginase treatment)	High levels of factor VIII
Protein C deficiency		High levels of factor IX
Protein S deficiency		High levels of factor XI
Factor V Leiden (FVL)		High levels of fibrinogen
Prothrombin 20210A	Antiphospholipid syndrome (APS)	High levels of TAFI
Dysfibrinogenemia	Myeloproliferative syndromes with JAK2V617F mutation	Low levels of TFPI
Factor XIII 34val	Paroxysmal nocturnal hemoglobinuria	High levels of PAI-3, heparin cofactor II, proteinZ-dependent protease inhibitor (ZPI), protein Z
Fibrinogen (G) 10034T		
ABO blood group polymorphisms		
Prothrombin Yukuhashi (II R596L)		
Factor IX Padua (IX R338L)		

TAFI: thrombin-activatable fibrinolysis inhibitor; TFPI: tissue factor pathway inhibitor; PCI: protein C inhibitor; PAI-3: plasminogen-activator inhibitor-3.

TABLE 13.II.—*Prevalence and Odds Ratio for VTE of the most common hereditary and acquired hematological alterations associated with clinical thrombophilia.*

Parameters	Prevalence in general population	Prevalence in patients with VTE	RR for 1st VTE – positive *vs.* negative (95% CI)	RR for VTE recurrence – positive *vs.* negative (95% CI)	References
Heterozygous AT deficiency	0.02-0.17%	1-5%	12.17 (5.45-27.17)	2.07 (1.50-2.87)	Mahmoodi *et al.* 2010[3] Lijfering *et al.* 2009[4] Rossi *et al.* 2011[5] Middeldorp *et al.* 2023[6] Van Cott *et al.* 2020[7]
Homozygous AT deficiency			Not compatible with the life except the type II HBS		
Heterozygous PC deficiency	0.2-0.5%	1-3%	7.47 (2.81-19.81)	2.13 (1.26-3.59)	Mahmoodi *et al.* 2010[3] Margaglione *et al.* 2011[8] Lijfering *et al.* 2009[4] Rossi *et al.* 2011[5] Middeldorp *et al.* 2023[6]
Homozygous PC deficiency			Very high risk		Vossen *et al.* 2005[9] Lijfering *et al.* 2009[4]
Heterozygous PS deficiency	0.1-0.7%	1-2%	5.98 (2.45-14.57)	1.30 (0.87-1.94)	Mahmoodi *et al.* 2010[3] Margaglione *et al.* 2011[8] Vossen *et al.* 2004[10] Vossen *et al.* 2005[9] Rossi *et al.* 2011[5] Middeldorp *et al.* 2023[6]
Homozygous PS deficiency			Very high risk		Vossen *et al.* 2005[9]
FV Leiden heterozygous	2-7%	15-28%	3-7 2.71 (2.06-3.56)	1.36 (1.19-1.57)	Margaglione *et al.* 2011[8] Vossen *et al.* 2004[10] Vossen *et al.* 2005[9] Rossi *et al.* 2011[5] Luxembourg *et al.* 2021[11] Middeldorp *et al.* 2023[6]
FV Leiden homozygous	0.06-0.25%	-	11.45 (6.79-19.29)	2.10 (1.09-4.06)	Vossen *et al.* 2004[10] Vossen *et al.* 2005[9] Luxembourg *et al.* 2021[11] Middeldorp *et al.* 2023[6]
FII G20210A heterozygous	1-2%	6-16%	3-7 2.35 (1.46-3.78)	1.34 (1.05-1.71)	Margaglione *et al.* 2011[8] Lijfering *et al.* 2009[4] Rossi *et al.* 2011[5] Luxembourg *et al.* 2021[11] Middeldorp *et al.* 2023[6]
FII G20210A homozygous	Rare	Rare	6.74 (2.19–20.72)		De Stefano *et al.* 2004[12] Vossen *et al.* 2005[9] Lijfering *et al.* 2009[4] Luxembourg *et al.* 2021[11] Middeldorp *et al.* 2023[6]
Combined heterozygosity in FV Leiden and FII G20210A or other genetic risk factor (two or more defects)	Rare 1 per 1.000	Rare	–10-20		Vossen *et al.* 2004[10] Lijfering *et al.* 2009[4] Luxembourg *et al.* 2021[11] Middeldorp *et al.* 2023[6]
FVIII>150%	11%	25%	2		Jenkins *et al.* 2012[13] Lijfering *et al.* 2009[4]
Antiphospholipid syndrome	2%	4-15%	7	1.92 (0.99-3.72)	Pengo *et al.* 2012[14] Middeldorp *et al.* 2023[6]
JAK2 mutation		32% mainly with splachnic vein thrombosis	53		Dentali *et al.* 2009[15]
Dysfibrinogenemia	Very rare	Very rare	High risk		Travlou *et al.* 2010[16] Kraiem *et al.* 2010[17] De Moerloose *et al.* 2010[18]

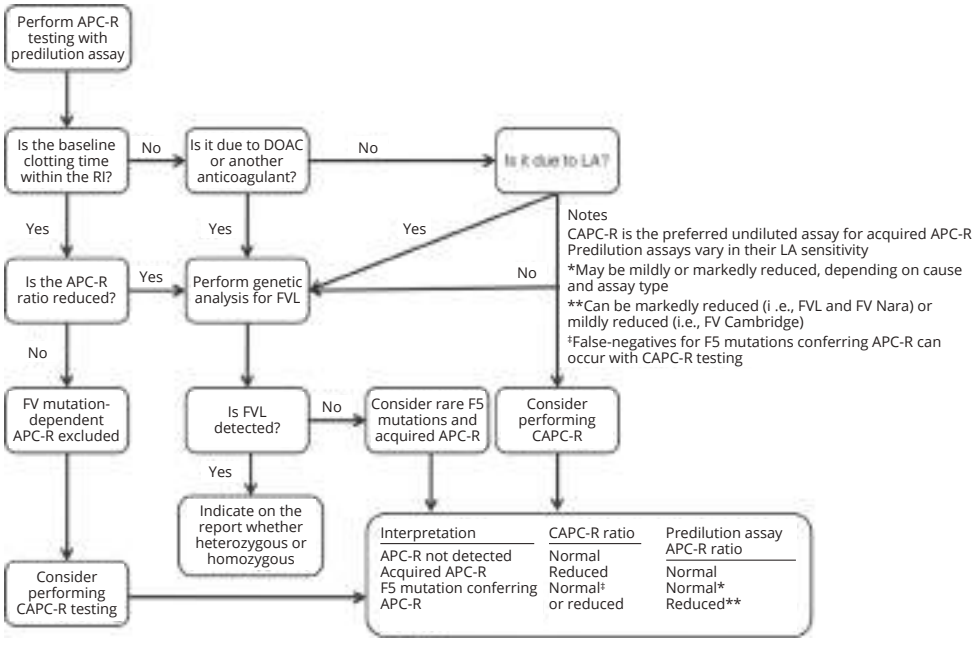


Figure 13.1.—Activated protein C resistance (APC-R) testing algorithm.[21]

in 1 per 1000 individuals in the general population and in 1% of non-selected VTE patients. VTE risk increases approximately five-fold in heterozygous and ten-fold in homozygous carriers.[22, 23]

*F2 C.*97G>A variant*

The ***F2 C.*97G>A* variant** is the second-most-common inherited thrombophilia, with a prevalence in Europe of approximately 2%, with an increasing southern–northern gradient. The point mutation *G20210A* identified in 1996 on the prothrombin gene variant is a single mutation in the 3′ untranslated region of the gene causing increased levels of prothrombin.[20, 22] It is rarer in people from Africa and Asia. The transmission of the *F2 C.*97G>A* variant is autosomal dominant. The presence of this variant heterozygosity confers an approximately three-fold increased risk for a first VTE event.[22, 24]

Antithrombin (AT) deficiency

AT is a serine protease inhibitor (serpin) which is the main inhibitor of thrombin and all other coagulation serine proteases. In addition to the active site (reactive site: RS) responsible for the coagulation factor inhibition, AT contains a heparin-binding site (HBS). The inhibitory function of AT is enhanced at least a thousandfold in the presence of bound heparin. Currently, over 300 loss-of-function variants have been identified in the AT gene (*SERPINC1*) located on chromosome 1 (http://www.hgmd.cf.ac.uk). AT deficiency was the first inherited deficiency thrombophilia identified in 1965.[25] Its prevalence is extremely rare, from 0.02% to 0.2% in the general population, but patients with AT deficiency have a high-risk ratio for a first episode of VTE and a great risk for recurrence. AT deficiency Type I found in approximately 80% of cases, is a quantitative defect characterized by a parallel reduction of functional AT protein and the plasma AT antigen level. Type II is a qualitative defect characterized by a normal synthesis of a dysfunctional AT (Table 13.III;[22] Figure 13.2[7]). According to the meta-analysis of observational studies by Di Minno *et al.*,[23] the relative risk of a first episode of VTE associated with heterozygous AT deficiency is increased 15-fold and the risk of recurrence four-fold. Many variants of SERPINC1 have been identified and other deficiencies linked to AT hypo-glycosylation associated with a heterogeneous clinical phenotype (http://www.hgmd.cf.ac.uk). Overall, the risks are similar in those with type I and type II defects except for type II HBS defects, which appear to have a four-fold lower risk.[26]

Protein C (PC) deficiency

PC deficiency is a vitamin-K-dependent plasma glycoprotein synthesized by the liver. Similarly to PS, activated PC (APC) inhibits thrombin generation by proteolytic inactivation of coagulation cofactors FVa and FVIIIa. The PC pathway plays a significant role in regulating the thrombotic process, especially in the microcirculation. Over

TABLE 13.III.—*Hereditary thrombophilia with deficiencies of natural inhibitors.*[22]

Antithrombin deficiency	Type I	Type IIHBS (heparin-binding site)	Type IIRS (reactive site)	Type IIPE (pleiotropic)
Heparin cofactor activity (FIIa- or FXa-based assay)	↓	↓	↓	↓/N
Progressive activity	↓	N	↓	↓/N
AT antigen	↓	N	N	↓/N
Protein C deficiency	Type I	Type 2a (IIAM) (amidolytic)	Type 2b (IIAC) (anticoagulant)	
PC anticoagulant activity (clot-based assays)	↓	↓	↓	
PC amidolytic activity (chromogenic assays)	↓	↓	N	
PC antigen	↓	N	N	
Protein S deficiency	Type I	Type II (qualitative)	Type III	
Ps activity (clot-based assays)	↓	↓	↓	
Free PS antigen	↓	N	↓	

AT: antithrombin; PC: protein C; PS: protein S.

200 loss-of function mutations have been identified in the PC gene (*PROC*) located on chromosome 2 (http://www.hgmd.cf.ac.uk). The prevalence of PC deficiency is 0.2% to 0.4% in the general population and 3.0% in unselected VTE patients. Type I or quantitative deficiency, which is the most frequent, is characterized by a parallel reduction in the plasma levels of PC antigen and activity.[22, 27] Type II is rare with a dysfunctional PC, characterized by normal antigen but reduced activity. PC dysfunction can concern the enzymatic function of PC (type IIa [IIAM], or amidolytic deficiency) or the procoagulant function of PC not associated with the enzymatic activity (type IIb [IIAC], or anticoagulant deficiency[27] (Table 13.III).[22] Heterozygous PC deficiency is the most frequent one. Homozygous PC deficiency leads to a more severe clinical picture, sometimes revealed by purpura fulminans in newborns, a potentially fatal condition characterized by microvascular thrombosis and skin necrosis. The relative risk of a first episode of VTE associated with PC deficiency is increased seven-fold and the risk of recurrence three-fold[23] (Figure 13.3).[28]

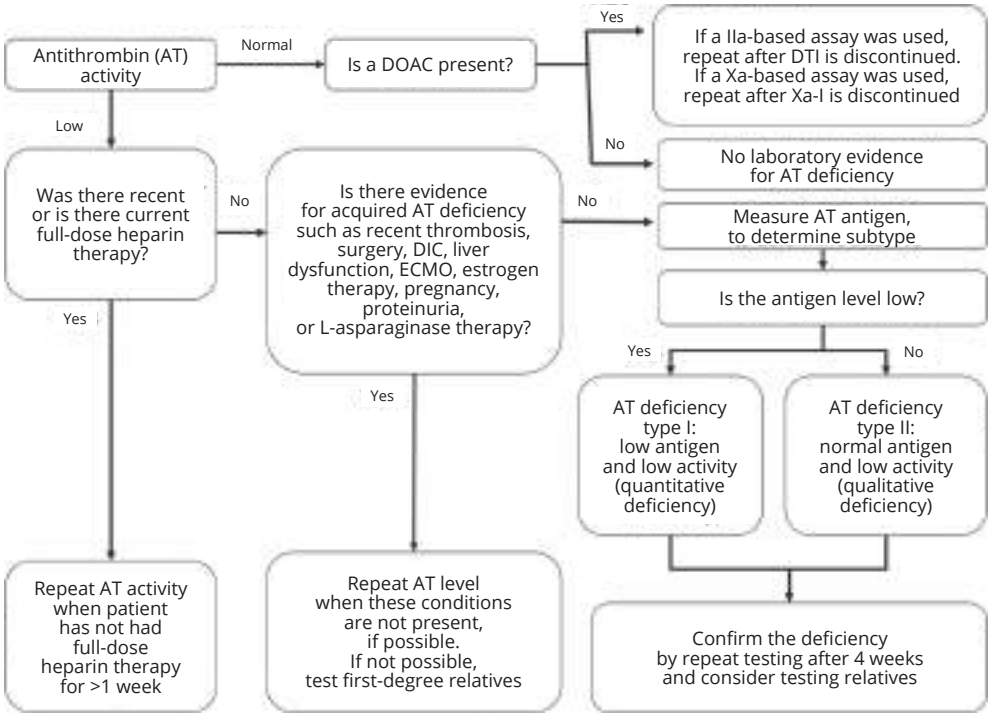


Figure 13.2.—Algorithm AT deficiency diagnosis.[7]

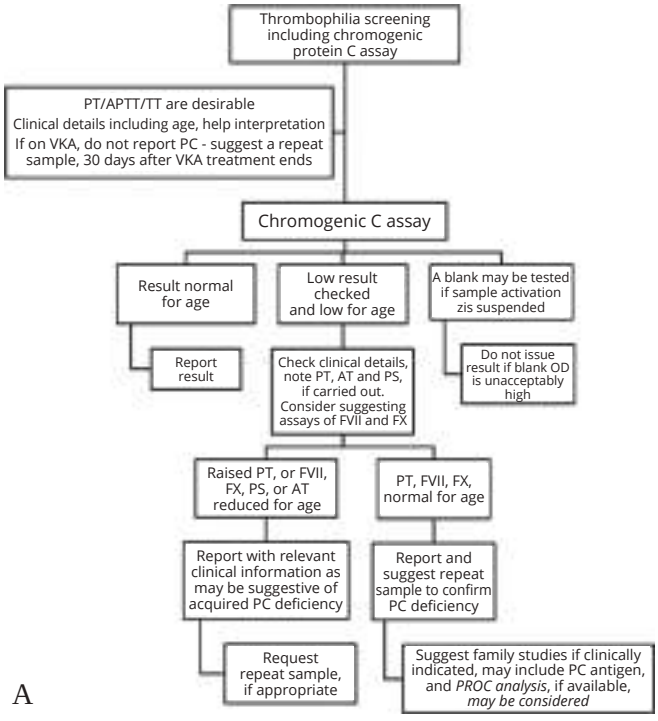


Figure 13.3.—A, B) Protein C deficiency diagnosis algorithm.[28]

Protein S (PS) deficiency

PS is a vitamin-K-dependent glycoprotein not exclusively occurring in the liver, but also produced by endothelial cells, megakaryocytes, Leydig cells, and the brain. The gene encoding PS (*PROS1*) is located on chromosome 3. The N-terminal part of the mature protein contains a GLA domain binding calcium ion and conditioning its affinity for membrane phospholipids. The C-terminal part includes a domain binding to the C4b binding protein (C4bBP). In plasma, free PS is a non-enzymatic cofactor of APC (40%) and the other one (60%) bound to C4bBP. PS is also a co-factor of the tissue factor pathway inhibitor (TFPI) in the inhibition of factor Xa. Inherited PS deficiency is transmitted as an autosomal dominant trait and its prevalence in the general population is between 0.03% and 0.13%.[22, 27, 29] The relative risk of a first episode of VTE associated with PS deficiency is increased five-fold and the relative risk of recurrence 2.5-fold.[23] PS deficiency Type I is a quantitative deficiency characterized by decreased plasma levels of functional and antigen total or free PS. Type III is also a quantitative deficiency with reduced functional activity and free PS but normal total PS levels.[24] Type II qualitative deficiencies are associated with a normal level of total and free PS and a decreased APC cofactor activity. The molecular basis for PS deficiency has been established, and almost 200 mutations of *PROS1* have been identified (http://www.hgmd.cf.ac.uk). *PROS1* genotyping does not explain all inherited abnormalities of PS which can be linked to constitutional glycosylation abnormalities. Type II variants could be less thrombotic than quantitative type variants.[30] The Heerlen variant (*p.Ser501Pro*) alters a glycosylation site, reducing its circulating half-life with a modest decrease in plasma PS levels. Data on the VTE risk associated with the Heerlen mutation are contradictory.[31]

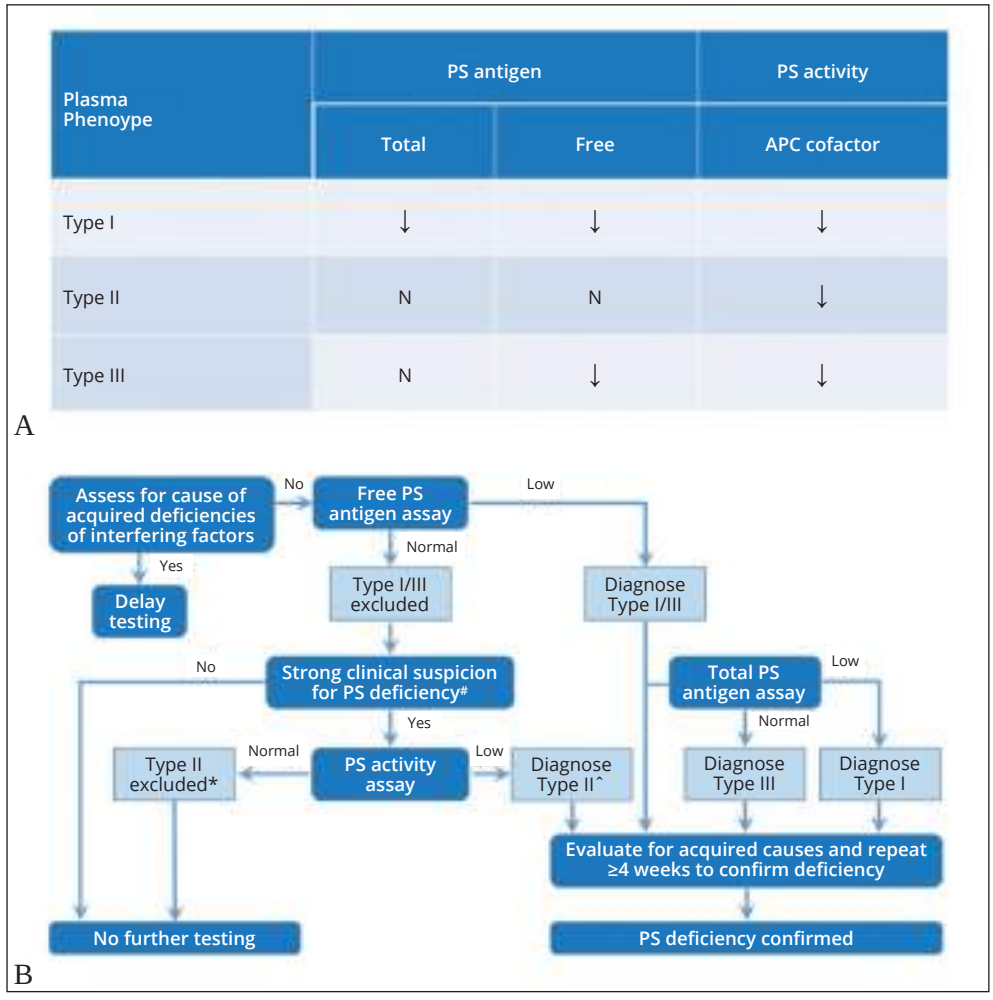
There are no clinically useful differences in thrombotic risk between different subtypes of PS deficiency nor type I and type II PC deficiency[32] (Figure 13.4).[33]

MTHFR mutations and hyperhomocystenemia

The meta-analysis of 2005

The relationship of homocysteine blood levels and the risk of DVT was assessed in a meta-analysis published in 2005 which involved 24 retrospective (N.=3289 cases) and three prospective N.=476 cases) studies.[34] In the same publication a meta-analysis of 53 studies (N.=8364 cases) examined the association of the MTHFR TT genotype, which increases homocysteine in the presence of a low folate intake, with the risk of DVT.

Figure 13.4.—A, B) Protein S Deficiency diagnosis algorithm.[33]



It was found that a 5 µmol/L higher homocysteine level is associated with a 27% (95% CI: 1 to 59) higher risk of DVT in prospective studies and a 60% (95% CI: 10 to 134) higher risk in retrospective studies.

Overall, the *677TT* genotype was associated with a 20% (95% CI: 8 to 32) higher risk of DVT compared with the *677CC* genotype. However, there were continental differences. The *677TT* genotype was associated with a 15% (OR 1.15, 95% CI 1.02 to 1.30) increased risk of DVT in Europe (30 studies), had no difference on DVT in North America (11 studies) (OR: 1.03, 95% CI: 0.82 to 1.29) and and a 60% increase in studies elsewhere (12 studies) (OR: 1.60, 95% CI: 1.27 to 1.02). The authors suggested that this difference may be explained by the higher dietary intake of folate and riboflavin in North America compared with Europe and other areas[35] and it provided support for a causal association between homocysteine and DVT. In addition, the genetic study demonstrating effect modification in North America suggests that a higher vitamin intake may have protective effect that needs confirmation by large RCTs.

The WHS and WAFACS cohort studies

The association between plasma homocysteine with incident VTE was examined in two large prospective cohorts of women, the Women's Health Study (WHS), a prospective cohort of 27,556 women ≥45 years old free of cardiovascular disease or VTE.[36] The authors used a second cohort of the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) to corroborate their findings.

In multivariable models adjusting for age, BMI and other traditional VTE risk factors the association with homocysteine persisted (HR: 1.31, 95% CI: 1.06 to 1.63). Elevated homocysteine was associated with unprovoked

PE (HR: 2.13, 95% CI: 1.30 to 3.51) and DVT (HR: 1.59, 95% CI: 1.05to 2.40), but not provoked events. This study showed not only a dose-response relationship between homocysteine and incident VTE, but also a heightened risk association at concentrations greater than 12.9 µmol/L.

In the WAFACS study, women in the highest quartile of homocysteine had an increased risk of DVT (HR: 2.15, 95% CI: 1.17 to 3.96; P for trend =0.002). The highest incidence rate of DVT was in overweight women with high levels of homocysteine.

RCTs of homocysteine lowering therapy

The VITRO (Vitamins and Thrombosis) Study enrolled 701 patients with a history of VTE.[37] Of these 341 had homocysteine levels ≥75th percentile and 360<75th percentile. All were randomized to a combination of folic acid, vitamin B6 and vitamin B12 or placebo. There was no reduction in VTE events in either subgroup.

The HOPE-2 Trial (Heart Outcomes Prevention Evaluation 2) enrolled 5522 men and women older than 54 years with a history of ASCVD or diabetes plus an additional risk factor for cardiovascular disease.[38] They were randomized to a combination of folic acid, vitamin B6 and vitamin B12 or placebo. There was no reduction in the rates of DVT, PE or unprovoked VTE. However, there was a significant VTE reduction of 43% (95% CI: 9% to 67%; P=0.019) in the subgroup of obese women (BMI≥30 kg/m^2).

Other genetic mutations

Other genetic abnormalities involving *SERPINE1* gene mutation and encoding plasminogen activator inhibitor type 1 (*PAI-1*) or factor XIII mutations, *ABO* gene polymorphisms, Factor XII mutation or dysfibrinogenemia for example should not be included in thrombophilia panels at present.[1, 2, 6, 19, 20] Their association with thrombosis is not convincingly consistent or their effect is too small to modify the management. Concerning high levels of factor VIII, factor IX, factor XI or TAFI, and Protein Z deficiency or decrease of TFPI, clinical significance of genotypic or phenotypic variation in these is uncertain and testing for clinical purposes is not recommended.

Clinical manifestations of hereditary thrombophilias

Clinical manifestations of hereditary thrombophilias are heterogeneous.[5, 23] A family history of VTE in asymptomatic patients without defined hereditary thrombophilia produces also a three-fold increase in the risk of VTE.[23] Furthermore, all types of hereditary thrombophilia do not induce the same increase of VTE risk (Table 13.IV). VTE is frequently associated with DVT and/or PE, but rare locations are reported such as mesenteric, renal, portal or jugular veins or thrombosis of upper limb veins. In extremely rare cases, massive thromboses have been observed in the new-born or skin necrosis at the start of vitamin K antagonist treatments. These rare manifestations are mainly related to homozygous deficiencies in PC or PS.[39] Thus, since the risk of VTE presents a significant variability among the various hereditary thrombophilic disorders, biological thrombophilias are classified as high, moderate, and low thrombotic risk (Table 13.IV). Noteworthy, the same hereditary thrombophilia may present with heterogenous clinical phenotype even in members of the same family. The risk of recurrence is higher when the first episode is unprovoked[2, 6, 19] and risk factors for the first and recurrent episodes are not the same.[40] Unprovoked VTE occurs more frequently in patients with hereditary thrombophilia than in patients without thrombophilia (Hazard Risk Ratio =22).[3, 6]

VTE in patients with hereditary thrombophilia can be associated with a triggering factor such as surgery, trauma, *postpartum*, immobilization, acute medical illness, hormone treatment or chemotherapy, or with the coexistence of other intrinsic risk factors such as pregnancy, age, cancer or other underlying diseases. The more risk factors present in a patient, the higher is the VTE risk. Identification of risk factors on an individual basis and classification of patients in risk groups is of major importance to optimize tailored thromboprophylaxis.

Acquired thrombophilias

The most important acquired hematological conditions related to hypercoagulability and VTE are antiphospholipid syndrome, acquired deficiency of natural inhibitors of co-

Table 13.IV.—*Classification of thrombophilia according to the risk for VTE.*

High risk thrombophilia	Moderate risk thrombophilia	Low risk thrombophilia
Antithrombin deficiency	Heterozygous PC deficiency	FV Leiden heterozygous
Combined hereditary thrombophilia	Heterozygous PS deficiency	FII G20210A heterozygous
Homozygous FV Leiden or FII G20210A		
Antiphospholipid syndrome		
Homozygous deficiency of PC		
Homozygous deficiency of PS		

TABLE 13.V.—*Acquired deficiencies in coagulation inhibitors.*

Acquired AT deficiency	Acquired PC deficiency	Acquired PS deficiency
Neonates	Neonates	Neonates
Liver dysfunction	Liver dysfunction	Liver dysfunction
Liver cirrhosis	Liver cirrhosis	Liver cirrhosis
Liver cancer	Liver cancer	Liver cancer
Sepsis	Disseminated Intravascular Coagulation (DIC)	Rejection of hepatic graft
Disseminated intravascular coagulation (DIC)	Sepsis	Inflammatory syndromes
Pre-eclampsia	Rubella	Lupus
Active Crohn's,	Adult Respiratory Distress Syndrome (ARDS)	Hemodialysis/plasmapheresis
Ulcerative colitis	Purpura fulminans	Estrogen therapy
Uremic hemolytic syndrome	Hemodialysis/plasmapheresis	Chemotherapy or hormone therapy for breast cancer
Hemodialysis/plasmapheresis	Vitamin K deficiency	Myeloproliferative syndromes
Nephrotic syndrome	Treatment with L-asparaginase or methotrexate or enodoxan or 5-fluoracil	Purpura fulminans
Leukemia	Active Crohn's Ulcerative colitis	Sickle cell disease
Estrogen therapy		Pregnancy
Pregnancy		Active Crohn's Ulcerative colitis
Chylothorax (Pediatric cardiac surgery)		
Treatment with L-asparaginase		
Heparin (antithrombin levels <70 IU/dL are not due to heparin alone)		

agulation, myeloproliferative syndromes, the presence of *JAK2V617F* mutation and nocturnal paroxysmal hemoglobinuria (NPH). Some other hematological disorders are of mixed or unknown origin (Table 13.I).[1, 2, 6, 19, 20] The causes of acquired deficiency of natural coagulation inhibitors are summarized in Table 13.V.

The antiphospholipid syndrome

The antiphospholipid syndrome (APS) identifies a heterogeneous condition for increased risk of vascular occlusion and/or pregnancy complications. APS is an autoimmune disorder characterized by a biological profile with the presence of antiphospholipid antibodies (aPL) and/or anticardiolipin antibodies (aCL) and/or antibodies against the β2 glycoprotein I (anti- β2GPI) of IgG or IgM class which are directed against proteins with an affinity for negatively charged phospholipids.[41] Confirmation of diagnosis of the clinical syndrome also requires the presence of venous and/or arterial thromboembolic phenomena and/or obstetric problems (one or more fetal losses after 10 weeks; premature delivery because of severe pre-eclampsia or placental insufficiency; three or more miscarriages before 10 weeks' gestation). Clinical and serological features necessary to diagnose APS are based on the revised Sapporo criteria[42] (Table 13.VI – see Section 24 dedicated to antiphospholipid syndrome).

The catastrophic antiphospholipid syndrome

The catastrophic antiphospholipid syndrome (CAPS) is a life-threatening medical condition with a 50% mortality.[43] In 25% of cases DIC is present. CAPS diagnosis is based on the involvement of at least three organs, systems or tissues, development of clinical manifestations at the same time or within one week, confirmation of small-vessel occlusion by histopathology and the laboratory criteria for APS (see Section 24 dedicated to antiphospholipid syndrome).

Thrombophilia screening

Thrombophilia screening should be a global, comprehensive, personalized evaluation of the patient's prothrombotic state based on the interaction of multiple inherited and/or acquired predisposing factors. Thrombophilia investigation should not be performed just for defining the duration of anticoagulation, but it helps in estimating the individual recurrence risk for thrombotic disease, the need for thrombotic prophylaxis or for the decision to prolong anticoagulation therapy.[6, 32, 44]

TABLE 13.VI.—*Diagnosis of antiphospholipid syndrome.*

Clinical criteria	Laboratory criteria	Diagnosis of APS
Arterial thrombosis Venous thrombosis Vascular occlusion at unusual sites Complications of pregnancy	Lupus anticoagulant antiphospholipid antibodies Anticardiolipin antibodies Antibodies against β2 glycoprotein I	Patients are considered to have the APS if they have at least one clinical and one laboratory criterion at the same time confirmed 12 weeks apart

The aim of thrombophilia screening is to detect patients with a high risk of VTE in whom prevention should be undertaken or patients who may need some specific or prolonged antithrombotic treatment. Screening is greatly influenced by the age at the first episode of VTE, its provoked or unprovoked characteristics and by the presence or absence of family history. Non-surgical major transient risk factors are confinement to bed in hospital for at least 3 days with an acute illness ("bathroom privileges only"), or a combination of minor transient risk factors such as admission to hospital for less than 3 days with an acute illness, confinement to bed out of hospital for at least 3 days with an acute illness, or leg injury associated with decreased mobility for at least 3 days.[6]

It is generally accepted that thrombophilia screening should not be performed in unselected patients.[2, 6, 32, 44]

Women of childbearing age are those who benefit most from thrombophilia screening because of the increased risk of VTE during contraception and pregnancy. In contrast, VTE is frequently associated with risk factors such as cancer, surgery, or immobilization in men and women above 60 years.

In patients with a history of VTE, it is unclear whether prevention of VTE would be different from patients without thrombophilia, suggesting that screening is not mandatory. Consequently, it has been suggested that thrombophilia screening is not necessary after an episode of VTE whether it be unprovoked or provoked by pregnancy or estrogen treatment, in contrast to VTE provoked by a minor transient risk factor. In addition, detection of a genetic thrombophilia in an index patient may not change prevention of recurrences in him or her but could allow detection in a still asymptomatic family member who would benefit from prevention in high-risk situations such as pregnancy, contraception, surgery or long-haul flights.

A family history of VTE in first degree relatives before the age of 50 is a risk factor independently of the presence of a constitutive thrombophilia, raising the question of the utility of its detection. However, VTE in the relative must have been proven and documented and, that is sometimes difficult to confirm.

Recommendations

Who should be tested for thrombophilia?

According to the literature and the accumulated experience of centers specialized on thrombophilia, testing for hereditary and acquired types of thrombophilia should be performed in the following patients to guide anticoagulant strategy (**Level of evidence: low, recommendation moderate or as stated if otherwise)**:

1. patients with first episode of unprovoked VTE **below the age of 50, with or without familial history of thrombosis**;

2. in patients with VTE provoked by a non-surgical major transient risk factor;

3. in women with VTE provoked by pregnancy or postpartum;

4. in women with combined oral contraceptive therapy as the only risk factor;

5. patients with recurrent VTE irrespective of the presence of risk factors;

6. patients with recurrent SVT in the absence of varicose veins;

7. patients with symptomatic VTE at unusual sites such as cerebral venous thrombosis, acute splanchnic venous thrombosis in the absence of liver cirrhosis (mesenteric or hepatic veins);

8. patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related to sepsis;

9. asymptomatic individuals with proven family history of VTE and/or family history of thrombophilia (first- or second-degree relatives, multiple family members with VTE, if the family member with VTE was young);

10. in ambulatory or hospitalized patients with cancer who are classified to be at low or moderate risk of VTE, who have a family history of VTE in first-degree relatives;

11. we suggest selective testing of asymptomatic first-degree relatives of probands with protein C, protein S and antithrombin deficiency where this may influence the management and life choices depending on personal circumstances **(Level of evidence low, recommendation weak)**;

12. screening for antiphospholipid antibodies is recommended following unprovoked VTE because this may alter management including choice of antithrombotic therapy **(Level of evidence low, recommendation strong)**;

13. screening for antiphospholipid antibodies is suggested in patients with VTE provoked by a minor risk factor, as this may alter management including choice of antithrombotic therapy **(Level of evidence low, recommendation weak)**;

14. patients with acute multiple thrombotic events and evidence of organ failure suggestive of CAPS should be tested for antiphospholipid antibodies **(Level of evidence low, recommendation strong)**;

15. testing for antiphospholipid antibodies should be considered in young (<50 years of age) patients in the absence of identifiable risk factors for cardiovascular disease

because this may alter management including choice of antithrombotic therapy **(Level of evidence low, recommendation strong)**;

16. in patients with stroke, an abnormal full blood count should prompt consideration for testing with a myeloproliferative neoplasm (MPN) panel and for paroxysmal nocturnal hemoglobinuria PNH **(Level of evidence low, recommendation weak)**;

17. testing for antithrombin deficiency may be considered in pregnant women with a known family history of this deficiency or evidence of heparin resistance **(Level of evidence low, recommendation weak)**;

18. in women with a history of unprovoked VTE, repeated testing for antiphospholipid antibodies should be performed outside pregnancy **(Level of evidence low, recommendation weak)**;

19. we suggest testing for PNH in patients with thrombosis at unusual sites and abnormal hematological parameters (*i.e.*, cytopenia and abnormal red cell indices) or evidence of hemolysis (*i.e.*, raised lactate dehydrogenase, bilirubin and reticulocyte count) **(Level of evidence low, recommendation weak)**;

20. we recommend testing for MPN panel (including JAK2 V617F, JAK2 exon 12, CALR, MPL mutation analysis) in patients with thrombosis at unusual sites and with full blood count abnormalities suggestive of a myeloproliferative neoplasm **(Level of evidence low, recommendation strong)**;

21. we suggest testing for *JAK2* mutation in patients with splanchnic vein thrombosis or Cerebral Venous Sinus Thrombosis in the absence of clear provoking factors and a normal Cell Blood Count **(Level of evidence low, recommendation weak)**.

Who should not be tested for thrombophilia?[32, 39, 45]

1. In asymptomatic individuals, Genetic testing to predict a first episode of venous thrombosis is not recommended **(Level of evidence low, recommendation moderate)**;

2. all patients with a first episode of spontaneous or unprovoked VTE are not candidates for thrombophilia screening to guide treatment duration. **(Level of evidence low, recommendation weak)**. In fact, the decision for indefinite antithrombotic therapy may have already been made in most patients with unprovoked VTE;

3. in patients with VTE provoked by surgery who have completed primary short-term treatment, we suggest not to perform thrombophilia testing (**Level of evidence: very low**);

4. in patients with an "unspecified type of VTE" (*i.e.* without reference to provoked or unprovoked) we suggest not to perform thrombophilia testing to guide anticoagulant treatment duration **(Level of evidence low, recommendation weak)**;

5. testing for deficiencies of physiological anticoagulants should not be performed during the acute phase of thrombosis, but only after three months of anticoagulation for acute thrombosis **(Level of evidence low, recommendation weak)**.

The results of laboratory screening require interpretation by a specialist hematologist. Patients with hereditary or acquired thrombophilia should be advised and followed-up by a specialist hematologist. It would be advisable not to include thrombophilia screening in the initial baseline study of the infertile couple. There is no evidence to support a clear association between thrombophilia and implantation failure or infertility. Thrombophilia testing in this setting may increase cost, with minimal potential benefit and lead to inappropriate use of anticoagulants with possible deleterious adverse effects.[46]

How to test for thrombophilia?[32, 39, 45]

"Ordering thrombophilia tests is easy; determining whom to test and how to use the results is not."[2]

1. The main tests to be performed are: blood cell count, prothrombin (PT) and activated thromboplastin time (APTT), coagulation inhibitors (AT, PC, PS activities), Factor V Leiden gene mutation (*F5 c.1601G>A* variant), FII G20210A mutation (*F2 c.*97G>A*), lupus anticoagulant detection, antiphospholipid and anti-β2 GP1antibodies (IgG and IgM);

2. molecular diagnosis and genetic assays are not impacted by the presence of anticoagulant treatment;

3. clotting-based assays may be influenced by the acute phase of thrombosis, pregnancy, oral contraception or by anticoagulant treatments such as vitamin K antagonists (PC and PS assays) or direct oral anticoagulants;

4. because of the acquired transient modification of AT, PC, and PS that can be encountered during the acute phase of thrombosis, it is recommended to realize thrombophilia testing between the third and sixth months after a VTE event;

5. thrombophilia testing can be performed while the patient is on anticoagulant treatment. Potential interferences of DOACs with tests used to detect inherited deficiencies require DOAC neutralization for thrombophilia testing (DOAC stop or DOAC removal filters);

6. elevated levels of procoagulant factors may increase the risk of thrombosis but the relationship is not straight-

forward and routine testing of coagulation factors (factors II, X, IX, XI, VIII and fibrinogen) to assess the risk of thrombosis is not currently recommended **(Level of evidence low, recommendation weak)**;

7. tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein Z-dependent protease inhibitor (ZPI) and its cofactor, protein Z, are also natural anticoagulants, the clinical significance of genotypic or phenotypic variation in these is uncertain and testing for clinical purposes is not recommended **(Level of evidence low, recommendation weak)**;

8. non-clotting-based assays as PCR for detection of Factor V Leiden and Factor II gene mutations can be performed at any time **(Level of evidence low, recommendation strong)**;

9. a precise diagnosis of AT deficiency is mandatory since potential heparin treatment resistance can be an issue. **(Level of evidence low, recommendation strong)**;

10. diagnosis of hereditary deficiency of AT, PC or PS should be only established after ruling out acquired deficiency of these proteins **(Level of evidence low, recommendation strong)**.

Management of patients with genetic thrombophilia

Due to the lack of randomized clinical trials with strong methodological design, the recommendations for VTE prophylaxis and treatment in thrombophilia patients are at a low level of evidence and mainly based on expert opinion. Decisions for prolonged prophylaxis or treatment are often taken on an individual basis regardless of their persisting thrombophilic status.[47] In general, treatment effect for VTE occurrence is efficient with a significant risk reduction (RR: 0.54, 95% CI: 0.32 to 0.91) and a relatively small absolute increase in harming treatment effect for major bleeding (RR: 2.17, 95% CI: 1.40 to 3.35).[6, 32, 44]

Observational studies indicate that anticoagulants are equally effective in patients with and without thrombophilia; therefore, the presence of thrombophilia should not influence the choice of anticoagulant or the intensity of therapy **(Level of evidence low, recommendation low)**.

1. The risk of VTE recurrence after stopping anticoagulant therapy may be higher in patients with thrombophilia.[48] However, that risk is not uniform. It is obvious in case of severe hereditary thrombophilia (*e.g.*, AT deficiency), higher in patients with combined Protein C and Protein S deficiencies or combined heterozygous FV Leiden and *FIIG20210A* mutations and not so high in case of homozygous FV-Leiden mutation or *FIIG20210A* mutation (Table 13.II).[3-18] Therefore, we recommend an indefinite antithrombotic treatment in these high-risk patients as secondary prevention strategy **(Level of evidence low, recommendation strong)**;

2. in patients with hereditary thrombophilia, the prolongation of anticoagulant treatment should be considered after careful evaluation of the following factors **(Level of evidence low, recommendation weak)**:

- number of previous VTE episodes and their association with triggering risk factors;
- VTE proximal location and severity of residual sequelae;
- type of thrombophilia;
- bleeding risk factors;
- patient's preferences.

Antiphospholipid Syndrome

A recent random-effects network meta-analysis involving six RCTs and seven non-randomized studies with a total of 719 patients has demonstrated that in comparison to single antiplatelet therapy, the combined use of antiplatelet and warfarin produced a significant reduction in the risk of recurrent overall thrombosis (RR: 0.41, 95% CI: 0.20 to 0.85) **(Level of evidence high, recommendation strong)**.[49] Treatment with DOACs was associated with a significant increase in the risk of recurrent arterial thrombosis (RR 4.06. 95% CI 1.33 to 12.40) when compared to single antiplatelet therapy. There was not any significant difference in major bleeding when different strategies were compared (see Section 24 dedicated to antiphospholipid syndrome).

PNH patient

We recommend that history of TE in the context of PNH is an indication to start complement inhibition, as this significantly reduces the risk of progression and prevents future TE events as well[50] **(Level of evidence low, recommendation strong)**.

We suggest that patients without a history of TE do not require primary prophylaxis with anticoagulation if they start eculizumab **(Level of evidence low, recommendation weak)**. We suggest that patients with a history of TE continue anticoagulation, as well as eculizumab, unless there exists a clear reason to stop (*e.g.*, bleeding, severe thrombocytopenia **(Level of evidence low, recommendation weak)**.

We recommend that development of new TE in a PNH patient should prompt immediate initiation of therapeutic anticoagulation, as well as eculizumab if not already

prescribed **(Level of evidence high, recommendation strong)**.

In case of pregnancy, we suggest prophylactic or therapeutic anticoagulation with LMWH be started in pregnant PNH patients, and continued until at least 6 weeks postpartum, **(Level of evidence low, recommendation weak)**.

We suggest high-risk obstetricians be involved early for any PNH patient planning a pregnancy.

Pregnancy and thrombophilia

A positive family history for VTE further increases the risk of pregnancy associated VTE 3.7-fold to 8.5-fold.[51] Hereditary thrombophilia increases the risk of pregnancy associated VTE up to 34-fold.[52] Women are at an even higher risk for pregnancy associated VTE in the 6-8 weeks postpartum period than during pregnancy.[53, 54] In women without history of thrombosis or thrombophilia but positive family history, other potential associated thrombotic risk factors can be present (age ≥35 years old, immobilization, multiparity, gemellarity),

It is recommended to use a body weight adjusted dose of LMWH for treatment and prophylaxis during pregnancy. In case of chronic venous disease, compression stockings are recommended throughout pregnancy and the postpartum period to facilitate the blood flow and to reduce the stasis discomfort (class 2 for prophylaxis and class 3 for treatment).

For women without previous thrombosis and who are heterozygous for the FVL or PGM and in those who have heterozygous protein C or S deficiency, regardless of family history of VTE, we suggest against using antepartum antithrombotic prophylaxis and to use a thromboprophylaxis only in the 6-8 weeks postpartum period **(Level of evidence low, recommendation weak)**.

For women with antithrombin deficiency who have a family history of VTE and for those who are homozygous for factor V Leiden mutation or who have combined thrombophilias, regardless of family history of VTE, we suggest an antepartum antithrombotic followed by prolonged post-partum prophylaxis at therapeutic doses **(Level of evidence low, recommendation weak)**.

For women with previous thrombosis and genetic thrombophilia, regardless of family history of VTE, we suggest starting antithrombotic prophylaxis in antepartum followed by prolonged post-partum prophylaxis **(Level of evidence low, recommendation weak)**.

For pregnant women who require prophylaxis, we recommend LMWH prophylaxis with standard dose antithrombotic prophylaxis in the antepartum period and in the postpartum period **(Level of evidence low, recommendation weak)**.

Treatment of VTE in pregnant women with thrombophilia is usually not different and can be extrapolated from VTE treatment in pregnant women without thrombophilia **(Level of evidence high, recommendation strong)**.

AT concentrates are suggested at the acute phase of thrombosis in women with hereditary deficiency in AT **(Level of evidence low, recommendation weak)**. AT concentrates at doses of 30 to 50 IU/kg body weight may be recommended in AT deficient women the morning of delivery and the following two days **(Level of evidence low, recommendation weak)**.

Laboratory surveillance: After initial platelet count measurement, routine monitoring of platelet count and anti-Xa activity during LMWH treatment are not recommended **(Level of evidence low, recommendation moderate)**.

It is suggested to look for HIT in case of inflammatory and painful cutaneous heparin injections sites and development of DVT in patients having thromboprophylaxis **(Level of evidence low, recommendation moderate) (see Section 20 on HIT)**.

Due to the lack of blinded randomized clinical trials the recommendations or VTE prophylaxis and treatment of VTE in pregnant women have low level of evidence (risk/benefit ratio not evident from observational studies). This means that recommendations may change later when new information becomes available although randomized studies are very difficult in pregnancy. Because of lack of evidence-based recommendations, decisions for prophylaxis are often taken on an individual basis.

Assisted reproductive techniques and thrombophilia

Thromboprophylaxis is not systematically recommended in women who have assisted reproductive techniques whether or not they have thrombophilia. However, in women who have severe ovarian hyperstimulation, LMWH at a prophylactic dose is suggested during the first trimester of pregnancy **(Level of evidence moderate, recommendation moderate)**.

Duration of anticoagulation in patients with VTE in the presence of thrombophilia

There are no randomized trials that have compared the influence of hereditary thrombophilia on anticoagulant treatment – regarding the choice of the anticoagulant drug and the duration of the treatment.[53, 54]

Observational studies indicate that anticoagulants are equally effective in patients with and without thrombo-

philia; therefore, the presence of thrombophilia should not influence the choice of anticoagulant or the intensity of therapy **(Level of evidence low, recommendation weak)**.

The risk of recurrent VTE after stopping anticoagulant therapy is not uniform for all forms of thrombophilia. It is higher in patients with severe hereditary thrombophilia (*i.e.*, AT deficiency, combined deficiencies, homozygous FV-Leiden mutation or *FIIG20210A* mutation, or combined heterozygosity in FV Leiden and *FIIG20210A* mutations) as well as in patients with antiphospholipid syndrome compared with those with thrombophilia of moderate severity (Table 13.II).[3-18]

For the decision on the duration of the anticoagulant treatment in patients with thrombophilia the general recommendations of Section 16 on anticoagulant treatment should be applied **(Level of evidence moderate, recommendation moderate)**.

DOACS and thrombophilia

Direct Oral Anticoagulants (DOACs) are more attractive for long term treatment than VKA showing a better benefit/risk profile, a bigger therapeutic window and no food interaction. Their use in thrombophilia remains controversial due to paucity of data.[55] Only one clinical, double-blind RCT evaluated the efficacy of dabigatran in patients with thrombophilia. A *post-hoc*, sub-group analysis was conducted on the data from the RE-MEDY Trial. Approximately 18% of the patients in each arm (dabigatran and active-control) had known thrombophilia at baseline with FVL mutation as the most common thrombophilia.[56] Dabigatran demonstrated non-inferiority in recurrent VTE or VTE-related deaths compared with warfarin.[56] Due to their frequency, it is probable that a significant proportion of patients included in phase III trials had undiagnosed moderate thrombophilia without any efficacy or safety concerns.[55] However, concerning major thrombophilias, caution is required and DOACs are not recommended in triple positive APS patients or APS with previous arterial thrombosis.[57]

There is no specific guidance for DOAC use in patients with inherited thrombophilia. Though limited results from case studies and clinical trials may indicate overall success of DOACs compared with warfarin in treating this population, substantial evidence supporting widespread use is lacking.[58, 59]

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SECTION 14

Prevention of VTE in patients with COVID-19

The risk

In the early months of 2020, it was realized that COVID-19 infection from the SARS-CoV-2 virus was associated not only with pneumonia, acute respiratory syndrome, sepsis and multiorgan failure but also macrovessel cardiovascular thrombotic events such as DVT and PE, arterial thrombosis, and myocardial infarction in addition to unique microvascular thromboses including *in-situ* pulmonary microthrombi and intravascular coagulopathy as part of a thromboinflammatory process.[1-3] Autopsies from Germany in the first 12 patients that died revealed the presence of DVT in 7 in whom VTE was not suspected before death and that PE was the direct cause of death in 4 of the 12 patients. Larger autopsy series revealed a high incidence of unsuspected VTE or pulmonary arterial thrombosis in up to 60% of patients, especially those with underlying cardiovascular disease.[4]

It was soon realized that COVID-19 infection produced a distinct endothelial inflammation and a procoagulant state. There was a direct (*via* infection) and indirect (*via* cytokine response and activated platelets) injury to the vascular endothelium which was associated with a decrease in endothelial nitric oxide (NO) contributing to endothelial dysfunction.[5-7] In addition, COVID-19 infection stimulated massive production of cytokines which increased the production of clotting factors and complement by the liver, resulting in contact system activation and increased NETosis.[8, 9] For example, fibrinogen, which is normally 2-4 g/L and increases to 5-6 g/L in pregnancy, a known hypercoagulable state, rises to 10-14 g/L in patients with COVID-19 infection.[10] Increased levels were also reported for lactate dehydrogenase, C-reactive protein, and coagulation factors VIII and XII and in severe disease a decrease in antithrombin levels.[11] Compared with disseminated intravascular coagulation (DIC), COVID-19 induced coagulopathy is associated with a similar increase in prothrombin time, milder thrombocytopenia and more marked D dimer elevation.[12]

Early reports from China that were confirmed in large series in the United States indicated that very elevated D-dimers (>4 or 6 times the upper limit of local laboratory normal) were markers of increased risk of thrombosis and death in hospitalized COVID-19 patients[13, 14] Thus, it became obvious that at least two components of Virchow's triad had been extremely activated. The third component of the triad, venous stasis, would also be activated in hospital patients, but it would be extremely activated in patients on positive pressure ventilation because of the induced muscle paralysis and the positive lung pressure transmitted to the abdomen reducing venous return.[15]

Indeed, two early studies in China indicated that in the absence of prophylaxis the incidence of symptomatic VTE in Intensive Care Unit (ICU) patients was 20-40%.[16, 17] A subsequent study from three academic centers in the Netherlands reported that 32% of patients developed VTE despite pharmacological prophylaxis.[18] In another early study, symptomatic VTE was found in 13% of a series of 198 patients and after screening 55 of these patients with ultrasound, a further 14 (7.1%) were found to have DVT. In this study, clinical VTE was much higher in ICU than the ward and was associated with death (HR: 2.7, 95% CI: 1.3 to 5.8). After adjustment for age, sex and ICU stay the increased mortality risk was still significant (HR: 2.4, 94% CI: 1.02 to 5.5).[19]

Screening by using CT pulmonary angiography performed in 63 outpatients to differentiate between pneumonia and PE and in 72 non-ICU inpatients because of clinical deterioration and increased oxygen needs, identified PE in 32 (24%) of the patients.[20]

Many other studies followed, and in a subsequent meta-analysis of 40 studies involving 7966 COVID-19 patients published in 2021 the incidence of symptomatic DVT and PE in the ICU was 25% and 17% respectively; it was 7% and 4% in non-ICU patients. In studies where screening with ultrasound and CT-angiography was performed, the incidence of DVT and PE in ICU was 33% and 22% respectively.[21]

In a population-wide cohort study of 48 million adults in England and Wales there were 125,985 hospitalized and 1,319,789 non-hospitalized patients within 28 days of COVID-19 diagnosis during January 1 to December 7, 2020.[22] Adjusted hazard ratios for first VTE diagnosis in hospitalized COVID-19 patients compared with no COVID-19 declined from 33.2 (95% CI: 31.3 to 35.2) in week one to 1.80 (95% CI: 1.50 to 2.17) during weeks 27 to 49. The hazard ratio for first DVT compared with no COVID-19 was 6.44 (95% CI: 4.28 to 9.70) in the first week and remained high until week eight 7.29 (95% CI: 5.56 to 9.56); it was 2.55 (95% CI: 2.01 to 3.25) in the third month. The hazard ratio for first PE compared with no COVID-19 was 19.3 (95% CI: 15.7 to 23.6) in the first week and remained high until weeks five to eight 14.4 (95% CI: 12.2 to 17.0); it was 5.67 (95% CI: 4.23 to 7.60) in the third month.

In a large self-controlled case series and matched cohort study in Sweden 1,057,174 persons who tested positive for SARS-CoV-2 between 1 February 2020 and 25 May 2021 were matched on age, sex, and county of residence to 4,076,342 controls.[23] The incidence rate ratio for first DVT was increased for 3 months: 5.9 (95% CI: 5.12 to 6.18) in the first month, 2.59 (95% CI: 2.12 to 3.15) in the second month, 1.42 (95% CI: 1.09 to 1.85) in the third month. The incidence ratio for PE was increased for six months: 31.59 (95% CI: 27.99 to 35.63) in the first month, 4.14 (3.44 to 4.99) in the second month, 2.48 (95% CI: 1.95 to 3.15) in the third month and 1.40 (95% CI: 1.11 to 1.77) in the period between the third to the sixth month. The risk of a first PE was highest during the first pandemic (increase of 54-fold) compared with the second wave (increase 25-fold) and 3rd wave (increase of 44-fold). The authors concluded that these findings could impact recommendations on diagnostic and prophylactic strategies against VTE after COVID-19 (**see section 26 Key Questions to be Answered by New Research**).

Prophylactic methods

General considerations

The epidemiologic and pathologic evidence of the importance of thromboembolic disease in driving poor COVID-19 outcomes, even among patients on prophylactic doses of anticoagulation, led to considerable interest in non-standardized antithrombotic regimens. Some centers published their experience with these regimens in observational comparative effectiveness studies.[24-26] Three messages emerged from such observational studies: 1) Therapeutic-dose heparin thromboprophylaxis was associated with improved outcomes, including decreased thrombosis and death;[24] 2) a single meta-analysis of 7 studies (2 RCTs and 5 observational retrospective) suggested that intermediate dose thromboprophylaxis compared with standard thromboprophylaxis appeared to be rather safe;[25] and 3) a retrospective analysis of 4389 patients found that in comparison to no anticoagulation (N.=1530), therapeutic anticoagulation (N.=900) and prophylactic anticoagulation (N.=1959) were associated with a lower in hospital mortality (adjusted HR: 0.53, 95% CI: 0.45 to 0.62). The authors also reported that of 26 autopsies, 11 (42%) had thromboembolic disease not clinically suspected and 3 of 11 were on therapeutic anticoagulation.[26] The authors of the above studies indicated the need for RCTs to substantiate these observations. Many RCTs followed in response to the demand for high quality evidence.[27]

A. RCTs in non-hospitalized patients

VTE INCLUDED IN THE PRIMARY COMPOSITE ENDPOINT

RCTs using anticoagulation

ACTIV-4b RCT

The ACTIV-4b (Accelerating COVID-19 Therapeutic Interventions and Vaccines) RCT was a double-blind, placebo-controlled trial of anticoagulant and antiplatelet therapy for the prevention of the **composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause in outpatients** with symptomatic but stable COVID-19.[28]

Patients were randomized 1:1:1:1 to **placebo, aspirin 81 mg daily, prophylactic-dose apixaban (2.5 mg twice daily), or therapeutic-dose apixaban (5 mg twice daily)** for 45 days. The trial was conducted remotely with limited face-to-face contact with participants who gave informed consent electronically and had trial drugs mailed to them. The trial was terminated early due to lower-than-anticipated event rates with only 558 patients recruited out of the proposed 7000.

When the trial was stopped, only 3 of 558 patients had primary endpoint events (0.5%), without differences between groups. VTE incidence was zero in the placebo group, 1.4% in the apixaban 5 mg twice a day group, 0.7%

in the apixaban 2.5 mg bd group and zero in the aspirin group.

The authors concluded that anticoagulation and antiplatelet therapy may not benefit outpatients with COVID-19. There was no difference in hemorrhagic events compared with a placebo.

Prevent-HD RCT

This study assessed the efficacy and safety of rivaroxaban 10 mg daily compared with placebo in the prevention of venous and arterial thromboembolism, hospitalization, and death in 1284 non-hospitalized patients with symptomatic COVID-19 and at least one thrombotic risk factor.[29]

The study was terminated prematurely due to enrolment challenges and a lower-than-expected blinded pooled event rate.

The primary efficacy outcome (first occurrence of a composite of symptomatic VTE, myocardial infarction, ischemic stroke, acute limb ischemia, non-central-nervous system systemic embolism, hospitalization, and death through day 35) occurred in 3.4% in the rivaroxaban group and in 3.0% in the placebo group (HR: 1.16, 95% CI: 0.63 to 2.15; P=0.63). No patient in either group experienced critical-cite or fatal bleeding.

Symptomatic VTE did not occur in any patients in the rivaroxaban group. It occurred in 3 (0.47%) patients in the placebo group.

The ACT RCT in community patients

In this study, individuals aged 30 and over, within seven days of diagnosis at high risk of progression were randomized to colchicine 0.6 mg twice daily for three days (N.=1939) followed by 2.6 mg daily for 25 days *vs.* usual care (N.=1942).[28] The primary outcome was the composite of hospitalization or death at 45 days.

Also, in a second randomization patients were allocated to receive aspirin 100 mg once daily (N.=1945) *vs.* usual care (N.=1936) for 28 days. The primary outcome was the composite of major thrombosis (myocardial infarction, stroke, acute lower limb ischemia or PE), hospitalization or death.[30]

In the colchicine RCT, the rate primary outcome was 3.4% in the colchicine group and 3.3% in the control group (HR: 1.04, 95% CI: 0.90 to 1.21; P=0.58).

In the aspirin RCT, the rate of the primary outcome was 26.4% *vs.* 28.4 (HR: 1.02, 95% CI: 0.72 to 1.43; P=0.93. **VTE occurred in 1 (0.1%) in aspirin group and in 4 (0.2%) in the control group (HR: 0.25, 95% CI: 0.03 to 2.24; P=0.22)**.

VTE not included in the primary composite endpoint. Information provided on symptomatic DVT or PE

RCTs using anticoagulation

Ethic RCT

The ETHIC RCT **compared enoxaparin for 21 days (40 mg once daily if they weighed <100 kg and 40 mg twice daily if they weighed ≥100 kg) with standard of care (without enoxaparin)** in the outpatient setting.[31] This trial was also terminated early due to slow enrolment after enrollment of 219 patients. **The incidence of the primary endpoint, a composite of all-cause mortality and hospitalization at 21 days was the same (11%) in each group**. The incidence of VTE at 21 days was 1% in each group; at 90 days it was 1% in the enoxaparin group and 2% in the standard of care group.

At 21 days, two (2%) of 105 patients in the enoxaparin group (one minor bleed and one bleed of unknown severity) and one (1%) of 114 patients in the standard-of-care group (major abnormal uterine bleeding) had a bleeding event.

OVID RCT

The OVID RCT involved 472 patients and **compared enoxaparin 40 mg with placebo** also in the outpatient setting.[32] **The primary outcome was a composite of any untoward hospitalization and all-cause death within 30 days of randomization**.

The 30-day risk of the primary outcome was the same (3%) in each group. The incidence of PE was 0.4% in the enoxaparin group and 1.7% in the placebo group (P=0.19). No major bleeding events were recorded.

The study was terminated prematurely due to the low probability of showing superiority of the primary endpoint under the initial study design assumptions.

VTE not included in the primary composite endpoint. Information not provided on symptomatic DVT or PE

RCT using sulodexide

Regarding RCT, Gonzales-Ochoa *et al.* **compared oral sulodexide 1000 LRU/day *vs.* placebo** in the outpatient setting.[33] A total of 243 patients were included in the per-protocol analysis from June 5 to August 30, 2020. Of these, 124 received sulodexide, and 119 received a placebo. Only 17.7% of the patients in the sulodexide group required hospitalization, compared with 29.4% in the placebo group (P=0.03). This benefit persisted in the intention-to-treat analysis (15% in the sulodexide group *vs.* 24% with placebo (P=0.04). One patient had major bleeding on the placebo arm.

The potential benefit of sulodexide attributed to endothelial protection (one component of Virchow's triad) needs to be explored in future RCT in high-risk patients with COVID-19.

B. RCTs in non-critically ill hospitalized patients

VTE INCLUDED IN THE PRIMARY COMPOSITE ENDPOINT

RCTs using anticoagulation

HEP-COVID RCT

The HEP-COVID trial conducted from May 2020 through May 2021 at 12 US hospitals tested **therapeutic *vs.* intermediate to prophylactic-dose heparin** (LMWH or UFH). HEP-COVID randomized 253 hospitalized patients with COVID-19 and extremely elevated D-dimer levels.[34] Randomization occurred within 72 hours from admission and was stratified by ICU or non-ICU status, with 67.2% of patients not admitted to the ICU.

The **primary outcome was a composite of venous or arterial thromboembolism and all-cause death at 30 days**. All patients without a primary or key secondary outcome event underwent **lower limb Doppler compression ultrasonography** at hospital day 10-14 or at discharge if sooner. Follow-up continued until 30 days after randomization. This was a RCT with a traditional antithrombotic clinical trial design, selecting higher risk patients who were **screened with ultrasound** so that the total incidence of both symptomatic and asymptomatic VTE could be determined.

The incidence of the primary efficacy outcome was 41.9% (28.2% VTE, 3.2% arterial thromboembolism, 10.5% death) in the standard-dose group *vs.* 28.7% (11.7% VTE, 3.2% arterial thromboembolism, 19.4% death) in the therapeutic-dose group (RR: 0.68, 95% CI: 0.49 to 0.96) **driven by a reduction in VTE (29% *vs.* 10.9%; RR: 0.37; 95% CI: 0.21 to 0.66; P<0.001)**; the majority of thromboembolic events consisted of symptomatic DVT and non-fatal PE.

There were two major bleeding events (1.6%) in the standard-dose *vs.* six (4.7%) in the therapeutic dose groups (RR: 2.88, 95% CI: 0.59 to 14.02; P=0.17) that were not fatal.

In an analysis stratified by ICU *vs.* non-ICU status, therapeutic-dose heparin reduced the incidence of the primary outcome in non-ICU patients (36.1% *vs.* 16.7%; RR: 0.46, 95% CI: 0.27 to 0.81, P=0.004) but not in ICU patients (55.3% *vs.* 51.1%; RR: 0.92, 95% CI: 0.62 to 1.39; P=0.71).

BEMICOP RCT

The BEMICOP (**Therapeutic *vs.* Prophylactic bemiparin** in hospitalized patients with non-severe COVID-19 Pneumonia) trial failed to find a difference in outcomes for patients treated with therapeutic-dose bemiparin (115 units/kg daily) *vs.* standard prophylaxis (3500 units daily).[35]

BEMICOP, conducted in five Spanish hospitals from October 2020 through May 2021, randomized 65 patients with COVID-19 and elevated D-dimer without critical illness. There was no difference in the trial's primary outcome – the **composite of death, ICU admission, need for mechanical ventilation, development of moderate to severe respiratory distress, or venous or arterial thrombosis** within 10 days – by a trial arm (21.9% *vs.* 18.2%; OR: 1.26, 95% CI: 0.37-4.26).

Two arterial thromboembolic/VTE events occurred in the standard prophylaxis group and none in the therapeutic group. The trial was stopped early for futility.

FREEDOM COVID RCT

The FREEDOM COVID trial evaluated the efficacy and safety of **therapeutic-dose anticoagulation** in non-critically ill patients with COVID-19.[36] **The 30-day primary endpoint was a composite of all-cause mortality, requirement for ICU level-of-care, systemic thromboembolism (DVT, PE, arterial thrombosis, or embolism) or ischemic stroke**.

A total of 3,398 non-critically ill patients hospitalized with COVID-19 were randomized to prophylactic-dose enoxaparin (N.=1141), therapeutic-dose enoxaparin (N.=1136), or therapeutic-dose apixaban (N.=1121). The primary outcome occurred in 13.2% of patients in the prophylactic-dose group and 11.3% in the combined therapeutic-dose groups (HR: 0.85, 95% CI: 0.69 to 1.04; P=0.11). **However, key secondary outcomes including all-cause mortality, occurred in 7.0% of patients treated with prophylactic-dose enoxaparin and 4.9% of patients treated with therapeutic-dose anticoagulation (HR: 0.70, 95% CI: 0.52 to 0.93; P=0.01), and intubation, which occurred in 8.4% vs. 6.4% of patients respectively (HR: 0.75, 95% CI: 0.58 to 0.98; P=0.03)**.

The incidence of DVT was 0.6% *vs.* 0.4% (P=0.28) and PE 0.3% *vs.* 0.5% (P=0.34) in the therapeutic *vs.* prophylactic group. Major bleeding in all three groups was infrequent. The authors concluded that in non-critically ill patients hospitalized with COVID-19, the 30-day primary composite outcome was not significantly reduced with therapeutic-dose anticoagulation compared with prophylactic-dose anticoagulation, but that fewer patients who were treated with therapeutic-dose anticoagulation required intubation or died.

COVI-DOSE RCT

In the most recent multicenter RCT, 1000 patients (80.1% non-critically ill and 19.9% critically ill) were assigned to receive an intermediate weight-adjusted prophylactic dose or a fixed-dose of subcutaneous LMWH during hospital stay.[37] The primary endpoint, symptomatic VTE occurred in 6 (1.2%) of 502 patients in the weight-adjusted dose group and in 10 (2.1%) of 498 patients in the fixed dose group (HR: 0.59, 95% CI: 0.22 to 1.63; P=0.31). There was a twofold increased risk in major or clinically relevant non-major bleeding: 5.9% in the weight-adjusted dose group and 3.1% in the fixed-dose group (P=0.034). The conclusion was that the observed rate of VTE was lower than expected and the study was unable to show a significant difference in VTE risk between the two LMWH regimens.

VTE not included in the primary composite endpoint. Information provided on symptomatic DVT or PE

RCTs using anticoagulation

The REMAP-CAP, ACTIV-4a, and ATTACC RCTs

The investigators enrolled a cohort of patients without critical illness, using the same multiplatform design as the trial in critically ill patients (see below).[38] This RCT randomly assigned 2219 patients hospitalized with COVID-19 without critical illness at enrolment to **therapeutic-dose anticoagulation or usual-care thromboprophylaxis**. Patients were excluded if they were already on dual antiplatelet therapy or had a high risk of bleeding. As in the RCT enrolling critically ill patients, **the primary outcome was organ support-free days through day 21 after randomization**.

Investigators for the three trials harmonized their protocols and statistical analysis plans to study the effect of anticoagulation in patients hospitalized with COVID-19 in one multi-platform clinical trial early in the pandemic. Patients were randomized to either parenteral therapeutic-dose anticoagulation or usual-care thromboprophylaxis. Therapeutic-dose anticoagulation was administered according to local site protocols (enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily, dalteparin 100 units/kg twice daily or 200 units/kg daily, tinzaparin 175 anti-Xa units/kg daily, or heparin by continuous infusion) for up to 14 days or until recovery (hospital discharge or discontinuation of supplemental oxygen). According to local clinical practice, the usual-care thromboprophylaxis was defined as either standard low-dose anticoagulation or intermediate-dose thromboprophylaxis.

In the therapeutic anticoagulation group, 19.8% of patients received organ support over 21-day follow-up compared with 23.6% of patients in the usual-care thromboprophylaxis group (OR: 0.79, 95% CI: 0.63 to 0.97). Treatment effects did not vary by age, level of respiratory support at enrolment, the dose of thromboprophylactic drug, or baseline D-dimer. **Therapeutic anticoagulation reduced the composite of major thrombotic events or death** (8.0% *vs.* 9. OR: 0.72, 95% CI: 0.53 to 0.98). There was a reduction in the incidence of a major thrombotic events of borderline significance (1.1% *vs.* 2.1%; P=0.067). It did not have a significant effect on progression to intubation or death (10.9% *vs.* 12.1%; OR: 0.82, 95% CI: 0.63 to 1.07), in-hospital death (7.3% *vs.* 8.2%; OR: 0.83, 95% CI: 0.60 to 1.15), or ISTH major bleeding (1.9% *vs.* 0.9%; OR: 1.80, 95% CI: 0.90 to 3.74).

Several smaller trials have tested a similar strategy of therapeutic anticoagulation *vs.* prophylactic anticoagulation with mixed findings. These are summarized below.

RAPID RCT

The RAPID (Therapeutic Anticoagulation *vs.* Standard Care as a Rapid Response to the COVID-19 Pandemic) RCT was conducted at 28 hospitals in six countries.[39] RAPID enrolled 465 adults with COVID-19 and increased D-dimer levels admitted to hospital wards and randomized these patients to **therapeutic- or prophylactic-dose heparin**. Nearly all patients were treated with LMWH (98% of the therapeutic-dose arm and 94% of the prophylactic-dose component).

The trial's **primary outcome, a composite of death, invasive mechanical ventilation, noninvasive mechanical ventilation, or admission to an ICU through 28 days**, occurred in 16.2% of patients assigned to therapeutic heparin and 21.9% allocated to prophylactic heparin (OR: 0.69, 95% CI: 0.43 to 1.10; P=0.12). All-cause death, a key secondary outcome (though one the trial was not powered for), was lower in patients randomized to therapeutic heparin *vs.* prophylactic heparin (1.8% *vs.* 7.6%; OR: 0.22, 95% CI: 0.07 to 0.65).

Symptomatic VTE occurred in two patients (0.9%) assigned to therapeutic heparin and six (2.5%) to prophylactic heparin (OR: 0.34, 95% CI: 0.07 to 1.71; P=0.19). Major bleeding occurred in two patients (0.9%) assigned to therapeutic heparin and four (1.7%) to prophylactic heparin (OR: 0.52. 95% CI: 0.09 to 2.85; P=0.69).

ACTION RCT

The ACTION (Anticoagulation Coronavirus) RCT, conducted at 31 sites in Brazil from June 2020 through Febru-

ary 2021, did not show a benefit of therapeutic anticoagulation.[40] ACTION involved 614 patients with a confirmed diagnosis of COVID-19, with symptoms for up to 14 days before randomization, regardless of clinical stability (though 94% were not critically ill). They were randomized to **therapeutic anticoagulation with rivaroxaban 20 mg once daily** to be continued for 30 days **or standard prophylactic anticoagulation** (84% received enoxaparin 40 mg daily, 13% continued after hospital discharge).

The trial's **primary outcome, a hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen**, was not different between the therapeutic and prophylactic anticoagulation groups.

Therapeutic anticoagulation did not produce a significant reduction of the incidence of the composite of VTE, myocardial infarction, stroke, or major adverse limb event (7.4% *vs.* 9.9%; OR: 0.75, 95% CI: 0.45 to 1.26).

ISTH major or clinically relevant non-major bleeding occurred more frequently in the therapeutic anticoagulation arm. Major bleeding was 8% *vs.* 2% (RR: 3.64, 95% CI: 1.61 to 8.27) and clinically relevant non-major bleeding was 5% *vs.* 1% (RR: 3.92, 95% CI: 1.92 to 8.00).

ANTICOVID RCT

In this RCT a total of 334 patients with hypoxemic COVID-19 pneumonia requiring supplemental oxygen and having no initial thrombosis on chest computed tomography with pulmonary angiogram were included into the study. Mechanical ventilation (noninvasive or invasive) was not required in 84% of patients.[41]

The aim of this trial was to determine the efficacy of therapeutic anticoagulation (TA) and high-dose prophylactic anticoagulation (HD-PA) in **decreasing mortality and/or disease duration** compared with each other and with standard-dose prophylactic anticoagulation (SD-PA). The secondary combined efficacy and safety outcome was a **composite of thrombosis** (ischemic stroke, non-cerebrovascular arterial thrombosis, DVT, pulmonary artery thrombosis, and central venous catheter related DVT), **major bleeding or all cause death**.

There was not any significant difference in the probabilities of a more favorable outcome (decreasing mortality and/or disease duration) between the groups (P<0.37).

There was not any significant difference in the rate of major bleeding. It occurred in 3 patients in the SD-PA group, 4 patients in the HD-PA group and 4 patients in the TA group.

There was a significant net clinical outcome (efficacy and safety) in the HD-PA group compared with SD-PA group: absolute difference of -13.5 (-2.6 to -24.3), P=0.02, but not when TA was compared with SD-PA: absolute difference of -9.8 (1.4 to -21.1), P=0.12 or when TA was compared with HD-PA: absolute difference of 3.6 (13.8 to -6.5), P=0.60.

Venous and pulmonary artery thrombosis occurred in 42 (36.7%) of the 114 patients receiving SD-PA, 10 (9.1%) of 110 patients receiving HD-PA and 8 (7.3%) out of 110 patients receiving TA (for SD-PA *vs.* HD-PA or TA, P<0.001 and for HD-PA *vs.* TA, P=0.62).

Observational studies using antiplatelet agents in hospitalized patients

In a multicenter, retrospective, observational study 984 hospitalized patients presenting with COVID-19 in 2020 were stratified according to aspirin intake during the 7 days before hospitalization (N.=253) or not (N.=731). After correcting for prophylactic anticoagulation and other co-morbidities using multivariable analysis, aspirin intake was independently associated with a lower incidence of a composite endpoint of in hospital death and/or need for respiratory support upgrade (HR: 0.64, 95% CI: 0.46 to 0.89; P=0.009).[42]

A subsequent observational cohort study of 112,269 hospitalized patients with moderate COVID-19, enrolled from January 2020 to September 2021, at 64 US health systems confirmed the reduction in hospital mortality by aspirin: 10.2% *vs.* 11.8% (OR: 0.85, 95% CI: 0.79 to 0.92; P<0.001).[43] The incidence of PE was also reduced: 1% *vs.* 1.4% (OR: 0.71, 95% CI: 0.56 to 0.90; P=0.004), but not that of DVT which was 1.0% in both groups. Patients on aspirin did not have higher rates of GI hemorrhage, cerebral hemorrhage, or blood transfusion.

The above observational studies stimulated the performance of RCT to test the efficacy of antiplatelet therapy in non-critically ill patients with COVID-19.

RCTs using antiplatelet agents

ACTIV-4a RCT

Between February 2021 and June 2021, the ACTIV-4a investigators randomized 562 non-critically ill patients at 60 hospitals in four countries to therapeutic-dose heparin plus a P2Y12 inhibitor (ticagrelor in 63%, clopidogrel in 37%) for 14 days or therapeutic-dose heparin alone.[44] **The composite primary outcome, organ support–free days up to day 21 after randomization, did not differ between the two arms**; the median number of organ support–free days was 21 in both (OR: 0.83, 95% CI: 0.55 to 1.25).

The incidence of thrombotic events which included DVT was 3.19% in the combined group and 1.9% in the

therapeutic dose of heparin only group (P=0.35). There was a non-significant trend of ISTH major bleeding in the P2Y12 inhibitor arm (2% *vs.* 0.7%; OR: 2.67, 95% CI: 0.53 to 13.4).

RECOVERY RCT

The RECOVERY trial enrolled 14,892 patients hospitalized with COVID-19, **including those critically and non-critically ill**, at 171 hospitals in the United Kingdom and Asia between November 2020 and April 2021.[45] Patients were randomized to aspirin 150 mg daily or usual care. **The trial's primary outcome, 28-day mortality, was** 16.6% in the aspirin arm and 17.2% in the usual-care arm (RR: 0.96, 95% CI: 0.89 to 1.04).

Aspirin did not affect the need of invasive mechanical ventilation or the composite of mechanical ventilation or death. Aspirin produced a reduction of borderline significance in the risk of a composite of thrombotic events, including VTE, stroke, myocardial infarction, or systemic arterial embolism from 5.3% to 4.6%, (RR: 0.88, 95% CI: 0.76 to 1.01; P=0.07). This reduction of borderline significance was driven by the relatively large number of PE: 294 (4.0%) *vs.* 332 (4.4%), (P =0.22) and DVT of 27 (0.4%) *vs.* 40 (0.5%), P=0.14).

There was a significant increase in the incidence of major bleeding events: 115 (1.6%) *vs.* 76 (1.0%). (RR: 1.55; 95% CI: 1.16 to 2.070; P=0.0028).

The ACT RCT in hospitalised patients

In this study, 2749 adults with COVID-19 within 72 hours of hospitalization or worsening clinically were randomized to colchicine 1.2 mg followed by 0.6 mg two hours later and then 2.6 mg daily for 28 days *vs.* usual care.[46] The primary outcome was the composite of the need for high flow oxygen, mechanical ventilation, or death at 45 days.

Also, in a second randomization 2,119 patients were allocated to rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily *vs.* usual care for 28 days. The primary outcome was the composite of major thrombosis (myocardial infarction, stroke, acute lower limb ischemia or PE), need for high flow oxygen, mechanical ventilation, or death.[46]

In the colchicine RCT, the rate primary outcome was 28.2% in the colchicine group and 27.2% in the control group (HR: 1.04, 95% CI: 0.90 to 1.21; P=0.58).

In the rivaroxaban plus aspirin RCT, the rate of the primary outcome was 26.4% *vs.* 28.4 (HR: 0.92, 95% CI: 0.78 to 1.09; P=0.32. **VTE occurred in 13 (1.2%) in the rivaroxaban aspirin group and in 10 (0.9%) in the control group (HR 1.31, 95% CI: 0.58 to 3.00; P=0.52)**.

C. RCTs in critically ill hospitalized patients

VTE included in the primary composite endpoint

RCTs using anticoagulation

INSPIRATION RCT

The INSPIRATION **(**Intermediate *vs.* Standard-Dose Prophylactic Anticoagulation in Critically Ill Patients With COVID-19) trial enrolled 562 critically ill patients with COVID-19 admitted to the ICU at 10 Iranian hospitals from July to November 2020.[47] These patients were randomized 1:1 to either **intermediate-dose anticoagulation** (enoxaparin 1 mg/kg daily, with dose adjustments for patients with weight >120 kg or creatinine clearance <30 mL/min) **or prophylactic-dose anticoagulation** (enoxaparin 40 mg daily, with the same dose adjustments) continued for 30 days regardless of hospitalization status. Intermediate-dose anticoagulation had no significant effect on the incidence of the trial's primary outcome: **a composite of centrally adjudicated arterial or venous thrombosis, need for extracorporeal membrane oxygenation, or death within 30 days** (OR: 1.06, 95% CI: 0.76 to 1.48). The incidence of the secondary endpoint of symptomatic VTE was 3.3% in the intermediate dose group and 3.5% in the standard prophylactic dose group (OR: 0.93, 95% CI: 0.37 to 2.32). By contrast, intermediate-dose anticoagulation significantly increased the risk of Bleeding Academic Research Consortium types 3-5 (major) and type 2 (clinically relevant non-major) bleeding.

VTE not included in the primary composite endpoint. Information provided on symptomatic DVT or PE

RCTs using anticoagulation

In their RCT, Perepu *et al.* enrolled 176 patients with COVID-19 at three US centers from April 2020 through January 2021.[48] To be included, patients had to be hospitalized in the ICU or have an Overt Disseminated Intravascular Coagulation Score ≥3; 62% of patients were enrolled based on being hospitalized in the ICU. The **primary outcome was all-cause mortality** at 30 days. **Secondary outcomes included arterial or venous thromboembolism and major bleeding**. Eligible patients were **randomized 1:1 to intermediate-dose anticoagulation (enoxaparin 1 mg/kg daily, dose adjusted for obesity) or standard prophylactic-dose anticoagulation (enoxaparin 40 mg daily, dose adjusted for obesity)**. At 30 days, 13 of 87 patients in the intermediate-dose anticoagulation arm had died (14.9%), compared with 18 of 86 patients in the standard prophylactic-dose arm (20.9%) (OR: 0.66, 95% CI:

0.30 to 1.45). The incidence of the secondary endpoint, DVT was 7% in the standard dose group and 8% in the intermediate dose group (OR: 1.79, 95% CI: 0.51 to 6.25). There was no difference in major or minor bleeding between the groups.

REMAP-CAP, ACTIV-4a, ATTACC (Multiplatform trials)

A composite report from the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), ACTIV-4a, and ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) trials **compared therapeutic- with prophylactic-dose anticoagulation** in patients with COVID-19 requiring ICU-level respiratory or cardiovascular organ support (oxygen by high-flow nasal cannula, noninvasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes).[49] Investigators for the three trials harmonized their protocols and statistical analysis plans to study the effect of anticoagulation in patients hospitalized with COVID-19 in one multi-platform clinical trial early in the pandemic. Patients were randomized to either parenteral therapeutic-dose anticoagulation or usual-care thromboprophylaxis. Therapeutic-dose anticoagulation was administered according to local site protocols (enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily, dalteparin 100 units/kg twice daily or 200 units/kg daily, tinzaparin 175 anti-Xa units/kg daily, or heparin by continuous infusion) for up to 14 days or until recovery (hospital discharge or discontinuation of supplemental oxygen). According to local clinical practice, the usual-care thromboprophylaxis was defined as either standard low-dose anticoagulation or intermediate-dose thromboprophylaxis. The trial began enrolment in April 2020 and was ultimately stopped for futility in December 2020 after the enrolment of 1207 patients (of whom 1,098 had primary outcome data available) at 393 sites in 10 countries. **The trial's primary outcome, organ support-free days (with patients who died in the hospital assigned a value of −1) through 21 days, did not differ between the therapeutic-dose anticoagulation and usual-care groups (OR: 0.83, 95% CI: 0.67 to 1.03), with a point estimate favoring lower-dose anticoagulation**. There was similarly no difference in survival to hospital discharge (62.7% *vs.* 64.5%; OR: 0.84, 95% CI: 0.64 to 1.11), the composite of major thrombotic events or death (40.1% *vs.* 41.1%; OR: 1.04, 95% CI: 0.79 to 1.35), and International Society on Thrombosis and Hemostasis (ISTH) major bleeding (3.8% *vs.* 2.3%; OR: 1.48, 95% CI: 0.75 to 3.04). Therapeutic-dose anticoagulation produced a non-significant reduction in the incidence of major thrombotic events (6.4% *vs.* 10.4%) and any thrombotic events (7.2% *vs.* 11.1%).

Taken together, the above trials indicated that therapeutic-dose anticoagulation does not benefit and potentially harms critically ill COVID-19 patients.

D. RCT conducted after discharge from hospital

VTE INCLUDED IN THE PRIMARY COMPOSITE ENDPOINT

RCTs using anticoagulation

MICHELLE RCT

The MICHELLE (Rivaroxaban *vs.* No Anticoagulation for Postdischarge Thromboprophylaxis After Hospitalization for COVID-19) trial, conducted at 14 centers in Brazil from October 2020 through June 2021, tested a strategy of extended thromboprophylaxis in 320 patients discharged from the hospital after a COVID-19 diagnosis, of whom 52% were hospitalized in the ICU.[50] To be included, patients had to have an International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE Risk Score ≥4 or a score of 2-3 with D-dimer >500 ng/mL. Patients were randomized, at the time of hospital discharge, to **rivaroxaban 10 mg daily for 35 days after hospital discharge or a placebo**. The primary outcome was a composite of symptomatic or fatal VTE, asymptomatic VTE on screening bilateral lower limb venous ultrasound and CT- pulmonary angiography performed at day 35, symptomatic arterial thromboembolism, or cardiovascular death. **Extended thromboprophylaxis with rivaroxaban reduced the incidence of the primary outcome from 9.4% in the placebo group to 3.1% in the rivaroxaban arm (RR: 0.33, 95% CI: 0.12 to 0.90; P=0.023). Rivaroxaban also decreased the incidence of VTE or cardiovascular death (RR: 0.11, 95% CI: 0.01 to 0.87)**. Major bleeding did not occur in any of the two groups.

ACTIV-4c RCT

The ACTIV-4c trial was a multicenter, adaptive, randomized platform trial evaluating the efficacy and safety of **apixaban 2.5 mg bid *vs.* placebo** on a **composite endpoint of death, arterial thrombosis, and venous thromboembolism** in patients with COVID-19 following hospital discharge. Patients were enrolled between February 2021 and June 2022.[51] Enrolment was terminated early, after 1,217 participants were randomly assigned because of a lower than anticipated event rate and a declining rate of COVID-19 hospitalizations. Only 11.0% had an International Medical Prevention Registry on Venous Throm-

boembolism risk prediction score greater than 4. Incidence of the primary end point was 2.13% in the apixaban group and 2.31% in the placebo group. Clinical VTE events were 5 (0.82%) *vs.* 5 (0.82%). Major bleeding occurred in 2 (0.4%) and 1 (0.2%) and clinically relevant nonmajor bleeding occurred in 3 (0.6%) and 6 (1.1%) apixaban-treated and placebo- treated participants, respectively. The authors concluded that the incidence of death or thromboembolism was low in this cohort of patients discharged after hospitalization with COVID-19. **Because of early enrolment termination, the results were imprecise, and the study was inconclusive**.

Meta-analyses of RCTs

General remarks

It has become obvious from the above that in most of the RCTs, VTE was often part of a composite endpoint which included death, progression to organ failure, arterial thromboembolism, VTE, myocardial infarction and stroke. Such a composite endpoint was essential because COVID-19 had a high mortality rate and survivors were more crippled by arterial than venous thromboembolism. Thus, most trials were underpowered in reporting efficacy of prophylaxis on VTE alone.

Since the majority of PE arise from lower limb DVT, the large number of PE in relation to the small number of symptomatic DVTs found in many of the studies suggests that DVT has been underdiagnosed or that COVID-19 may present with a greater incidence of *in-situ* pulmonary thrombosis. This may reflect the fact that most of the studies were not designed with VTE as a primary endpoint; also, the fact that severely ill patients are unlikely to complain of symptoms related to DVT.

Nevertheless, most trials reported on VTE and hemorrhagic events. As a result, meta-analyses having thromboembolic (arterial and/or venous) events as their primary endpoints have provided a synthesis of the available data and valuable information for the development of recommendations relevant to VTE for the clinician.

Systematic review and meta-analysis with all-cause mortality as the primary endpoint

The Ortega-Paz et al. *systematic review and meta-analysis (August 2021)*

One of the early systematic reviews and meta-analyses investigated the efficacy and safety of different prophylactic anticoagulation dosing regimens in critically ill and non-critically ill patients with COVID-19 who did not have a formal indication for anticoagulation.[52] The **primary efficacy endpoint was all-cause mortality, and the primary safety endpoint was major bleeding. Secondary efficacy endpoints were VTE (DVT or PE), myocardial infarction, stroke, and systemic arterial embolism**.

Seven RCTs involving 5,154 patients were identified. Four RCTs involved critically ill patients and three involved non-critically ill patients.

Compared with the standard-dose prophylactic anticoagulation, **escalated-dose prophylactic anticoagulation** was not associated with a reduction of all-cause mortality (17.8% *vs.* 18.6%; RR: 0.96, 95% CI: 0.78 to 1.18) but **was associated with increased major bleeding** (2.4% *vs.* 1.4%; RR: 1.73, 95% CI: 1.15 to 2.60).

The authors concluded that there was high-quality evidence for the use of standard-dose prophylactic anticoagulation over an escalated-dose regimen as routine standard of care for hospitalized patients irrespective of disease severity.

The overall incidence of VTE was 2.5% (66/2621) with the escalated dose and 4.7% (119/2528) with the standard prophylactic anticoagulation (RR: 0.55, 95% CI: 0.41 to 0.74). Thus, the escalated-dose regimen reduced VTE with a NNT of 46, but significantly increased the risk of bleeding with an NNH of 102.

In critically ill patients the escalated dose reduced VTE from 7.2% (68/941) to 4.1% (37/903) (RR: 0.57, 95% CI: 0.38 to 0.83) and increased major bleeding from 2.0% (19/944) to 3.2% (29/902) (RR: 1.60, 95% CI: 0.91 to 2.84).

In non-critically ill patients, the escalated dose reduced VTE from 3.2% (51/1587) to 1.7%% (29/1718) (RR: 0.53, 95% CI: 0.34 to 0.83) and increased major bleeding from 1.1% (17/1598) to 2.0% (34/1718) (RR: 1.86, 95% CI: 1.04 to 3.33).

Systematic Reviews and Meta-analyses with thrombotic events as prespecified endpoints

The Sholzberg et al. *systematic review and meta-analysis (August 2021)*

This was a systematic review and meta-analysis of RCTs to determine the effects of therapeutic heparin in hospital patients with COVID-19. Three RCTs compared **therapeutic heparin to lower doses of heparin** in 2854 moderately ill ward patients and three RCTs in 1191 severely ill critical care patients.[53]

Prespecified outcomes included **all-cause mortality, death or invasive of mechanical ventilation, death or organ support, death or major thrombotic event, death**

or any thrombotic event, major thrombotic events, and major bleeding. Major thrombotic events were defined as the composite of myocardial infarction, PE, ischemic stroke, or systemic arterial embolism. Any thrombotic events were defined as major thrombotic events or DVT.

In moderately ill patients there was a non-significant reduction in all-cause mortality (OR: 0.76, 95% CI: 0.57 to 1.02), **but there were significant reductions in the composite of death or invasive mechanical ventilation** (OR: 0.77, 95% CI: 0.60 to 0.98), **death or major thrombotic event** (OR: 0.64 95% CI: 0.48 to 0.86), **death or any thrombotic event** (OR: 0.58 95% CI: 0.45 to 0.77), **and major thrombotic events** (OR: 0.47, 95% CI: 0.24 to 0.90) in the therapeutic heparin group. There was a non-significant increase in major bleeding (OR: 1.45, 95% CI: 0.77 to 2.79).

In severely ill patients there was no significant reduction in all-cause mortality (OR: 1.17, 95% CI: 0.89 to 1.54), death or major thrombotic event (OR: 1.04, 95% CI: 0.80 to 1.36), death or any thrombotic event (OR: 1.04 95% CI: 0.81 to 1.34). However, **there was a significant reduction in major thrombotic events** (OR: 0.59, 95% CI: 0.38 to 0.901 in the therapeutic heparin group. This was driven by the multiplatform trial. There was a non-significant increase in major bleeding (OR: 1.62, 95% CI: 0.82 to 3.21).

The authors concluded that therapeutic heparin was beneficial in moderately ill ward patients but not in severely ill patients in critical care settings.

The Pilia et al. *systematic review and meta-analysis (August 2022)*

The aim of this systematic review and meta-analysis was to investigate the efficacy and safety of **heparin full-dose anticoagulation** in **hospitalized non-critically ill COVID-19 patients**. The primary endpoint was the rate of **major thrombotic events (arterial and venous) and the rate of major bleeding**. Four multicenter studies were identified involving 2926 patients.[54]

Major thrombotic events were 23/1524 (1.5%) in the full-dose anticoagulation *vs.* 57/1402 (4.0%) in the prophylactic dose group (RR: 0.39, 95% CI: 0.25 to 0.62; P<0.01). Clinically relevant bleeding occurred in 26/1524 (1.7%) in the full anticoagulation dose compared with 15/1403 (1.1%) in the prophylactic-dose group (RR: 1.60, 95% CI: 0.85 to 3.03; P=0.15).

Mortality was 101/1524 (6.6%) *vs.* 121/1402 (8.6%) (RR: 0.63, 95% CI: 0.33 to 1.19; P=0.15).

The authors concluded that full-dose anticoagulation with heparin was associated with lower rate of major thrombotic events without differences in bleeding and mortality in hospitalized non-critically ill COVID-19 patients.

The Pilia et al. *updated systematic review and meta-analysis (February 2023)*

This updated systematic review and meta-analysis identified six multicenter RCTs involving 3,297 non-critically ill inpatients from 13 countries across four continents.[55]

Mortality was 103/1662 (6.2%) in the full-dose group *vs.* 126/1635 (7.7%) (RR: 0.76, 95% CI: 0.59 to 0.98; P=0.037).

Major arterial and venous thrombotic events were 25/1662 (1.5%) in the full-dose anticoagulation *vs.* 63/1635 (3.9%) in the prophylactic or intermediate dose group (RR: 0.41, 95% CI: 0.26 to 0.64; P<0.01).

Clinically relevant bleeding occurred in 29/1662 (1.7%) in the full anticoagulation dose compared with 22/1636 (1.3%) in the prophylactic or intermediate dose group (RR: 1.42, 95% CI: 0.80 to 2.51; P=0.23).

The Dai et al. *systematic review and meta-analysis (November 2022)*

The aim of this systematic review and meta-analysis was to investigate the efficacy and safety of **extended thromboprophylaxis in postdischarge patients with COVID-19 at high-risk of TE**.[56] Eight studies, 7 observational and one RCT (MICHELLE see above) involving 10,148 patients were included. The patients in these studies met the following criteria: active cancer, immobility, respiratory failure, personal or family history of VTE or an IMPROVE VTE Score of ≥4 or a score of 2-3 with D-dimer level of >500 mg/mL or indications for anticoagulants at hospital discharge. More than 80% of patients in the thromboprophylaxis group received DOACS and 70% received prophylactic dose.

The composite outcome of thrombosis and all-cause mortality was associated with reduced incidence in the extended thromboprophylaxis group (OR: 0.52, 95% CI: 0.41 to 0.67; P=0.0.001). There was also, **a lower risk of postdischarge thrombosis in the group receiving extended prophylaxis (OR: 0.62, 95% CI: 0.42 to 0.94; P=0.023).** Extended thromboprophylaxis did not increase the risk of major bleeding events (OR: 1.64, 95% CI: 0.95 to 2.82; P=0.075).

Systematic review and meta-analysis with VTE (PE and symptomatic DVT) as prespecified endpoints

The Valeriani et al. *systematic review and meta-analysis (June 2022)*

The aim of this systematic review and meta-analysis was to investigate the **efficacy and safety of high-dose *vs.***

low-dose thromboprophylaxis in hospitalized patients with COVID-19. Nine RCTs involving 5470 patients were included, 2750 receiving high dose and 2652 low-dose thromboprophylaxis. Four trials included critically ill patients, four non-critically ill and one with both.[57]

Of all VTE events, 143 were PE (38 in high-dose and 94 in low-dose) and 84 were DVTs (37 in the high-dose and 46 in the low-dose prophylaxis). Thus, **VTE occurred in 2.9% of patients on high-dose and in 5.7% of patients on low-dose thromboprophylaxis (RR: 0.53, 95% CI: 0.41 to 0.69; NNT for an additional beneficial outcome 22)**. Based on these findings, high dose thromboprophylaxis would result in 27 fewer VTE events for every 1000 treated patients. Major bleeding occurred in 2.5% and 1.4% of patients respectively (RR: 1.78, 95% CI: 1.20 to 2.66; NNT for an additional harmful outcome 100).

The risk of VTE was significantly reduced by high dose thromboprophylaxis in non-critically ill (RR: 0.54, 95% CI: 0.35 to 0.86) but not in critically ill patients (RR: 0.69, 95% CI: 0.39 to 1.21).

All-cause mortality did not differ between groups (RR: 0.97, 95% CI: 0.75 to 1.26).

The authors concluded that in hospitalized patients with COVID-19, high-dose thromboprophylaxis is more effective than low-dose for the prevention of VTE but increases the risk of major bleeding.

Recommendations

For patients with an indication for anticoagulation (including diagnosed VTE, atrial fibrillation, or mechanical prosthetic valve) who have COVID-19 in any setting, **use treatment-dose anticoagulation** as otherwise indicated **(level of evidence weak, recommendation strong). Consider adding IPC (Level of evidence moderate, recommendation moderate)** by extrapolation from high-risk medical patients.

Hospitalized, critically ill patients

Hospitalized patients with COVID-19 who are critically ill, including those on high-flow oxygen by nasal cannula, **should not receive therapeutic- or intermediate-dose thromboprophylaxis** over standard low (prophylactic dose) thromboprophylaxis (based on REMAP-CAP, ATTACC, ACTIV-4a, INSPIRATION, and Perepu *et al.*) **(Level of evidence high, recommendation strong)**.

For **hospitalized patients with COVID-19 who are critically ill, we recommend treatment with prophylactic-dose anticoagulation with LMWH** (enoxaparin 40 mg daily, dalteparin 5000 units daily, tinzaparin 4500 units daily or LDUH 5000 units twice daily) over other types of anticoagulation, including DOACs (from ACTION trial) **(Level of evidence moderate, recommendation moderate)**. This recommendation is based on RCTs in COVID-19 patients and extrapolation from RCTs in medical patients without COVID-19.

Based on extrapolation from RCTs in high-risk medical patients **a combination of prophylactic LMWH combined with IPC may be considered (Level of evidence moderate, recommendation moderate)**.

Hospitalized patients with COVID-19 who are not critically ill

Hospitalized patients with COVID-19 who are not critically ill: 1) do not have an indication for anticoagulation; 2) not at high risk of bleeding (including use of dual antiplatelet therapy); and 3) have high risk features (*i.e.*, require supplemental oxygenation or have very elevated D-dimer **should receive therapeutic-dose anticoagulation** (enoxaparin 1 mg/kg twice daily, dalteparin 100 units/kg twice daily, tinzaparin 175 units/kg daily or heparin continuous iv infusion) over standard low (prophylactic dose) or intermediate-dose thromboprophylaxis (based on REMAP- CAP, ATTACC, ACTIV-4a, RAPID, and HEP-COVID, COVID-DOSE) **(Level of evidence high, recommendation strong)**.

If there is increased risk of bleeding, based on extrapolation from RCTs in high-risk medical patients, **a combination of prophylactic LMWH combined with IPC may be considered (Level of evidence moderate, recommendation moderate)**.

In all other hospitalized patients non-critically ill, prophylactic LWMH combined without or with IPC should be considered over no prophylaxis **(Level of evidence moderate, recommendation moderate)**.

Do not use DOACs except in the context of a RCT (based on BEMICOP and ACTION).

Patients discharged from hospital

For patients discharged from hospital at high-risk for VTE (IMPROVE VTE Score ≥4 or 2-3 with D-dimer >500 ng/mL), **rivaroxaban 10 mg daily for 35 days is recommended for extended thromboprophylaxis. (Level of evidence moderate, recommendation moderate)**. However, in patients who are not high-risk, routine extended postdischarge thromboprophylaxis is not recommended (from ACTIV-IVc) **(Level of evidence moderate, recommendation moderate)**.

Non-hospitalized patients

In non-hospitalized patients with COVID-19 at potential risk of disease progression and recent (up to 3 days) onset of the COVID-19 clinical symptoms, **oral sulodexide therapy may be considered** to reduce the risk of hospitalization **(Level of evidence moderate, recommendation moderate)**.

For stable outpatients with COVID-19, thromboprophylaxis with a DOAC or LMWH is not recommended (based on ACTIV-4b, ETHIC, OVID, and PREVENT-HD) **(Level of evidence high, recommendation strong)**.

Antiplatelet agents

Antiplatelet agents as add-on therapy in hospitalized COVID-19 patients in critical care or ward settings are unlikely to improve outcomes and may increase the risk of bleeding (based on RECOVERY and ACTIV-4a) **(Level of evidence high, recommendation strong)**.

Aspirin may be considered in patients not requiring hospitalization, provided there is no indication for anticoagulation **(Level of evidence low, recommendation weak)**.

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SECTION 15

Diagnosis of DVT and PE

Diagnosis of DVT

The clinician should maintain clinical vigilance to consider the possibility of DVT or PE which may occur with leg pain or shortness of breath respectively, but may alternatively be presented with subtle, atypical or no symptoms. Because the clinical symptoms and signs on their own are unreliable, a suspected DVT should be confirmed by an objective test. Currently, duplex scanning (ultrasonography), which combines venous compression with blood flow and velocity recordings, is the initial investigation of choice.[1-4] The sensitivity and specificity are in excess of 98% for DVT above the knee and in excess of 95% for DVT in the calf.[5-10] One of the advantages for ultrasound is that in the absence of DVT, it can often provide an alternative diagnosis for symptoms such as ruptured Baker cyst or muscle hematoma.

Although performing ultrasonography on every patient suspected of having DVT is feasible, it is expensive and is a strain on ultrasound resources. The combination of a clinical score with a D-dimer assay is an alternative initial approach that can spare many patients from an unnecessary ultrasound examination.

Several clinical scoring systems for DVT have been developed. These are the Wells,[11-13] Khan[14] Constans[15] and Büller[16] scoring systems. The Wells scoring system is the one most widely used and it can classify patients into low, moderate and high pre-test probabilities with a prevalence of DVT of 5%, 17% and 53% respectively.

D-dimer ELISA assay is the blood test for suspected DVT or PE.[17] This is a "rule out" test and VTE is extremely unlikely if the test is normal. However, the D-dimer lacks specificity and will be elevated in acute VTE as well as in many other illnesses such as myocardial infarction, cancer, sepsis, the postoperative state, during pregnancy and following childbirth.

The presence of a normal D-dimer test in patients with a low Wells pre-test probability can rule out DVT[11, 12] making further investigation with ultrasound unnecessary. It has been demonstrated by studies with a three month follow up that it is safe not to treat such patients with anticoagulants.[3, 18-20]

In a large, randomized study of symptomatic outpatients with a first episode of suspected DVT (ERASMUS), 2645 subjects were randomized to undergo either a "limited compression ultrasound" *i.e.*, of the proximal vein system (confined to the popliteal and common femoral vein), repeating the test after one week in those with positive D-dimer at baseline, or to have the whole-leg ultrasonography at the initial consultation.[21] Patients with normal ultrasound findings were followed up for three months. The two strategies were found to be comparable. Indeed, in the 3-month follow-up symptomatic VTE occurred in 7 of 801 patients (0.9%) in the "limited ultrasound" strategy group and in 9 of 763 patients (1.2%) in the "whole-leg" strategy group who had been labelled as free from DVT. The authors concluded that undergoing the extensive investigation of the calf vein system in all patients with suspected DVT resulted in the overdiagnosis (and consequent unavoidable anticoagulant therapy) of an exceedingly high rate of isolated calf vein thrombosis without improving the patient's follow-up.

Subsequently, the diagnostic value of an algorithm combining whole-leg and limited compression ultrasonography was tested in a prospective, cohort study at eight centres in five countries (PALLADIO).[22] Consecutive outpatients with suspected DVT underwent D-dimer measurement and pre-test clinical probability assessment,

according to the Wells criteria.[12] DVT was ruled out without further testing in the 351 patients with unlikely pre-test probability and negative D-dimer. The 401 patients in whom either pre-test probability was likely or who were positive for D-dimer underwent limited compression ultrasonography only. Finally, the 410 patients in whom pre-test probability was likely and who had a positive measurement for D-dimer underwent extended whole-leg compression ultrasonography. All patients in whom DVT was ruled out were followed up for 3 months. Overall, the 3-month VTE incidence in untreated patients after a negative diagnostic strategy was extremely low (0.87%; 95% CI: 0.44-1.70).[22] This approach is the one most likely to encounter the clinician's and patient's exigencies. It spares objective tests in one third of patients, and of the remaining limits the need for the extensive investigation of the calf vein system to the subgroup of those who despite a negative proximal vein system have a positive D-dimer and inexplicable calf complaints, and thus, limiting the indication for anticoagulant treatment to those patients who are likely to merit it.

The safety of excluding ultrasound examination for patients with a combination of negative Wells Score and negative D-dimer was also tested in another large prospective observational study of 3087 patients with clinical symptoms suggestive of DVT assessed in the emergency departments of a large healthcare system.[23] Ultrasound technologists and interpreting physicians were blinded to results of risk assessment. All patients had a bilateral whole-leg ultrasound, in addition to Wells score and D-dimer. A total of 3087 patients were enrolled. The overall prevalence of acute DVT was 7.3%. A negative plasma D-dimer level and Wells score was found in 2290 patients. A total of 222 patients had a positive plasma D-dimer level and Wells Score. Of the 2290 patients with a negative Wells Score and negative plasma D-dimer level, 4 had DVT (negative predictive value, 99.8%). In contrast, DVT was present in 181 (81.5%) of 222 patients with a positive Wells Score and plasma D-dimer level (positive predictive value, 81.5%). The plasma D-dimer level also correlated with the DVT location, and the D-dimer levels were highest for the patients with proximal DVT.

Diagnosis of PE

In cases in which physicians have an implicit sense that their patient is very unlikely to have PE (estimated likelihood <2%), large cohort studies have shown that the Pulmonary Embolism Rule-out Criteria (PERC) can safely rule out PE without further diagnostic imaging.[24] In practice, however, implicit estimation typically overestimates the probability of PE, which can limit the use of the PERC rule.

Physicians should be familiar with a validated decision rule to guide the use of D-dimer testing. Among patients with a low structured clinical probability score such as a Wells score of 4.0 or less, a revised Geneva Score of 10 or less, or a simplified Geneva Score of 4 or less, PE can be safely ruled out based on D-dimer levels when manufacturer-recommended cut-offs are used.[25]

Newer approaches have adjusted the D-dimer threshold for ruling out PE and are validated for D-dimer assays for which the manufacturer-recommended cut-off is equivalent to 500 ng/mL. These strategies include D-dimer levels that are adjusted for age[26, 27] or that are adjusted to the YEARS algorithm[28] or the Wells Score[29] for ruling out PE.

Diagnostic imaging is reserved for patients in whom PE cannot be ruled out based on a decision rule, given the potential harms of radiation exposure. CT pulmonary angiography is usually the most timely and accessible imaging technique. However, to minimize lung and breast-tissue irradiation in younger patients, ventilation/perfusion single-photon-emission CT (SPECT) is a low-radiation option.[30]

Isotope lung scanning has now been relegated to a second-choice imaging test reserved for patients in whom use of contrast agent might be hazardous such as those with renal failure and to avoid radiation in young people or the breast. Avoidance of an unnecessary spiral CT scan prevents patients from exposure to substantial ionizing radiation which has significant risks.[31, 32] In young non-pregnant women with suspected PE and normal chest X-ray, nuclear perfusion lung scan may be preferred to CT lung scan, because of concern about the degree of lifetime radiation exposure and risk of cancer (*e.g.*, breast cancer). In women with suspected or confirmed pregnancy, the mother may likewise prefer nuclear perfusion lung scanning as an alternative to CT lung scanning to reduce fetal radiation exposure.

Concluding remarks

This section presents a variety of diagnostic schemes that are all valid, making it problematic and even misleading to give priority of one over another. What is valid for outpatients is not necessarily right for inpatients or different presentations or in the presence of different comorbidities. Thus, unlike sections on prevention or therapy, this section does not provide formal recommendations.

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SECTION 16

Anticoagulation therapy for VTE

For other therapeutic aspects (thrombolysis, thrombectomy, treatment in cancer patients, IVC filters) please see subsequent sections.

General considerations

The objectives for treating acute VTE are to prevent death and disability from PE, development of pulmonary hypertension, recurrence of VTE, and development of PTS because of persistent venous obstruction and/or reflux because of dysfunction of the venous valves.[1] Extension of recurrent DVT into the collateral circulation produces further outflow obstruction and progressive swelling of the leg. Rapid extension can result in increased compartmental pressure possibly leading to phlegmasia cerulea dolens, which although rare and often associated with metastatic cancer, may lead to venous gangrene and limb loss.

It has been demonstrated that asymptomatic DVT including isolated calf vein thrombosis may lead to subsequent development of PTS[2] and that 18% of symptomatic calf DVTs are associated with proximal extension or recurrence[3] suggesting that below knee DVT merits treatment.

A systematic review and meta-analysis published in 2023 included seven prospective cohorts with a total of 1,105 patients who had isolated calf DVT and had reported on the development of PTS.[4] The PTS rate was 17% (95% CI: 11% to 26%). Three studies reported the severity of PTS: 78% were mild (Villalta Score 5-9); 11% were moderate (Villalta Score 10-14) and 11% were severe (Villalta Score ≥15). The authors concluded that the risk of PTS after isolated distal DVT was one in five and the risk of severe clinical manifestations including ulceration was one in 50. They added that RCTs to support interventions for prevention of PTS are urgently needed.

Anticoagulation regimens

A. Anticoagulation therapy with heparin followed by VKA

Unfractionated heparin followed by VKA

Unfractionated heparin followed by VKA was the standard therapy in the 1970s and 1980s.

In patients with DVT, therapy with VKA alone in the absence of initial heparin therapy was associated in one study with an unacceptable 20% rate of recurrent symptomatic VTE compared with 6.7% in those who had heparin followed by VKA (P=0.058).[5] Also, extension of DVT was observed in 39.6% of patients on VKA alone, but only in 8.2% of patients treated initially with heparin and subsequently VKA (P<0.001). Thus, initial parenteral heparin and subsequent long-term oral anticoagulation with VKA were both necessary.[1, 5]

Several studies suggested that when using UFH for the initial treatment of DVT, rapid achievement of an activated partial thromboplastin time (APTT) within the therapeutic range (2.0 to 3.0 times the control) within 24 hours reduced the rate of recurrent DVT.[6-8] However, other studies did not confirm this finding.[9, 10]

Vitamin K antagonist (VKA) treatment should be adjusted to maintain the INR between 2.0 to 3.0 (target INR 2.5). The risk of bleeding in relation to different INR ranges as reported by several studies is shown in Table 16.I.[11-16]

TABLE 16.I.—*Major bleeding complication rate according to INR intensity.*

Trial	INR range	Event rate per 100 person-years
Kearon *et al.*[11]	2.0-3.0	3.8
Schulman *et al.*[12]	2.0-2.85	2.4
Kearon *et al.*[13]	2.0-3.0	0.9
Kearon *et al.*[13]	1.5-1.9	1.1

An INR greater than 4.0 was associated with an increased frequency of hemorrhagic side effects.[17-19] VKA may be started on the first day of heparin therapy except when patients require thrombolysis or surgery, or where there are co-morbidities that predispose to major bleeding.[20-22]

LMWH followed by VKA

Findings from RCTs in the 1990s resulted in **LMWH replacing LDUH** in the initial treatment of DVT. These studies concluded that LMWH was at least as effective and safe as initial treatment for acute VTE compared with intravenous UFH.[23-33] **LMWH** was also reported to be as effective and safe as intravenous UFH in patients with acute PE.[34-36] Thus, anticoagulation usually started with **LMWH** for patients with PE.

Treatment with intravenous UFH, which generally requires hospitalization, is now less frequently used but remains a preferable therapy in patients with massive or submassive PE in the presence of chronic kidney disease in view of the increased risk of bleeding in such patients.

In contrast to UFH, **LMWHs have a consistent dose-response** with predictable bioavailability when given subcutaneously. They do not require hematological monitoring apart from the platelet count. They may be administered once a day.[26, 37-40] Prior to the introduction of DOACs, these properties had made LMWH the preferred treatment for patients with uncomplicated DVT as outpatients.[1, 41-49] At that time, LMWH was administered for at least five days[20, 21] and was discontinued when the patient's INR was stable within the therapeutic range of 2.0 to 3.0.

LMWH vs. *VKA*

Five studies involving 1818 patients compared the effect of therapeutic or near **therapeutic LMWH doses for 3-6 months** on VTE recurrence compared with conventional VKA therapy,[50-54] mainly **in non-cancer patients**, although three studies included some patients with cancer.[50, 53, 54] One reported the results in the patients with cancer separately.[53] The incidence of recurrent VTE was 4.0% in the LMWH groups and 6.2% in the VKA groups (RR: 0.68, 95% CI: 0.45 to 1.022).

Four studies involving 1201 patients studied the effect of therapeutic or near **therapeutic LMWH doses for 3-12 months** on VTE recurrence **compared with conventional VKA therapy in patients with cancer**.[55-58] The incidence of recurrent VTE was 7.5% in the LMWH groups and 16.1% in the VKA groups (RR: 0.46, 95% CI: 0.33 to 0.65).

The incidence of major bleeding in all the studies mentioned above involving non cancer and cancer patients was 3.2% in the LMWH group and 3.9% in the VKA group (RR: 0.83, 95% CI: 0.56 to 1.22).[1]

It appears that long-term LMWH is equally effective as standard therapy for preventing recurrent VTE in patients without cancer, but more effective for patients with cancer (see Section 17 on treatment of cancer-associated thrombosis).

Standard treatment of DVT (initial LMWH for five days followed by VKA) prevents thrombus extension and embolization but does not directly lyse the thrombus and this frequently results in partial recanalization. Several RCTs that compared **long-term treatment with LMWH with VKA therapy** demonstrated **better recanalization in the long term LMWH groups**.[52, 53, 59-62]

A meta-analysis of five RCTs that reported on total recanalization, published in 2011, demonstrated a risk ratio of 0.66 (95% CI: 0.57 to 0.77; P<0.0001) in favour of long-term LMWH.[63]

In a large multicenter RCT involving 480 patients there was a reduction in PTS in favor of LMWH (RR: 0.77; P=0.001).[51] Pooled analysis on two studies reporting on the subsequent development of leg ulcers[51, 64] yielded an 87% risk reduction for venous ulcers with LMWH (P=0.019).[63]

In patients with severe chronic kidney disease, LMWH in therapeutic doses poses a high risk of major bleeding due to prolonged half-life. Although the actual risk of major bleeding has not been assessed in prospective studies, it seems appropriate to individualize the doses according to the degree of renal failure and, wherever possible, to the plasmatic anti-Xa level.

Although protamine sulphate is efficacious in reversing LMWH-induced bleeding in some animal models, there are only limited data for humans.

Fondaparinux

An RCT has demonstrated that **fondaparinux** is as effective as intravenous UFH for the initial treatment of DVT and PE.[65, 66] Fondaparinux is administered once daily. HIT is rare. Attention to labelling is essential in patients with impaired renal function where the risk of bleeding is increased due to the prolonged half-life of fondaparinux with renal elimination.

Duration of anticoagulation with standard therapy

4-6 WEEKS *vs.* 3-6 MONTHS

Four RCTs involving 1988 patients with a first unprovoked DVT (mainly proximal) or PE **compared 4-6 weeks with three or six months of anticoagulation with VKA.** Follow-up was 1-2 years.[67-70] **The incidence of**

recurrence was reduced from 12.6% in the 4-6 weeks group to 6.7% in the 3-6 months group (RR: 0.53, 95% CI: 0.40 to 0.71). The incidence of major hemorrhage was increased from 0.61% in the 4-6 weeks group to 1.0% in the 3-6 months group (RR: 1.65, 95% CI: 0.60 to 4.53).

Three months *vs.* 6-12 months

Four RCTs involving 1,736 patients with first unprovoked DVT (mainly proximal) or PE compared **three months with six or 12 months of anticoagulation with VKA**.[71-74] Follow-up was one to three years. The incidence of recurrence was 9.7% in the three-month group and 9.6% in the 6-12-month group (RR: 0.99; 95% CI: 0.74 to 1.32). The incidence of major hemorrhage was increased from 0.93% in the three-month group to 2.4% in the 6-12-month group (RR: 2.5, 95% CI: 1.16 to 5.83).

3-6 months *vs.* indefinite anticoagulation

Four studies involving 676 patients, the majority with second unprovoked DVT (mainly proximal) or PE, compared **3 to 6 months of anticoagulation with VKA (INR 2-3) with indefinite duration of anticoagulation**.[11, 12, 14, 15] Follow-up was 1.4 to four years. **The incidence of recurrence was reduced from 18.8% in the 3 to 6-month group to 2.7% in the indefinite duration group (RR: 0.18; 95% CI: 0.09 to 10.36).** The incidence of major hemorrhage was increased from 1.5% in the 3–6-month group to 4.6% in the indefinite duration group (RR: 3.03, 95% CI: 1.12 to 8.19).

B. Anticoagulation therapy with DOACs

Rivaroxaban

Rivaroxaban is an oral direct inhibitor of Xa. **In a phase III non-inferiority RCT**, 3449 patients with acute, symptomatic DVT were **randomized to rivaroxaban** (15 mg twice daily for three weeks, followed by 20 mg once daily without initial parenteral anticoagulant therapy) **or enoxaparin followed by VKA for three, six or 12 months** (duration according to treating physician's discretion**). Recurrent VTE occurred in 2.1% in the rivaroxaban group and in 3.0% in the control group** (RR: 0.70, 95% CI: 0.46 to 1.07; P<0.0001 for non-inferiority and P=0.076 for superiority of rivaroxaban). Major bleeding or clinically relevant non-major bleeding occurred in 8.1% of patients in each group.[13]

In an RCT involving 4832 patients who had symptomatic PE with or without DVT, **rivaroxaban** (15 mg twice daily for three weeks, followed by 20 mg once daily) **was compared with standard therapy** (enoxaparin followed by an adjusted dose of VKA) for three, six, or 12 months. **Rivaroxaban was non-inferior to standard therapy for symptomatic recurrent PE (RR: 1.12, 95% CI: 0.75 to 1.68; P=0.003) for non-inferiority**. Major bleeding was 1.1% in the rivaroxaban group and 2.2% in the standard-therapy group (RR: 0.49, 95% CI: 0.31 to 0.79; P=0.003).[75] In conclusion, a fixed-dose regimen of rivaroxaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with significantly less major bleeding.

Apixaban

Apixaban, an oral inhibitor of factor Xa, **was compared with standard therapy** at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for six months in a double-blind RCT against conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute VTE.[76] **The primary efficacy outcome** (a composite of symptomatic recurrent VTE and VTE-related death) **occurred in 2.3% of patients randomized to apixaban, and in 2.7% of those allocated to the conventional therapy group.** Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received conventional therapy (P<0.001). In conclusion, a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with significantly less major bleeding.

Edoxaban

Edoxaban, another inhibitor of factor Xa, **was compared with standard therapy** in a double-blind RCT in almost 9000 patients with VTE.[77] After receiving 5 days of parenteral anticoagulation, patients were randomized to receive edoxaban at a dose of 60 mg once daily (halved in patients with moderate chronic kidney disease, body weight below 60 kg or simultaneous administration of strong inhibitors of P-glycoprotein), or warfarin. Patients received the study drug **for 3 to 12 months. Edoxaban was noninferior to warfarin** with respect to the primary efficacy outcome (a composite of fatal or non-fatal recurrent VTE occurring during the 12-month follow-up period, irrespective of the duration of treatment), which occurred in 3.2% of patients in the edoxaban group and in 3.5% in the warfarin group. The safety outcome occurred in 8.5% of patients in the edoxaban group and 10.3% in the warfarin group (P=0.004). In conclusion, edoxaban administered once daily after initial treatment with heparin was as effective as standard anticoagulation, but also safer, in a broad spectrum of patients with VTE, including a substantial subgroup of patients with severe PE.

Dabigatran

Dabigatran is an oral direct inhibitor of thrombin. In a phase III non-inferiority RCT, 2539 patients with acute symptomatic DVT who were initially given parenteral anticoagulation therapy for 8-11 days, were **randomized to** oral dabigatran, administered at a dose of 150 mg twice daily, **or warfarin** that was dose-adjusted to achieve an international normalized ratio of 2.0 to 3.0.[78] The primary outcome was the 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Safety end points included bleeding events, acute coronary syndromes, other adverse events, and results of liver-function tests. **Recurrent VTE occurred in 2.4% in the dabigatran group and in 2.1% in the control group (RR: 1.10, 95% CI: 0.66 to 1.84; P<0.001 for non-inferiority)**. Major bleeding occurred in 1.6% of patients in the dabigatran group and in 1.9% in the standard therapy group (RR: 0.83, 95% CI: 0.46 to 1.49). The authors concluded that a fixed dose of dabigatran is as effective as warfarin, has a safety profile that is like that of warfarin, and does not require laboratory monitoring in the dabigatran group.

Isolated calf DVT

In 1984, a randomized study of 51 patients with symptomatic isolated calf DVT, of whom **23 received warfarin for three months and 28 did not**, investigated the rate of recurrence.[79] Recurrences and their extent were confirmed with venography. Both groups received an initial course of heparin, and all patients wore compression stockings. During the first three months, recurrence occurred in 29% of patients in the non-warfarin group compared with none in the warfarin group (P<0.01). Five of these patients had a recurrence with proximal extension and one had a pulmonary embolus. At one year, one (4.3%) out of 23 patients in the warfarin group had a recurrence, compared with 19 (68%) out of 28 in the non-warfarin group (RR: 0.13, 95% CI: 0.02 to 0.99). The findings suggested that oral anticoagulants should be given to all patients with symptomatic isolated calf DVT and that three months seemed to be sufficient.

However, a study in 2016 (the CACTUS study) questioned these conclusions.[80] This was a double-blind, placebo-controlled RCT involving 259 low-risk outpatients (without active cancer or previous VTE) with a first acute symptomatic DVT in the calf who were assigned to receive either **LMWH** (nadroparin 171 UI/kg, subcutaneously, once daily) **or placebo** for 6 weeks. There was no significant difference between the groups in the composite primary outcome (a composite of extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic PE), which occurred in 4 (3%) patients in the LMWH group and in 7 (5%) in the placebo group (P=0.54). Bleeding occurred in five patients (4%) in the LMWH group and no patients in the placebo group (P=0.03). It was concluded that nadroparin was not superior to placebo in reducing the risk of proximal extension or venous thromboembolic events in low-risk outpatients with symptomatic calf DVT but did increase the risk of bleeding. Accordingly, in patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, guidelines suggested serial imaging of the deep veins for two weeks over anticoagulation; by contrast, in patients with severe symptoms or risk factors for extension, anticoagulation was suggested over serial imaging of the deep veins.[81]

Two schools of thought

The finding that in the presence of isolated calf DVT, fatal PE did not occur resulted in **a school of thought that routine anticoagulation was unnecessary** and surveillance with ultrasound would suffice, reserving anticoagulation for those in which the thrombus would extend into the popliteal or more proximal veins. However, the realization that local damage to the venous valves with the development of reflux, skin changes, and symptoms of persistent pain and edema in 10-23% of patients leading to chronic venous disease CEAP C4-C6 clinical classes and a DVT recurrence rate of up to 14%[82-84] led to the development of another school of thought that **such patients should be routinely anticoagulated** unless there were absolute contraindications.

Rivaroxaban for isolated calf DVT

In the most recent double-blind RCT (RIDTS) addressing the optimal duration of anticoagulation in patients with symptomatic isolated calf DVT, the administration of therapeutic doses of **rivaroxaban (20 mg once daily) for three months** was found to reduce the incidence of recurrent VTE over a 2-year follow-up period **compared with a shorter course (six weeks)** without increasing the hemorrhagic risk.[85] Indeed, among the 404 patients that were recruited, **the primary efficacy outcome** (composite of isolated distal DVT, recurrent isolated distal DVT, proximal DVT, symptomatic PE, or fatal PE) **occurred in 23 (11%) patients in the rivaroxaban arm and 39 (19%) in the placebo arm (RR: 0.59, 95% CI: 0.36 to 0.95)**. No major bleeding events occurred.

Systematic reviews and meta-analyses

A systematic literature review and meta-analysis of 24 studies on the duration of anticoagulant therapy in patients with isolated calf DVT, involving 2,936 patients was published in 2016.[86] Of these, five studies were RCTs, seven were prospective cohort studies, seven were retrospective studies and one was a combined prospective and retrospective cohort study. Four additional studies compared different durations of anticoagulation. **Recurrent VTE** (proximal propagation, recurrence of DVT or PE) **was reduced from 11.1% in patients not on anticoagulation to 6.5% in patients on anticoagulation (OR: 0.50, 95% CI: 0.15 to 0.73) without an increase in major bleeding**. Recurrent DVT was reduced from 6.5% to 1.5% (OR: 0.23, 95% CI: 0.08 to 0.65) and PE was reduced from 2.4% to 1.4% (OR: 0.48, 95% CI: 0.25-0.91). **The recurrence rate of VTE was reduced from 10.7% in those receiving anticoagulation for less than six weeks to 3.2% in those receiving anticoagulation for more than six weeks (OR: 0.39, 95% CI: 0.17 to 0.90)**. The authors concluded that in patients with isolated calf DVT, anticoagulation reduces the incidence of PE and recurrent DVT without increased risk of major bleeding. Although most patients on anticoagulants in the studies included in the meta-analysis were receiving VKA, the authors suggested that direct oral anticoagulants should be considered for treatment of isolated calf DVT, given their improved efficacy-to-safety profile.

The most recent Cochrane systematic review and meta-analysis[87] published in 2020 identified eight RCTs involving 1,239 patients with isolated calf DVT. In five trials anticoagulation therapy was up to three months and in three trials anticoagulation of different periods was used. Recurrence of VTE was reduced from 9.1% in the placebo/no intervention group to 2.9% in the VKA group (RR: 0.34, 95% CI: 0.15 to 0.77). **There was not any significant difference in the risk of PE, but the risk of DVT recurrence was reduced from 7.9% to 1.65% (RR: 0.25, 95% CI: 0.10 to 0.67)**. There was not any significant increase in major bleeding, but there was an increase in clinically relevant non-major bleeding from 1.8% to 7.0% (RR: 3.34, 95% CI: 1.07 to 10.46). In three RCTs comparing treatment with VKA for three or more months to six weeks, **treatment for three months or more reduced the incidence of VTE from 13.9% in the six-week group to 5.8% in the three or more months group (RR: 0.42, 95% CI: 0.26 to 0.68).** The risk of recurrent DVT was also reduced from 14.4% to 4.8% (RR: 0.32, 95% CI: 0.16 to 0.64).

Key messages

Based on the results of the above studies and a meta-analysis of all RCTs addressing the comparison between DOACs and conventional therapy for the initial and short-term therapy (3-6 months) treatment of acute isolated calf DVT treatment with DOACs is as effective as standard therapy and is associated with a reduction in the risk of major bleeding complications that is not only statistically significant but also clinically relevant, as intracranial and fatal bleeding are the most reduced types.[86-88]

C. Secondary prevention of VTE

The aim of extending the duration of treatment is to prevent recurrent DVT which depends on several risk factors. The risk is low if DVT occurs in the presence of a reversible risk factor, but the risk is high if DVT is unprovoked,[67-71, 89-96] occurs in the presence of active cancer or any other non-transient risk factor.[89, 93, 94, 97] Patients with symptomatic PE have a higher risk of PE recurrence than those with DVT alone.[98]

The lowest risk is found when surgery is the reversible risk factor.[90, 99] The estimated five-year cumulative risk of recurrent VTE after stopping anticoagulation is 3% if proximal DVT is provoked by surgery, 15% if provoked by a non-surgical reversible risk factor and 30% if unprovoked.[1] The RR: is 2.0 for proximal DVT or PE compared with calf DVT,[69, 71, 92, 96, 98] 1.5 if DVT is a second episode,[55, 97, 100] 2.0 if antiphospholipid antibody is present,[14, 101-103] 1.5 in the presence of a hereditary thrombophilia,[14, 90, 91, 103-111] 1.5 in the presence of residual thrombosis in the proximal veins[14, 70, 72, 103, 112-114] and 1.6 for male gender.[115, 116] The risk is higher in the presence of multiple risk factors, homozygous inherited thrombophilia, or a combination of heterozygous thrombophilias (see Section 13 on thrombophilia). In patients with unprovoked VTE, factors that are consistently associated with an increased risk of recurrent VTE after discontinuing anticoagulation are male gender, obesity, proximal location of DVT, thrombophilia and chronic kidney disease.[117] Old age does not seem to increase the risk of recurrent VTE.[118, 119]

Rivaroxaban

The efficacy of rivaroxaban in secondary prevention of recurrent VTE was tested in the EINSTEIN-extension study performed in parallel with the EINSTEIN study and was reported in the same publication. In this RCT, 1197 patients who had completed their anticoagulation (6-12 months) were randomized to continue with **rivaroxaban**

or placebo for a further 6-12-month period. **The recurrence rates for VTE were 1.3% in the rivaroxaban group and 7.1% in the placebo group (RR: 0.22, 95% CI: 0.11 to 0.45; P<0.001)**. The non-fatal major bleeding rate was 0.7% in the rivaroxaban group and zero in the placebo group (P=0.11).[13]

In a subsequent randomized, double-blind controlled trial (EINSTEIN CHOICE) 3,365 patients who had completed 6 to12 month therapy for DVT or PE were assigned in an 1-1-1 ratio to receive **20 mg of rivaroxaban, 10 mg of rivaroxaban or 100 mg aspirin** all given once daily with food for 12 months.[120] Recurrent VTE occurred in 1.5% of patients in the rivaroxaban 20 mg group, 1.2% in the rivaroxaban 10 mg group and 4.4% in the aspirin group. **The hazard ratios (HR) between the rivaroxaban 20 mg group and 10 mg group when compared with the aspirin group were 0.34 (95% CI: 0.20 to 0.59) and 0.26 (95% CI: 0.14 to 0.47) respectively**. There was no difference between the two rivaroxaban groups (HR: 1.34, 95% CI: 0.65 to 2.75; P=0.42). Major bleeding occurred in 0.5% in the 20 mg rivaroxaban group, 0.4% in the 10 mg rivaroxaban group and 0.3% in the aspirin group. Clinically relevant nonmajor bleeding occurred in 2.7% in the 20 mg rivaroxaban group, 2.0% in the 10 mg rivaroxaban group and 1.8% in the aspirin group. **Thus, compared with aspirin, rivaroxaban 10 mg or 20 mg per day reduced recurrent VTE by about 70%**. This 70% reduction occurred equally in both the provoked and unprovoked VTE groups of patients.

Apixaban

A double-blind randomized study involving 2486 patients **compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo** in patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy.[121] The study drugs were administered for 12 months.

Symptomatic recurrent VTE or death from VTE occurred in 8.8% patients in the placebo group, compared with 1.7% patients in the 2.5 mg of apixaban group and 1.7% patients in the 5 mg of apixaban group (P<0.001 for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The rates of clinically relevant non-major bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group (HR 1.20, 95% CI: 0.69 to 2.10; P=NS), and 4.2% in the 5-mg apixaban group (HR: 1.62, 95% CI: 0.96 to 2.73; P=NS).

It was concluded that extended anticoagulation with apixaban at either a therapeutic dose (5 mg) or a prophylactic dose (2.5 mg) reduced the risk of recurrent VTE compared with placebo without increasing the rate of major bleeding.

Dabigatran

The efficacy of **dabigatran** in secondary prevention of recurrent VTE was tested in two studies. In the first (RESONATE) 1,343 patients who had completed anticoagulation (6-18 months) were **randomized to continue with dabigatran or placebo** for a further six-month period.[122] **The recurrence rate for VTE was 0.4% in the dabigatran group and 5.6% in the placebo group (RR: 0.08, 95% CI: 0.02 to 0.25; P<0.001)**. Non-fatal major bleeding occurred in 0.3% of the dabigatran group and zero in the placebo group (P=0.996).

In the second study (RE-MEDY), published simultaneously, l2,856 patients who had completed anticoagulation (3-12 months) were **randomized to receive dabigatran or conventional warfarin** for up to 36 months.[122] **The recurrence rate for VTE was 1.8% in the dabigatran group and 1.3% in the warfarin group (RR: 1.44, 95% CI: 0.78 to 2.64; P<0.027 for non-inferiority)**. The rate of major bleeding was 0.9% in the dabigatran group and 1.8% in the warfarin group (HR 0.52, 95% CI: 0.27 to 1.02; P=0.058). In this study a higher number of acute coronary syndromes were observed during treatment with dabigatran compared with warfarin (0.9% *vs.* 0.2%; P=0.02).

Aspirin

Two RCT (WARFASA and ASPIRE) involving a total of 1,284 patients who had completed 6 to 18 months of oral anticoagulant treatment for a first unprovoked DVT have tested the efficacy of aspirin 100 mg daily in preventing DVT recurrence.[123, 124] In a pooled analysis of both studies the **DVT recurrence rate was 13.8% in the aspirin groups and 19.1% in the placebo groups (HR: 0.68; 95% CI: 0.51 to 0.90) (P=0.007)**.[124] Adverse events were similar in the 2 groups.

Sulodexide

In a multicentre, double-blind study, 615 patients with first-ever unprovoked VTE who had completed 3 to 12 months of oral anticoagulant treatment were **randomly assigned to sulodexide 500 lipasemic units twice daily or placebo for 2 years**, in addition to elastic stockings.[125]

VTE recurred in 15 of the 307 patients who received sulodexide and in 30 of the 308 patients who received

placebo (HR: 0.49, 95% CI: 0.27 to 0.92; P=0.02). The analysis in which patients lost to follow-up were assigned to failure yielded a risk ratio among treated *vs.* control subjects of 0.54 (95% CI: 0.35 to 0.85; P=0.009). No major bleeding episodes occurred; 2 patients in each treatment group had clinically relevant bleeding episodes. Adverse events were similar in the 2 groups.

It was concluded that sulodexide given after discontinuation of anticoagulant treatment compared with placebo reduced the risk of recurrence in patients with unprovoked VTE, with no apparent increase of bleeding risk.

A five-year follow-up for development of PTS was performed in a registry of patients with DVT.[126] Patients were admitted to the registry after completion of the anticoagulation period. A group of 167 patients received "standard therapy" of elastic compression, a second group of 124 patients received sulodexide and a third group of 48 received aspirin. The incidence of PTS was 14.9% at one year and 19.5% at 5 years in the "standard therapy" group. It was 8.8% at one year and 12.2% at 5 years in the sulodexide group (P<0.05). It was 23.5% at 54 months in the aspirin group compared with 12.2% in the sulodexide and 18.2% in the "Standard therapy" groups (P<0.05). The authors concluded that RCTs are needed to validate these results.

Efficacy of extended anticoagulation

In patients with unprovoked VTE almost every contemporary trial has found that prolonged anticoagulation with VKA reduces long-term recurrence by about two thirds,[96, 117] but increases the risk of major bleeding.[127, 128] In addition, while the case-fatality rate of major bleeding complications is consistently around 8-10%[127] that for recurrent VTE decreases to 3% after completing an initial treatment period of three to six months.[129, 130] Accordingly, the benefit-to-risk for indefinitely prolonging anticoagulation in patients with unprovoked VTE should be carefully assessed and individually tailored.

In patients with unprovoked VTE, the administration of a 'fixed' duration of anticoagulation using VKA of whichever length does not improve the long-term outcome over the conventional 3-month period. Based on the results of a meta-analysis of all available randomized clinical trials where different duration of anticoagulation had been tested, prolonging anticoagulation (up to 27 months) simply delayed the timing of recurrences.[96] This conclusion has recently been supported by the results of two French randomized clinical trials, the PADIS PE and the PADIS DVT studies, where the administration of two years of anticoagulation with VKA in patients with unprovoked PE and DVT, respectively, did not improve the clinical outcome over the conventional 6-month period.[131, 132]

The conclusions that are valid for patients with unprovoked VTE are likely to be extended to incorporate patients with VTE triggered by or associated with minor (either persistent or transient) risk factors of thrombosis. Indeed, in an analysis where the results of the Einstein Extension and of the Einstein Choice studies had been aggregated, the risk of recurrent VTE in patients with minor (either persistent or transient) risk factors of thrombosis was substantial and was diminished by each of the two doses of rivaroxaban that had been tested.[133]

D. Risk of bleeding *vs.* risk of VTE recurrence

The reluctance to prescribe extended anticoagulation because of the relatively high risk of major bleeding has now been overcome by: 1) the efficacy of low dose DOACs which is safer and more effective than VKA; 2) strategies to identify patients at increased risk of recurrence; 3) risk stratification models; and 4) bleeding risk models. The evidence for these is summarized below.

a. The efficacy of low-dose DOACs

Soon after the favorable results achieved by extended therapy by rivaroxaban or dabigatran for protection against recurrent VTE in patients with unprovoked VTE in comparison with placebo or warfarin,[13, 78] two RCT tested the value of prophylactic doses of apixaban and rivaroxaban for this indication. As presented above, the study that tested **apixaban** enrolled patients with unprovoked VTE to receive therapeutic doses (5 mg twice daily), prophylactic doses (2.5 mg twice daily) or placebo for 1 year after completion of conventional therapy.[121] The study that tested rivaroxaban had similar characteristics, but extended the recruitment to all patients in whom, regardless of the nature of the thrombotic event, there was uncertainty about the duration of anticoagulation, and used low-dose aspirin instead of a placebo.[120] Hence, patients were randomized to rivaroxaban 20 mg, rivaroxaban 10 mg or aspirin 100 mg once daily. The results of the two studies were similar, demonstrating the clear superiority of both doses tested over the comparator for prevention of recurrent symptomatic thromboembolic events, a substantial equivalence in terms of efficacy between therapeutic and prophylactic doses, and a substantial equivalence in terms of safety between prophylactic doses and the comparator that was used (placebo and aspirin, respectively).

In consideration of the high benefit/risk profile of prophylactic doses of DOACs for the long-term treatment of

patients with unprovoked VTE, low-dose DOACs have the potential to represent the reference standard for the long-term prevention of recurrent VTE in a wide spectrum of patients, including not only those with unprovoked VTE but also those with "weakly" provoked VTE, especially those with (minor) persistent risk factors, such as inflammatory bowel disease, obesity, congestive heart failure, minor thrombophilia, leg paralysis or paresis or renal failure.[133] By contrast, it seems prudent to maintain therapeutic doses of DOACs in patients at a particularly high risk of recurrences, such as those with active cancer or antiphospholipid syndrome, severe hereditary thrombophilias, and patients with recurrent VTE while on antiplatelet or anticoagulant treatment.

b. Strategies to identify patients at increased risk of DVT recurrence

(I) Residual thrombus and recurrence of DVT

In the DACUS study, ultrasound was used to determine the presence of residual thrombus.[134] Residual venous thrombus was considered present (RVT+) if on compression organized thrombus occupied more than 40% of the vein diameter. It was considered absent (RVT-) if thrombus occupied less than 40% of the vein diameter.

Patients with a first episode of DVT and treated with oral anticoagulant therapy with VKA for three months, were managed according to residual thrombus findings. Those who were RVT+ were randomized to either stop or continue anticoagulants for nine additional months, whereas in those who were RVT-, anticoagulant therapy was stopped. **Outcomes were recurrent venous thromboembolism and/or major bleeding**. Residual thrombosis was detected in 180 (69.8%) of 258 patients; recurrent events occurred in 27.2% of those who discontinued (25/92; 15.2% person-years) and 19.3% of those who continued with anticoagulant therapy (17/88; 10.1% person-years). The relative adjusted HR was 1.58 (95% CI, 0.85-2.93; P=0.145). Of the 78 (30.2%) patients with RVT-, only one of them (1.3%; 0.63% person-years) had a recurrence. The adjusted HR of patients with RVT+ *vs.* those with RVT- was 24.9 (95% CI: 3.4-183.6; P=0.002). One major bleeding event (1.1%; 0.53% person-years) occurred in patients who stopped and another two occurred (2.3%; 1.1% person-years) in those who continued anticoagulant therapy. **It was concluded that absence of residual venous thrombus (RVT-) identified a group of patients at very low risk for recurrent thrombosis who could safely stop anticoagulant therapy**.

The extended DACUS study was a prospective study to assess the optimal duration of VKA therapy considering the risk of DVT recurrence according to residual vein thrombus.[135] Patients with a first unprovoked DVT were evaluated for the presence of residual vein thrombosis after 3 months of VKA administration; those who were RVT- suspended VKA, while those who were RVT+ continued with anticoagulation for up to 2 years. Recurrent thrombosis and/or bleeding events were recorded during treatment (RVT+ group) and 1 year after VKA withdrawal (both groups). Among 409 patients evaluated for unprovoked DVT, 33.2% (136 of 409 patients) were RVT- and VKA was stopped. The remaining 273 (66.8%) patients who were RVT+ received anticoagulants for an additional 21 months. During this period of treatment, recurrent VTE and major bleeding occurred in 4.7% and 1.1% of patients, respectively. After VKA suspension, the rates of recurrent thrombotic events were 1.4% and 10.4% in the RVT- and RVT+ groups, respectively (RR: 7.4, 95% CI: 4.9 to 9.9). **These results indicate that in patients who are RVT-, a short period of treatment with a VKA is sufficient; in those who are RVT+, treatment extended to 2 years substantially reduces, but does not eliminate, the risk of recurrent thrombosis**.

(II) D-dimer and recurrence of DVT

D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first unprovoked proximal DVT or PE who had received a VKA for at least 3 months was performed in the study.[11] Patients with a normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume anticoagulation with VKA or to discontinue treatment. The study **outcome was the composite of recurrent DVT and major bleeding** during an average follow-up of 1.4 years. The D-dimer assay was abnormal in 223 (36.7%) of 608 patients. A total of 18 (15.0%) events occurred among the 120 patients who had elevated D-dimer and stopped anticoagulation compared with three (2.9%) events among the 103 patients who had elevated D-dimer and resumed anticoagulation, for an adjusted hazard ratio of 4.26 (95% CI: 1.23 to 14.6; P=0.02). VTE recurred in 24 (6.2%) of 385 patients with a normal D-dimer level. Among patients who stopped anticoagulation, the adjusted hazard ratio for recurrent thromboembolism among those with an abnormal D-dimer level, compared with those with a normal D-dimer level, was 2.27 (95% CI: 1.15 to 4.46; P=0.02). **It was concluded that patients with an abnormal D-dimer level at 1 month after the discontinuation of anticoagulation with a VKA have a**

significantly higher incidence of recurrent VTE, which can be reduced by the resumption of anticoagulation.

The above strategy on the use of D-dimer to determine which patients are at low risk of recurrence has been developed in the era when initial LMWH followed by VKA was the standard therapy. The value of this strategy has been recently evaluated in patients receiving DOACs as the initial treatment in the APIDULCIS study.[136] This was a multicenter, prospective cohort study, which involved 732 outpatients who had a first symptomatic proximal DVT and/or PE that was unprovoked or associated with minor and transient risk factors (N.=190) (minor surgery, pregnancy or puerperium, hormonal therapy, long travel, minor trauma-leg injury, reduced mobility, or hospitalization in a medical ward) and were initially treated with DOACs for ≥12 months. Patients with a serial negative D-dimer (15, 30, 60 days) after anticoagulation was stopped (N.=286) were left without further anticoagulation. At first positive D-dimer (N.=446) patients were given apixaban 2.5 mg twice daily for 18 months. The study was interrupted because of a high rate of the primary outcomes at a planned interim analysis. There were 19 symptomatic proximal DVT or PE and 2 major hemorrhagic episodes in the D-dimer negative group not on anticoagulants (7.3%) *vs.* 3 symptomatic proximal DVT or PE and 2 major hemorrhagic episodes in the D-dimer positive group treated with apixaban (1.1%), (HR: 8.2, 95% CI: 3.2 to 25.3).

The results indicate that in patients anticoagulated with DOACs for ≥1 year after a first unprovoked VTE, the decision to further extend anticoagulation should not be based on D-dimer testing.

Also, the results confirmed the high efficacy and safety of low dose apixaban against VTE recurrences.

(III) Strategy combining residual thrombus and D-dimer testing

In 620 consecutive outpatients with a first proximal DVT who had completed at least three months of anticoagulation (unprovoked in 483 and associated with minor risk factors in 137), the ultrasound presence of residual vein thrombosis (RVT+) was assessed and defined as an incompressibility of at least 4 mm.[137] In 517 patients who were RVT- and with negative D-dimer, anticoagulation was stopped and D-dimer was repeated after one and three months. Anticoagulation was resumed in 63 of the 72 patients in whom D-dimer reverted to positivity.

During a mean follow-up of three years, recurrent VTE developed in 40 (7.7%) of the 517 patients, leading to an annual rate of 3.6% in individuals with unprovoked DVT, and 2.2% in those with DVT associated with minor risk factors. Of the 233 patients with unprovoked DVT, 17 (7.3%) developed events in the first year of follow-up. Major bleeding complications occurred in 8 patients while on anticoagulation, leading to an annual rate of 1.2%.

It was concluded that **discontinuing VKA in patients with a first episode of proximal DVT based on the assessment of RVT and serial D-dimer led to an overall annual rate of recurrent VTE lower than 5.0%**.

c. Risk stratification models

An approach for assessing the risk of recurrent VTE and identifying patients in whom anticoagulation can be safely discontinued consists of linking clinical patient characteristics with laboratory testing. These are the HERD002 Canadian model,[103, 138] the Vienna Prediction Model[139, 140] and the DASH Prediction Model.[141]

(I) HERD002 Canadian Model

In the Canadian HERD002 model, women with unprovoked VTE and none or one of a few selected parameters (age older than 65, obesity, D-dimer positivity at the time of discontinuing anticoagulation and post-thrombotic manifestations) exhibited a considerably lower risk of recurrent VTE than the remaining patients.[138]

(II) The Vienna Prediction Model

The Vienna Prediction Model is a less commonly used stratification model.[139, 140] It is based on three key parameters: patient sex, site of VTE (calf, proximal or PE), and D-dimer level). It is difficult to apply at the bedside unless one uses the Vienna Nomogram.[142]

(III) The DASH Prediction Model

The DASH Prediction Model is based on D-dimer levels, age, sex, and hormone treatment (high risk in patients scoring >2), but it may fail to identify patients older than 65 years at high risk of recurrence.[141]

d. Bleeding Risk Tools

A number of predictive models have been developed, which have the potential to help predict the risk of bleeding while on anticoagulation. The most promising are the VTE-BLEED, the HAS-BLED and the CHAP models.

(I) The VTE-BLEED Model

A predictive model of note is VTE-BLEED, a tool used to predict major bleeding during chronic anticoagulation for VTE.[142] VTE-BLEED is based on the following six variables: 1) active cancer; 2) male sex with uncontrolled arte-

rial hypertension; 3) anemia; 4) history of bleeding; 5) age ≥60 years; and 6) renal dysfunction. The main benefit of VTE-BLEED is that it can differentiate between patients with VTE with a higher or lower risk of bleeding during long-term anticoagulation (≥90 days).

This model has been derived from a mixed cohort of 5142 patients treated with standard therapy or rivaroxaban. It has recently been validated in an unselected patient cohort in Japan treated mainly with VKA.[143] However, due to potential population-specific differences in the baseline risk of VTE and bleeding, the results of the Japanese study cannot be generalized to other populations.

(II) The HAS-BLED Model

HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly) is another well-known bleeding risk score that was originally developed to **estimate the risk of major bleeding in patients on vitamin K antagonists with atrial fibrillation**.

Evaluation of its predictive value for major bleeding risk has more recently been demonstrated in the first 6 months of anticoagulation therapy in patients with VTE but further adaptations and validation may be warranted, especially with the use of DOACs. [147,148.]

(III) The CHAP Model

In a prospective multinational cohort study of patients with unprovoked or weakly provoked VTE receiving extended anticoagulation after completing at least three months of initial treatment, Wells *et al*. identified and internally validated this novel model, which has the potential to accurately discriminate between patients at high and low risk of major bleeding, defined as higher and lower than 2.5 events per 100 patient-years, respectively, in the setting.[144] This model includes only four easily retrievable baseline parameters (creatinine, hemoglobin, age, and the concomitant use of an antiplatelet agent), and should be calculated on an individual basis as follows: 0.02 × [(creatinine in µmol/L × 0.0017) + (hemoglobin in g/L × -0.0127) + (age × 0.0251) + (1 × 0.8995 in case of antiplatelet use)] = predicted annual rate of major bleeding.

This model has recently been validated in the framework of the RIETE registry, where in a wide cohort of patients with unprovoked VTE it was found to accurately predict the bleeding risk both in the first three months and, separately, in the subsequent periods of anticoagulation.[145]

Recommendations

A. Patients with VTE without contraindications or cancer

In patients without contraindications (such as the antiphospholipid syndrome) or cancer, **DOACs** are the first line anticoagulant therapy. **While rivaroxaban and apixaban** can be used as monotherapy, **dabigatran and edoxaban** should be preceded by at least 5 days of parenteral anticoagulation with either LMWH or fondaparinux **(Level of evidence high, recommendation strong)**.

LMWH or fondaparinux for at least five days **overlapped by VKA** therapy are second line therapeutic approaches **(Level of evidence high, recommendation moderate)**. They should be commenced on day one and continued according to the INR targeted between a therapeutic range of 2.0-3.0. Initial therapy with LMWH or fondaparinux should be discontinued when a stable INR is within the therapeutic range (2.0-3.0).

Parenteral therapy is the treatment of choice for patients needing hospitalization because of high risk of bleeding or threatening clinical manifestations of PE (**Level of evidence moderate, recommendation strong)**.

B. Isolated symptomatic calf DVT

Isolated symptomatic calf DVT should be treated for three months **(Level of evidence high, recommendation strong) or** followed by serial ultrasonography on two occasions if anticoagulation is contraindicated due to high bleed risk or other factors **(Level of evidence moderate, recommendation moderate)**. For patients with calf DVT requiring anticoagulation, rivaroxaban is recommended over LMWH followed by VKA **(Level of evidence moderate, recommendation strong)**.

C. Patients with VTE and active cancer

In patients with active cancer **edoxaban, apixaban or rivaroxaban for 6 months** are the first line anticoagulant therapy **(Level of evidence high, recommendation strong)**. LMWH is an alternative approach, to be preferred in patients with thrombocytopenia, renal failure and in those at higher hemorrhagic risk because of gastrointestinal or genito-urinary cancer **(Level of evidence high, recommendation strong)** (see Section 17 on cancer for evidence and more details).

LMWH (dosed as per label) for 3-6 months is an alternative to VKA therapy **(Level of evidence high, recommendation strong)**.

D. Patients with antiphospholipid syndrome

In patients with antiphospholipid syndrome, VKA targeted to an INR range of 2.0-3.0 should be the first line anticoagulant therapy over DOACs **(Level of evidence high, recommendation strong)** (see Section 24 on Antiphospholipid syndrome).

E. Patients with chronic renal failure

In patients with end stage renal failure, UFH as well as other drugs with no or minimal dependence on the renal clearance should be used **(Level of evidence low, recommendation strong)**.

F. Duration of anticoagulation therapy

All patients should receive antithrombotic therapy for at least three months **(Level of evidence high, recommendation strong)**.

In patients with a major provoking risk factor that has been removed, three months is sufficient **(Level of evidence high, recommendation strong)**.

In patients with unprovoked VTE and in those with major persisting risk factors, the duration of anticoagulant therapy may be indefinite, provided the bleeding risk is low **(Level of evidence high, recommendation strong)**. The decision as to the length of therapy is based upon the balance of benefit and harm/bleeding and the patient's preference. Patients on continued therapy should undergo **periodic** reconsideration of benefit *vs.* risk of anticoagulation **(Level of evidence low, recommendation weak)**.

In patients with a minor provoking risk factor, the duration of anticoagulant therapy is uncertain, with expert opinion favoring a fixed short period **(Level of evidence low, recommendation weak)**. The use of a stratification model can help identify patients in whom anticoagulation can be safely withheld **(Level of evidence low, recommendation strong)**.

In patients with more than one episode of VTE, the duration of anticoagulant therapy is indefinite **(Level of evidence high, recommendation strong)**.

G. Extended anticoagulation

For the long-term prevention of recurrent VTE in patients requiring indefinite anticoagulation, rivaroxaban or apixaban in low doses should be considered after completing 3-12 months of conventional anticoagulation **(Level of evidence high, recommendation strong)**.

Therapeutic doses of DOACs should be considered in patients with malignancy, recurrent VTE and severe inherited thrombophilias **(Level of evidence low, recommendation strong)**.

VKA dose-adjusted to target a therapeutic INR range of 2.-3.0 is the second-line choice. However, it remains the treatment of choice for the long-term prevention of recurrent venous and arterial thrombotic events in patients with antiphospholipid syndrome **(Level of evidence high, recommendation strong)**.

Sulodexide, if available, is the third-line choice, to be considered in patients with contraindication to long-term treatment with DOAC or VKA such as those at high risk of bleeding **(Level of evidence moderate, recommendation moderate)**.

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SECTION 17

Treatment in cancer patients

The risk of recurrence

Cancer patients who develop an episode of thrombosis are at higher risk for subsequent recurrent thrombosis, with a reported frequency of 27.1 per 100 patient years for those with cancer compared with 9.0 per 100 patient years for those without cancer.[1] In the same study, the bleeding risk for cancer patients receiving oral anticoagulation therapy was 13.3 per 100 patient years and 2.1 per 100 patient years for non-cancer patients. A further study by Prandoni *et al.*, followed a cohort of 842 patients, 181 of whom had cancer-associated thrombosis and demonstrated a 12-month cumulative incidence of recurrent VTE of 20.7% for cancer patients compared with 6.8% for those without cancer[2] and more frequent bleeding in the cancer patients (12.4% *vs.* 4.9%; HR: 2.2).

Therapeutic methods

Initial treatment of VTE in cancer

Several trials that **compared unfractionated heparin (UFH) with LMWH** for initial treatment of DVT included patients with malignant disease. Meta-analyses of these studies indicated that UFH administered intravenously with routine monitoring of aPTT or LMWH administered subcutaneously according to body weight without need for monitoring of the dose, **are equally effective and safe for initial treatment of DVT.** Recommendations generated for non-cancer patients are therefore extrapolated for use in cancer patients with thrombosis.[3-6]

Few data are available for the pentasaccharide **fondaparinux**. Post-hoc analyses from two randomized trials of 237 cancer patients with VTE that compared the **safety, efficacy, and overall survival with fondaparinux *vs.* LMWH, followed in both groups by VKA**, showed a recurrence rate in patients with DVT of 5.4% in the enoxaparin group *vs.* 12.7% in the fondaparinux group (absolute difference 7.3%, 95% CI: 0.1, 14.5). Among the patients with PE, a recurrence was observed in 8.9% in the fondaparinux group *vs.* 17.2% in the UFH group (absolute difference 8.3% (95% CI: 16.7 to 0.1).[7] The analysis did not show any difference in terms of bleeding or overall survival between the groups.

LMWH therapy for the initial treatment of DVT offers an opportunity for outpatient management of patients with cancer-associated thromboembolic disease.[8-12] Initial management of PE in cancer patients has not been specifically addressed. However, trials have evaluated both **intravenous UFH and subcutaneous LMWH for treatment of PE**.[11, 13]

An observational study of 108 patients with PE, 22% of whom had cancer, evaluated the potential for outpatient use of the LMWH (dalteparin sodium).[14] Recurrent thrombosis occurred in 5.6% of the 108 patients with a major bleeding rate of 1.9%. Thus, cancer patients with PE may receive either UFH or LMWH for initial PE treatment unless they are hemodynamically unstable.

Systematic review and meta-analysis

A systematic review published in 2011 identified 13 studies that compared LMWH with UFH and two that compared fondaparinux with UFH.[15] Meta-analysis of 11 studies showed **a statistically significant reduction in mortality at three months follow-up with LMWH compared with UFH (RR: 0.71; 95% CI: 0.52 to 0.98)**. A meta-analysis of three studies **comparing LMWH with UFH showed no reduction in VTE recurrence (RR: 0.78, 95% CI: 0.29 to 2.08)**. There was no difference between heparin and fondaparinux for mortality (RR: 1.27, 95% CI: 0.88

to 1.84), recurrent VTE (RR: 0.95, 95% CI: 0.57 to 1.60), major bleeding (RR: 0.79, 95% CI: 0.39 to1.63) or minor bleeding (RR: 1.50, 95% CI: 0.87 to 2.59). The authors concluded that LMWH is possibly superior to UFH for the initial treatment of VTE in patients with cancer and that further trials are needed to clarify this issue.

Outpatient therapy with LMWH is preferred in cancer patients with a potentially shortened duration of life where quality of life is an essential issue.

Inferior vena cava filters

The safety and efficacy of **inferior vena cava filters** for management of cancer-associated thrombosis have not been evaluated. In general, unless anticoagulant therapy is contraindicated due to active bleeding, vena cava filters are not recommended in cancer patients. Early benefits are outweighed by longer-term risks for recurrent thrombosis in patients with malignant disease.[16]

Duration of anticoagulation in patients with active cancer

As indicated above, patients with malignancy compared with those without have a fourfold greater risk of recurrent thrombosis and a threefold greater risk of anticoagulant-associated bleeding.[17]

LMWH vs. VKA

A study involving 676 patients with cancer associated with VTE was sufficiently powered to define long-term treatment outcomes.[18] All patients received 5-7 days' treatment with the LMWH (dalteparin in a dose of 200 IU/kg) followed by **either LMWH** in the full treatment dose for the remainder of the month then 75-80% of the full treatment dose for the remaining five months, **or by VKA** treatment with a target INR of 2-3 **for six months. The trial demonstrated 52% reduction in the frequency of recurrent VTE over six months in favor of dalteparin (8.0% with dalteparin *vs.* 15.8% with VKA),** with no significant increase in the risk of bleeding complications.

In a prospective multicenter RCT (LITE) involving 19,200 patients with cancer and acute symptomatic proximal vein thrombosis usual care (intravenous heparin followed by long-term warfarin sodium) was compared with LMWH tinzaparin.[19] **At 12 months, the rate of recurrent VTE was 15% in the usual-care group *vs.* 7% in the tinzaparin group (P=0.044).**

In another RCT involving 241 patients with symptomatic proximal DVT of the lower limbs confirmed by duplex ultrasound scan were included.[20] After initial LMWH, patients received 6 months of **treatment with full therapeutic dosage of tinzaparin or acenocoumarol**. The primary outcome was the 12-month incidence of symptomatic recurrent VTE. Duplex scans were performed at 6 and 12 months. During the 12-month period, six patients (5%) of 119 who received LMWH and 13 (10.7%) of 122 who received VKA had recurrent VTE (P=0.11). **In patients with cancer, recurrent VTE tended to be lower in the LMWH group (two of 36 [5.5%]) *vs.* seven of 33 [21.2%]; P=0.06).** One major bleeding occurred in the LMWH group and three in the VKA group. Venous recanalisation increased significantly at 6 months (73.1% *vs.* 47.5%) and at 12 months (91.5% *vs.* 69.2%) in the LMWH group.

The DALTECAN and the TICAT observational studies confirmed the long-term safety outcomes with dalteparin and tinzaparin, respectively, for 12 months, with the majority of VTE recurrences and major bleeding complications occurring during the first 6 months of therapy.[21, 22]

Systematic reviews and meta-analyses

The superiority of long-term treatment with LMWH over VKA for secondary prevention of VTE in patients with cancer has been confirmed in several meta-analyses.[17, 23-26] **One such analysis that involved six RCTs comparing LMWH with VKA, published in 2017, showed reduction in risk of VTE with LMWH (HR: 0.47, 95% CI: 0.32 to 0.71)** without an increased risk of bleeding (RR: 0.91, 95% CI: 0.64 to 1.31) or thrombocytopenia (RR: 1.02, 95% CI: 0.60 to 1.74) but did not demonstrate a survival benefit (HR: 0.96, 95% CI: 0.81 to 1.14).[23]

The advent of the direct oral anticoagulants

In recent years, direct oral anticoagulants (DOACs) have emerged with the potential to replace conventional treatments for the initial and long-term treatment of VTE in cancer related DVT also.[27] They include inhibitors of factor Xa (rivaroxaban, apixaban and edoxaban) and inhibitors of factor IIa (dabigatran etexilate). They possess several advantages over conventional drugs, including the lack of interference with platelets in comparison to LMWH, and a more predictable dose-response in comparison to VKA without routine monitoring.

Special attention should also be paid to the patients treated with DOACs and cancer present in the gastrointestinal and urinary tracts, where the risk of bleeding remains significant.

The proper long-term strategy beyond the first six months in cancer patients with VTE requires further investigations.

The HOKUSAI VTE CANCER RCT

The study that paved the way for the use of DOACs for this indication was the HOKUSAI VTE CANCER RCT.[28] In this RCT, more than 1000 patients with active malignancy and a diagnosis of symptomatic or asymptomatic VTE were enrolled to receive **dalteparin** (200 IU/kg for at least six months, after a few days of parenteral treatment with conventional drugs) **for one month or edoxaban** (at the oral dose of 60 mg/day reduced to 30 mg/day in case of chronic kidney disease, low body weight or simultaneous use of strong inhibitors of P-glycoprotein). A primary-outcome event (defined **as a composite of recurrent VTE events and major hemorrhagic events**) occurred in 67 (12.8%) of the 522 patients in the edoxaban group and 71(13.5%) of the 524 patients in the dalteparin group (HR: 0.97, 95% CI: 0.70 to 1.36). **Recurrent VTE occurred in 41 (7.9%) patients in the edoxaban group and in 5 9(11.3%) patients in the dalteparin group (P=0.06).** Major bleeding occurred in 36 (6.9%) patients in the edoxaban group and in 21 (4.0%) patients in the dalteparin group (P=0.04). In summary, edoxaban was fully comparable with dalteparin, with a trend favorable to edoxaban in terms of thromboembolic recurrences, and significantly favorable to dalteparin in terms of bleeding events. The vast majority of bleeding events developed in patients with cancer of the upper gastrointestinal tract.

The SELECT-D RCT

In the SELECT-D study, 406 patients with active malignancy and a diagnosis of symptomatic or asymptomatic VTE were randomly assigned to receive **rivaroxaban** (15 mg twice daily for three weeks followed by 20 mg once daily) **or dalteparin** according to the scheme used in the HOKUSAI VTE CANCER RCT.[29] **The 6-month cumulative VTE recurrence rate was 11% with dalteparin and 4% with rivaroxaban (HR: 0.43, 95% CI: 0.19 to 0.99)**.

The 6-month cumulative rate of major bleeding was 4% for dalteparin and 6% for rivaroxaban (HR: 1.83, 95% CI: 0.68 to 4.96). Corresponding rates of CRNMB were 4% and 13% respectively (HR: 3.76, 95% CI: 1.63 to 8.69). Rivaroxaban was associated with relatively low VTE recurrence, but higher CRNMB compared with dalteparin.

The CARAVAGGIO RCT

In the CARAVAGGIO Study, 1155 patients with neoplastic disease who had experienced a VTE episode (symptomatic or detected accidentally during cancer staging investigations) were randomized to receive **oral apixaban therapy for six months** (10 mg twice daily for one week, followed by 5 mg twice daily for the remaining observation) **or parenteral therapy with dalteparin** according to the scheme used in the Hokusai VTE cancer RCT.[30] During the six months of observation, recurrent VTE occurred in 32 (5.6%) of 576 patients in the apixaban group and in 46 (7.9%) of 579 patients in the dalteparin group (HR: 0.63, 95% CI: 0.37 to 1.07).

Major bleeding occurred in 22 (3.8%) and in 23 (4.0%) of the apixaban and dalteparin groups, respectively (HR: 0.82, 95% CI: 0.40 to 1.69). In summary, thromboembolic recurrences and major bleeding developed in similar proportions in the two groups of patients, with a trend favorable to apixaban for the reduction of thromboembolic events. At variance with the previous two studies,[28, 29] there was no evidence of a higher risk of bleeding in patients with cancer of the gastrointestinal tract.[31]

The CANVAS RCT

The most recent non-inferiority RCT evaluated **any DOAC with LMWH or fondaparinux** for preventing recurrent VTE and for rates of bleeding in patients with cancer following an initial VTE event.[32] The primary outcome was recurrent non-fatal VTE at 6-month follow-up. **The rates of recurrent VTE were 6.1% in the DOACs group and 8.8% in the LMW/fondaparinux group consistent with prespecified non-inferiority criterion**. There was no significant difference in major bleeding.

Systematic review and meta-analysis of 2022

According to the results of a recent meta-analysis pooling data from the HOKUSAI VTE CANCER RCT, SELECT-D, CARAVAGGIO, ADAM VTE, CANVAS and CAST DIVA randomized studies **comparing DOACs** (including apixaban and rivaroxaban) with LMWH treatment,[33-35] **VTE recurred in 99 (5.3%) out of 1850 patients allocated to the DOACs and in 152 (8.3%) out of 1840 allocated to LMWH (OR: 0.63, 95% CI: 0.52 to 0.85)**, and major bleeding in 4.3% and 3.7%, respectively (RR: 1.17, 95% CI: 0.82 to 1.67).[36] However, only a small proportion of cancer patients were eligible for these trials. The definition of active cancer was widely different between studies and mostly not consistent with the LMWH trials. In addition, severe liver and renal dysfunctions, which contraindicate the use of DOACs, are quite common in cancer patients. Gastrointestinal toxicity from cancer and its treatment is likely to impact on intake and absorption of oral drugs. There is the potential for drug interactions with DOACs including very commonly used chemotherapy drugs.

Finally, there is uncertainty about the proper management of patients requiring emergency procedures and in those with thrombocytopenia.[32]

Recommendations

DOACs (rivaroxaban, apixaban, edoxaban) **should be the anticoagulant of choice** in the treatment of cancer-associated thrombosis, as they are associated with a similar benefit–risk profile, whilst obviating the inconveniences of heparins, provided they fulfil the criteria required for enrolment in the Hokusai-VTE-Cancer, SELECT-D RCTs and CARAVAGGIO RCRs **(Level of evidence high, recommendation strong)**.

LMWHs should be the treatment of choice for patients in whom DOACs cannot be given (problems of intake, absorption or intolerance) or are contraindicated **(Level of evidence high, recommendation strong)**.

LMWHs should also be the treatment of choice for patients with gastrointestinal or genitourinary cancer **(Level of evidence moderate, recommendation moderate)**.

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SECTION 18

Inferior vena cava filters

General considerations

Indications for IVC filter insertion can be categorized as **absolute, relative, and prophylactic.** In reality all vena cava filters are "prophylactic." However, this term has been used to describe the indication for patients at risk who have no identifiable PE or DVT.

Absolute indications in patients with VTE include: 1) DVT or PE associated with a contraindication to anticoagulation; 2) documented failure of anticoagulation *e.g.*, recurrent PE despite adequate anticoagulation; and 3) complications requiring cessation anticoagulation. Evidence suggests that most patients treated with vena cava filters have none of the three accepted absolute indications.[1, 2]

Relative indications in patients with VTE exist when the risk of PE is high despite anticoagulation or when the risk of bleeding complications would be high with anticoagulation. Such indications include large free-floating thrombus in the vena cava, massive PE, DVT in patients with limited cardiopulmonary reserve or where patients are suspected of being noncompliant with anticoagulation.

Prophylactic indications occur in patients who have neither DVT nor PE but in whom the perceived risk of VTE is high and the efficacy of alternative forms of prophylaxis is considered poor or associated with high bleeding risk.

Methods

Randomized controlled trials

A RCT of IVC filters *vs.* no filter placement evaluated the adjunctive benefit of filters in 400 patients with acute proximal DVT undergoing routine anticoagulation.[3] The primary endpoint was PE at 12 days and 2 years. **At day 12, two patients assigned to receive filters (1.1%), compared with nine patients assigned to receive no filters (4.8%), had symptomatic or asymptomatic PE (OR: 0.22, 95% CI: 0.05 to 0.90). At two years, 37 patients assigned to the filter group (20.8%) compared with 21 patients assigned to the no-filter group (11.6%) had recurrent DVT (OR: 1.87, 95% CI: 1.10 to 3.20)**. There were no significant differences in mortality or the other outcomes. At day 12, three patients assigned to LMWH (1.6%) compared with eight patients assigned to UFH (4.2%), had symptomatic or asymptomatic PE (OR: 0.38, 95% CI: 0.10 to 1.38). The authors concluded that in high-risk patients with proximal DVT, the initial beneficial effect of vena cava filters for the prevention of PE was counterbalanced by an excess of recurrent DVT without any difference in mortality. Their data also confirmed that LMWH was as effective and safe as unfractionated heparin for the prevention of PE.

In a more recent RCT involving 399 patients with severe acute PE the use of retrievable vena cava filters together with anticoagulation compared with anticoagulation alone did not reduce the risk of recurrent symptomatic PE at three months. Results for symptomatic DVT, major bleeding and death were similar at six months.[4]

Systematic reviews and meta-analyses

A Cochrane review of IVC filters to prevent PE published in 2007 confirmed lack of information for the efficacy of filters.[5] The authors concluded that strong recommendations cannot be given for IVC filters based on established evidence.

A more recent systematic review and meta-analysis of 8 controlled studies (one randomized, three with prospective controls and four with historical controls) involving a total of 324 trauma patients was published in 2014.[6] Both

groups received either LDUH or LMWH prophylaxis. Although most studies had a borderline significance, the overall meta-analysis of 6 studies which reported on PE showed **fewer PE with IVC filter use compared with no IVC filter use without evidence of heterogeneity (RR: 0.20; 95% CI: 0.06 to 0.70).** In three studies reporting on fatal PE the incidence of fatal PE was reduced in the group with IVC filter (RR: 0.09, 95% CI: 0.01 to 0.81). There was no evidence of a reduction in overall mortality. The authors rated the strength of the evidence as low to support a reduction in PE and fatal PE with the use of IVC filters.

Complications

It has been observed that thrombotic risk and retrievability (of optional filters) vary between filters.[7] Filters that cause regions of flow stagnation and recirculation at the vena cava wall or turbulence in the vein have an increased risk of thrombosis.[8, 9] These hemodynamic observations have translated into clinically relevant findings as observed in a randomized trial.[10]

Increasing numbers of retrievable filters are being used. A systematic review of retrievable IVC filters comprising 37 studies and 6,834 patients found a low mean retrieval rate of 34%.[11] Complication rates included DVT (5.4%), filter migration (1.3%), and vena cava thrombosis/stenosis (2.8%). IVC filter fractures comprised 22% of filter complications.

In another recent review, problems after IVC filter insertion were categorized as early or late complications.[12] Early complications included incomplete or asymmetric deployment, mispositioning or tilting, with a reported incidence of 1-12.4%. Late complications including filter migration, filter disruption, caval thrombosis, caval perforation and recurrent pulmonary embolism were reported in 1.7-33% of the cases. Some complications were more frequent with some types of filters including filter migration as well as IVC thrombosis.

Recommendations

Patients who have PE likely related to DVT or proximal DVT with contraindications to anticoagulation should receive an IVC filter **(Level of evidence moderate, recommendation strong)**.

Patients who have recurrent acute PE despite adequate therapeutic anticoagulation should receive an IVC filter **(Level of evidence low, recommendation strong)**.

Patients with acute PE and poor cardiopulmonary reserve should be considered for an IVC filter **(Level of evidence low, recommendation weak)**.

Patients who receive a retrievable IVC filter should be evaluated for filter removal within the specific filter's retrieval window **(Level of evidence low, recommendation strong)**.

An IVC filter should not be used routinely as an adjunct to anticoagulation **(Level of evidence low, recommendation strong)**.

Patients receiving an IVC filter due to a contraindication to anticoagulation should be restarted on anticoagulation whenever the contraindication no longer exists **(Level of evidence low, recommendation strong)**.

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SECTION 19

Thrombectomy and catheter directed thrombolysis

General considerations

Anticoagulation was and remains the standard of care for treating DVT and preventing extension or recurrence. However, anticoagulation, does not dissolve thrombus, but rather prevents extension while intrinsic thrombolytic pathways are slowly taking over. Interventional treatments to rapidly remove the clot and prevent associated short and long-term morbidity and mortality have always been attractive. Historically, venous surgical thrombectomy had been associated with rethrombosis and systemic thrombolysis with excessive bleeding.

Over the past decade, interventional DVT therapies have steadily migrated towards more minimally invasive techniques such as catheter directed thrombolysis (CDT) and mechanical thrombectomy targeting severe acute symptomatology and prevention of post-thrombotic syndrome (PTS) or reduction of its severity. While indications and appropriate patient selection are still an area of controversy, increasing awareness, mounting evidence and experience have earned these modalities a favored place in iliofemoral DVT management.

Therapeutic methods and recommendations

Surgical thrombectomy

Surgical thrombectomy was popularized 30 years ago. Early surgical thrombectomy in a small RCT of patients with iliofemoral DVT was associated with increased iliac vein patency compared with standard anticoagulation therapy alone after a 10-year follow-up (83% *vs.* 41%) and decreased incidence of PTS from 93% in the absence of thrombectomy to 58% when thrombectomy was performed (RR: 0.63, 95% CI: 0.44 to 0.90).[1, 2]

An observational study involving 83 patients with iliofemoral DVT showed that venous thrombectomy combined with an AV fistula in almost all cases, even with crural involvement in 63% of cases and stenting in 22 cases, could achieve acceptable results with a 75% patency and occurrence of moderate PTS at 5-year mean follow-up. None of the patients had severe PTS (CEAP C5 or C6).[3]

In a more recent study of 71 patients, surgical thrombectomy was compared with CDT and non-inferiority was demonstrated. Of note, stenting was performed in both groups. At two years, 85% of patients in the surgical thrombectomy group and 87% of those in the thrombolysis group did not develop PTS.[4]

Irrespective of the above results, surgical thrombectomy remains a major surgical procedure. However, contemporary minimally invasive techniques that have shortened lytic exposure, thereby increasing safety while enhancing good technical outcomes, have rendered surgical thrombectomy less popular.

Catheter directed thrombolysis

CDT from early observational cohort studies and comparative non-randomized studies appeared to be associated with increased vein patency, valve preservation and a reduction in the incidence of PTS compared with conventional anticoagulation therapy.[5-7]

Early RCTs

Two early RCTs **compared CDT with standard anticoagulation therapy in patients with proximal DVT** and indicated potentially favorable results for CDT.

The first one involved 35 patients with iliofemoral DVT.[8] At 6 months, **patency rate was better in cases treated with thrombolysis:** 13/18 (72%) *vs.* 2/17 (12%), P<0.001. **Venous reflux was higher in patients treat-**

ed with anticoagulant: 7 patients (41%) *vs*. 2 (11%), P=0.04.

The second RCT (CaVenT study) reported initially on short term (6 month) patency[9] and continued recruitment to a total of 209 patients of which only 50% had iliofemoral DVT.[10] **After 6 months, iliofemoral patency was found in 32 (64.0%) in the CDT group *vs*. 19 (35.8%) in controls, corresponding to an absolute risk reduction (RR) of 28.2% (95% CI: 9.7% to 46.7%; P=0.004). At 24 months PTS developed in 41% of patients in the catheter-directed thrombolysis group and 56% of patients in the standard anticoagulation therapy group (RR: 0.74; 95% CI: 0.55 to 1.00; P=0.047).** Of note, major bleeding events occurred in 2.9% of patients. The NNT to prevent PTS in one patient was 7. At 5 years the rates of PTS were 43% (95% CI: 33-53) in the catheter-directed thrombolysis group and 71% (95% CI: 61-79) (P<0.0001) in the control group. The NNT decreased to 4. No difference was found in QOL.[11]

The ATTRACT RCT

The ATTRACT trial, the largest RCT to date involved 691 patients with iliofemoral (IF) or femoropopliteal (FP) DVT.[12] They were randomized to standard anticoagulant therapy alone (AT) or pharmacomechanical catheter-directed thrombolysis (PCDT+AT). The primary outcome was defined as Villalta Score >4 or development of venous ulcer or unplanned endovenous procedure to treat symptoms after 6 months from randomization. Secondary endpoints were leg pain (Likert Scale of 7 points), calf circumference (CM) and health related QoL change from baseline to 24 months (SF36 and VEINES-QOL). At 24 months the primary outcome was 47% in the CDT+AT group and 48% in the AT group (P=0.56) indicating no benefit for an intervention. Again, bleeding events were more frequent in the procedural group (1.7% *vs*. 0.3%) although none was cerebral or life threatening.

A subgroup analysis of the 311 patients with iliofemoral DVT in the ATTRACT study showed that moderate and severe PTS (Villalta Scale >9) was present in 18% in the CDT+AT group and 28% in the AT group (P=0.021) and severe PTS (Villalta Scale >14) was present in 8.7% in the CDT+AT group and 15% in the AT group (P=0.048).[13] In these subgroups the mean Villalta score was 3.82 in the CDT+AT group and 5.43 in the AT group (P<0.001). At 30 days after treatment the mean reduction of pain score from baseline was -2.36 in the CDT+AT group and -1.80 in the AT group (P=0.0082). Mean QoL score at 24 months was 21.5 in the CDT+AT group and 16.2 in the AT group (P=0.043). Although the primary endpoint in the ATTRACT Trial was not reached, in patients with iliofemoral DVT CDT+AT resulted in reduction of PTS of any severity using VCSS, reduction of moderate/severe PTS using Villalta score, reduction of severe PTS using Villalta score, reduction of pain and swelling and improved disease specific QoL.

The CAVA RCT

The most recent RCT, the CAVA study **compared ultrasound-accelerated catheter-directed thrombolysis with standard therapy only for acute iliofemoral DVT**.[14] This multicenter RCT recruited 162 patients who had a median follow-up of 12 months. Major bleeding occurred in four (5%) patients in the intervention group. PTS occurred in 22 (29%) patients in the intervention group and 26 (35%) in the standard treatment alone group (OR: 0.75, 95% CI: 0.38 to 1.50). However, **a difference in PTS incidence was shown after a median follow-up of 39 months, with reported rates being 47% in the intervention group *vs*. 69% in the group with standard therapy (OR: 0.40, 95% CI: 0.19 to 0.84) (P=0.01)**. This difference was the result of a significantly higher number of new diagnoses of mild PTS at the final follow-up visit in the standard treatment group. For neither definition of PTS, a clinically relevant change in any of the patient reported QoL scores was found.[15]

Important messages and comments

An important message suggested by the above studies is that CDT is more appropriate for patients with iliofemoral DVT and its effect extends to a continued reduction in PTS beyond 2 years after treatment. More studies with longer follow-up are needed.

The conflicting results of these RCTs have raised criticism mainly towards diverse patient inclusion criteria or technical variations (*e.g.*, stenting rates, timing of intervention, inflow optimization).[16, 17] In addition, we need to acknowledge that catheter-based interventions come at a cost. CDT has been associated with higher rates of blood transfusion, pulmonary embolism, bleeding events and vena cava filter placement. In some countries, CDT is also associated with longer hospital stay and three times the hospital cost.[18]

A meta-analysis of these lytic trials published in 2023 suggests that CDT in acute proximal DVT decreases the rate of PTS and moderate to severe PTS with a number needed to treat of 12 and 18, respectively. However, this is complicated by a significantly higher rate of major bleeding with a number needed to treat of 37.[19]

Another comprehensive review and meta-analysis based on 46 studies and involving 3028 patients having CDT published in 2023 demonstrated major bleeding to be 1.2% (95% CI: 0.8 to 1.7%) and minor bleeding 8.7% (95% CI: 6.6 to 10.7). Pooled major bleeding incidence of low and high dosage protocols were 1.0% (95% CI: 0.5 to 1.5) and 2.3% (95% CI: 0.9 to 3.7) respectively (P=0.839). Incidence of PE was 1.1% (95% CI: 0.6 to 1.6) and of death was 0.6% (95% CI: 0.3 to 0.9).[20]

Mechanical and aspiration thrombectomy

Over the past decade pharmacomechanical thrombolysis has altered the safety profile and the complex hospital logistics (*e.g.*, need for ICU stay) of these interventions. There is now immense progress in the development of novel devices that can more effectively remove thrombus reducing or eliminating the need for thrombolysis and associated bleeding events, prolonged hospitalization, and costs.[17] Contemporary practice is shifting towards single session, no ICU stay, mechanical thrombectomy intervention. Multiple thrombectomy devices are available in the market but an individual analysis of each one of them is beyond the scope of this document.[21-24]

There is mounting evidence from ongoing registries and institutional series on their safety and effectiveness, but there is no long term (>2 years) data on PTS prevention and no comparative analysis against anticoagulation.

Of note, the first RCT was recently initiated, and it is industry sponsored by INARI Medical (DEFIANCE Trial).[25] This RCT will enroll 300 patients from up to 60 centers worldwide to compare mechanical thrombectomy with anticoagulation for the treatment of iliofemoral DVT. The primary endpoint for the trial is a hierarchical composite of treatment failure and PTS syndrome severity at 6 months.

Eligibility of patients for catheter directed thrombolysis, aspiration or mechanical thrombectomy

Amongst those with an acute iliofemoral DVT, typically less than two weeks old, with or without IVC involvement, eligibility for a catheter intervention includes patients who present with a threatened limb (phlegmasia) or are symptomatic (pain and swelling with inability to walk) on exertion. While the threatened-limb population should not be delayed, the symptomatic patients can be observed 24-48 hours on anticoagulation before any decision to intervene. Patients selected for an intervention should be physically active and have a reasonable life expectancy to maximize benefit and justify the costs and risks. Interventional treatment should generally not be considered for femoropopliteal DVT.[26-29]

Bleeding risk assessment can guide the type of catheter intervention, mainly the use of thrombolytics. As a principle, patients at bleeding risk (*e.g.*, recent surgery or trauma, pregnancy, or post-partum) should not be offered thrombolytic therapy bur rather percutaneous thrombectomy options than can be done with minimal or no lytic exposure. These procedures should be offered in centers with multidisciplinary teams, that have appropriate expertise and experience to maximize their safety profile and long-term benefits.

Recommendations

Early thrombus removal strategies should be considered in selected patients with symptomatic iliofemoral DVT **(Level of evidence moderate; recommendation strong)**.

Mechanical or aspiration thrombectomy techniques should be preferred over CDT thrombolytic techniques in patients with moderate to high bleeding risk **(Level of evidence low, recommendation strong)**.

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SECTION 20

Heparin-induced thrombocytopenia

General considerations

Types of HIT and pathogenesis

There are two types of heparin-induced thrombocytopenia (HIT). HIT Type I presents within the first two days after exposure to heparin, and the platelet count normalizes with continued heparin therapy. This is a non-immune disorder that results from the direct effect of heparin on platelet activation. HIT Type II is an immune-mediated disorder that typically occurs 4 to 14 days after exposure to heparin and has life- and limb-threatening thrombotic complications. In general, medical practice, the term HIT refers to HIT Type II.[1]

This chapter will discuss HIT Type II and refer to it as HIT.[2] This side-effect of heparin is caused by antibodies that bind to the complex of heparin and platelet factor 4 (PF4) released from activated platelets.[3-5] Heparin bound to PF4 induces a structural change in the PF4 molecule, exposing a neoepitope that is immunogenic.[6] The Fab portion of an immunoglobulin G (IgG) binds the PF4 neoepitope, and the Fc portion of the IgG binds platelet FcγIIa receptors.[7] Platelet activation with release of more PF4, platelet aggregation, and generation of procoagulant platelet microparticles result.[8, 9] Leukocyte and endothelial cell activation are provoked, augmenting thrombin generation, the hypercoagulable state, and the inflammatory state.[10-13] Sustained platelet activation contributes to thrombocytopenia, and thrombin generation results in HIT-associated thrombosis.[14]

HIT[15, 16] is to be distinguished from other causes of thrombocytopenia, as well as benign thrombocytopenia such as the non-immune HIT Type I and the pseudothrombocytopenia artefact.

Incidence

The incidence of HIT is up to 5% as a response to UFH and up to 0.5% as a response to LMWH following major surgery.[17-20] Risk levels depend on the current clinical condition, medical or surgical history, and the patient's general health.[21-29] HIT occurs most frequently after cardiac or orthopedic surgery and in medical patients presumably due to a high degree of platelet activation and PF4 release but can be found in other patient populations and clinical settings.[21-29] The incidence of HIT also relates to the duration and dosage of heparin therapy, though there are published cases in which HIT follows a single dose or even the incidental use of heparin to flush a line. Arterial and venous thromboembolic complications in patients with HIT include DVT, PE, myocardial or other organ infarction, thrombotic stroke, limb ischemia/gangrene, vein graft occlusion, and injection site skin lesions.[20, 21, 25, 29-31] Without interruption of the HIT pathology, mortality among patients with thrombosis is 30%, and up to 20% of those who survive require amputation.[21, 30, 31]

Prevention

It follows that preventive measures to avoid HIT include the use of LMWH, fondaparinux, and non-heparin anticoagulants rather than UFH, and avoiding unnecessary and prolonged exposure to UFH.

Diagnosis

The diagnosis of HIT requires a comprehensive interpretation of clinical and laboratory information.[29, 32-34] Exclusive reliance on laboratory tests for the diagnosis of HIT can lead to erroneous diagnostic conclusions. As HIT carries a significant risk of life-threatening thrombosis, it may be necessary to initiate therapy while waiting for laboratory results.[33] On the other hand, if HIT is absent, unnecessary treatment with the alternate anticoagulants argatroban and bivalirudin can carry a significant risk of life-threatening bleeding.

Since thromboembolic complications in HIT can be devastating, a high level of clinical suspicion should exist. Early recognition is fundamental. Surveillance of non-acute patients begins with consecutive platelet counts, at least once every 48 hours during and after heparin therapy.[33, 34] HIT-related thrombocytopenia is defined as a 30% to 50% decrease in platelet count from the pre-heparin level.[33, 34] Thrombocytopenia is usually mild to moderate, typically falling to less than 150×10^9/L, with platelet counts only rarely less than 15×10^9/L.[21, 35] An abrupt decrease in platelet count in the absence of other causes, that does not result in thrombocytopenia (*e.g.*, platelet count may fall from 350 to 175×10^9/L), and unexplained thrombosis, are also characteristic of HIT.[20, 21] HIT patients rarely experience bleeding.

In *de-novo* HIT, the platelet count begins to fall 4 to 14 days after initiation of heparin therapy.[20, 21, 33, 34] If the patient has been exposed to heparin in the 30 days prior to the current therapy, thrombocytopenia may appear within hours.[35, 36] The condition termed delayed HIT may appear up to 30 days subsequent to discontinuation of therapy.[37] Challenging clinical presentations occur in patients after surgery as post-operative thrombocytopenia is frequently present, particularly after cardiac surgery.[38] In these patients, HIT should be suspected if the platelet count recovery in the immediate post-operative period is interrupted by a sudden and marked platelet count decrease (a biphasic postoperative platelet count recovery), or if there is a persistent postoperative thrombocytopenia.[39-41]

Risk scores

Best practice recommends that clinical probability scoring be performed as a first approach when evaluating a patient for a possible diagnosis of HIT. The obtained probability score is then used to determine the laboratory test ordering and clinical management.[32, 33, 42] Scores should be reassessed as needed. As there are many causes of thrombocytopenia in hospitalized patients, HIT scoring systems improve diagnosis. The associated clinical management algorithms improve patient management while preserving resources (including cost) and reducing patient risk. The commonly used 4Ts clinical score estimates the likelihood of HIT based on the degree of **T**hrombocytopenia, **T**iming of platelet count drop in relation to heparin exposure, presence of **T**hrombosis, and absence of o**T**her causes of thrombocytopenia[42] (Table 20.I).[43] The HIT Expert Probability (HEP) Score is another scoring system that evaluates thrombosis and thrombocytopenia.[44] A third scoring system for patients who have undergone cardiac surgery, in which the cardiopulmonary bypass pump was used, assesses the timing and extent of platelet count recovery during the postoperative period.[45]

Low probability scores provide reliable negative predictive value such that the diagnosis of HIT is excluded; specialized laboratory testing and alternate anticoagulant therapy are not required.[33, 42, 46] Intermediate and high scores signal the ordering of specialized laboratory tests to demonstrate the presence or absence of heparin-dependent HIT antibodies that have the functional capacity to activate platelets; this confirms a diagnosis of HIT.[33, 42, 46]

Laboratory assays

There are two types of laboratory assays for HIT.[47] Taking into account the advantages and pitfalls of each assay type, tandem use has been determined to optimally establish a diagnosis of HIT in a timely manner. The rapid, sensitive

TABLE 20.I.—*The 4Ts Clinical Scoring System for determining the pretest probability of heparin-induced thrombocytopenia (HIT).*

Clinical feature	4Ts SCORE		
	2	1	0
Thrombocytopenia	>50% decrease in platelet count to nadir of ≥20×10^9/L	30-50% decrease in platelet count, >50% if directly resulting from surgery, or to nadir of 10-19×10^9/L	<30% decrease in platelet count, or to nadir of <10×10^9/L
Timing of platelet count decrease, thrombosis, or other sequelae of HIT (first day of heparin therapy is day 0)	Onset of decrease on days 5-10, or onset of decrease on day 1 if previous heparin exposure within past 5-30 days	Apparent decrease on days 5-10, but unclear due to missing platelet counts; or decrease after day 10; or decrease on day 1 if previous heparin exposure within past 31-100 days	Decrease at ≤4 days without recent heparin exposure
Thrombosis, skin lesions, acute system reaction	Proven new thrombosis or skin necrosis; acute systemic reaction after heparin exposure	Progressive, recurrent, or suspected thrombosis; erythematous skin lesions	None
O**T**her causes for thrombocytopenia	No explanation for platelet count decrease	Possible other cause	Probable other cause

Modified from: Crowther *et al.* 2010.[43]
A combined score of 6 to 8: high probability of HIT; 4 to 5: intermediate probability; 0 to 3: low probability.

HIT antibody immunoassay serves as the screening test.[33] As these immunoassays are prone to a high false-positive rate,[48] positive results must be confirmed by a platelet-based functional assay to assure that the identified HIT antibodies interact with and activate platelets in a heparin-dependent manner.[33, 47] The washed platelet ^{14}C-serotonin release assay (SRA),[49] available from high-quality specialized laboratories, is the platelet function assay of choice for confirmation of clinical HIT.[20, 33, 34, 42] Light transmittance platelet aggregometry can also be performed, but sensitivity and specificity is typically less than that of the SRA. Quality laboratory testing for clinically relevant HIT antibodies requires knowledge and skill to select appropriate assays, to perform accurate testing, and to interpret results.

Management

The clinical score, thus the level of thrombosis risk, determines anticoagulation management. For intermediate and high probability scores, heparin is immediately discontinued (before laboratory results are available) and anticoagulant therapy is initiated with a non-heparin drug.[33, 34, 50] Effective alternatives to manage these patients with a high risk of thrombosis or established thrombosis are the parenteral argatroban,[51-53] bivalirudin,[54, 55] and danaparoid.[56-58] Since these non-heparin drugs do not cross-react with HIT antibodies, they provide needed anticoagulation without augmenting the HIT pathology, and their potent anticoagulant effect combats the high procoagulant state of HIT.[59] If the HIT immunoassay and functional assay are positive, confirming clinical HIT, non-heparin anticoagulation is continued. Data is scarce for fondaparinux and DOACs in the management of HIT with thrombosis.

For clinically stable patients with intermediate and high probability scores but without thrombosis, treatment with a non-heparin anticoagulant such as fondaparinux or a DOAC (apixaban, rivaroxaban, dabigatran) can be considered, begun while awaiting laboratory results, and continued if the HIT functional assay is positive.[33] At this time, published data for rivaroxaban use in patients with HIT is more robust than it is for other DOACs.

For patients with intermediate and high probability scores, immunoassay positive but functional assay negative, the parenteral non-heparin anticoagulant should be continued if thrombosis is present.[33] For clinically stable patients without thrombosis, the choice of anticoagulant depends on individual patient factors.

For intermediate and high probability scores but immunoassay negative, and for low probability scores, HIT is unlikely. UFH or LMWH treatment may be continued, or a non-heparin anticoagulant can be used if desired.[33] For clinically stable patients recovering from acute HIT (platelet count above 150×10^9/L), fondaparinux or a DOAC may be used and preferred over a vitamin K antagonist (VKA).[33]

The duration of anticoagulation depends on the presence of thrombosis.[33] In patients with acute HIT but no evidence of thrombosis, screening for asymptomatic thrombosis is recommended, including a lower extremity Doppler compression ultrasound. Anticoagulation should be given until platelet counts recover to at least 150×10^9/L. It is suggested that treatment does not continue beyond three months unless there is no platelet count recovery.[33] For patients with HIT complicated by thrombosis, anticoagulation continues for 3 to 6 months.[33] Re-exposure to heparin in a patient with a history of HIT is generally considered contraindicated; however, there are reports of safe use of heparin given to patients who had recovered from HIT when the antibodies were no longer detected.[2]

The choice of anticoagulants is determined by patient factors (kidney function, liver function, bleeding risk, clinical stability, presence of life- or limb-threatening thrombosis), pharmacological properties of the drug (route of administration, half-life, bleeding risk), and other drug factors (experience of use by the clinician, ability to monitor the drug, drug availability, cost). LMWH can cross-react with HIT antibodies[59, 60] and is contraindicated for use in patients with HIT.[33, 34] VKA use is contraindicated during acute HIT since it can induce thrombosis.[33, 34] In general, platelet transfusions are not recommended for treatment of HIT;[33, 34] although platelet transfusion may be considered in patients with active bleeding or high risk of bleeding. The use of vena cava filters is not recommended for management of patients with HIT due to the potential that they can induce thrombosis.[29, 33, 34]

For patients initially treated with a parenteral anticoagulant transitioning to an oral agent, it is recommended to switch to a DOAC when the patient is clinically stable.[33] If a VKA is used, it should be initiated when platelet counts have recovered to at least $150\text{x}10^9$/L and normalized to a steady state,[33, 34] to avoid VKA-induced limb gangrene or skin necrosis.[61, 62] The VKA is then brought on under bridging with argatroban, bivalirudin, or danaparoid.

Although there is less experience, there are guidelines for anticoagulant management of specific, challenging clinical situations in patients with a background of HIT. These clinical settings include cardiac surgery, vascular surgery, cardiac catheterization, percutaneous coronary

intervention, and renal dialysis. Using special protocols (some continue to be optimized) argatroban, bivalirudin, or danaparoid may be used in such patients.[2, 33, 34, 63]

HIT is a complex clinical disorder with challenging diagnostic and management decisions. The above clinical recommendations are described for the majority of patients. Where clinical scenarios or practical constraints do not fit the described scenarios, clinical decisions are made on the basis of the individual patient. For detailed recommendations on the diagnosis and management of HIT, refer to the 2018 American Society of Hematology (ASH) clinical guideline publication from an international panel of experts.[33]

Recommendations

Prevention

Preventive measures to avoid HIT include avoiding unnecessary and prolonged exposure to UFH, and the use of LMWH, fondaparinux, and a DOAC rather than UFH where possible **(Level of evidence low, Recommendation moderate)**.

Diagnosis

Early diagnosis and treatment of HIT are important to improve clinical outcomes and reduce harm associated with thrombosis **(Level of evidence low, recommendation moderate)**.

Clinical suspicion of HIT should be present whenever heparin is used. Diagnosis of HIT is based on a comprehensive interpretation of clinical and laboratory information.

For the first 14 days of treatment, platelet counts should be performed every other day in patients treated with UFH or LMWH if the patient's risk of developing HIT is intermediate or high. UFH or LMWH exposure in the previous 30 days and a history of HIT increase the risk of developing HIT. Delayed HIT can occur within 30 days after discontinuing heparin therapy. Patients with comorbidities are at higher risk of poorer clinical outcomes.

The 4Ts clinical scoring system should be performed as a first step on all patients suspected of HIT to estimate the probability of HIT **(Level of evidence moderate, recommendation strong)**.

A low probability score excludes the diagnosis of HIT. Patients with intermediate and high scores receive specialized laboratory testing and alternate anticoagulant therapy.

The HIT antibody immunoassay serves as the screening test for HIT (performed first), and the functional platelet-based SRA (performed after a positive immunoassay) confirms that a positive immunoassay is due to clinically relevant HIT antibodies. A negative immunoassay excludes the diagnosis of HIT.

Treatment

For patients with intermediate and high scores, the initial therapeutic decision should not wait for laboratory test results due to the high procoagulant nature of HIT. **UFH and LMWH should be stopped immediately and based upon the clinical findings of thrombocytopenia and/or new thromboembolic events, an alternate non-heparin anticoagulant initiated.** It is not sufficient to merely remove heparin **(Level of evidence low, recommendation strong)**.

Confirmed HIT should be treated with a parenteral non-heparin anticoagulant such as argatroban, bivalirudin, or danaparoid, particularly if thrombosis is present (Level of evidence low, recommendation strong). Drug choice will depend on patient renal function, liver function, risk of bleeding, and physician's comfort level with the drug.

Fondaparinux or a DOAC (rivaroxaban, apixaban) can be used for treatment of stable patients without thrombosis (**Level of evidence low, recommendation moderate)**.

HIT is unlikely with intermediate or high probability scores in the presence of a negative immunoassay, and with low probability scores. In these patients, UFH or LMWH treatment may be continued, or a non-heparin anticoagulant may be used **(Level of evidence low, recommendation moderate)**.

LMWH, VKA, and use of a vena cava filter are contraindicated in patients with HIT **(Level of evidence low, recommendation moderate)**.

Platelet transfusions are not recommended for treatment of HIT unless there is a severe bleeding risk **(Level of evidence low, recommendation moderate)**.

Anticoagulation should continue until platelet counts recover to at least 150×10^9/L **(Level of evidence low, recommendation weak)**.

Duration of treatment

Treatment does not continue beyond **three months** unless there is no platelet recovery. **For patients with HIT complicated by thrombosis, anticoagulation should be continued for 3 to 6 months (Level of evidence low, recommendation weak)**.

For patients initially treated with a parenteral anticoagulant transitioning to an oral agent when clinically

stable, it is recommended to switch to a DOAC (rivaroxaban, apixaban) based on extrapolation from non-HIT patients **(Level of evidence moderate, recommendation moderate)**.

If a VKA is to be used, it should be initiated when platelet counts have recovered to at least $150x10^9$/L and given with overlapping administration of the parenteral anticoagulant for at least five days **(Level of evidence moderate, recommendation moderate)**.

For patients with acute HIT who cannot delay cardiac or vascular surgery, bivalirudin anticoagulation is suggested **(Level of evidence low, recommendation weak)**.

For patients with acute HIT who require cardiac catheterization or percutaneous coronary intervention, bivalirudin or argatroban can be used instead of heparin **(Level of evidence low, recommendation weak)**.

For patients who have a history of HIT, heparin can be used if the patient tests negative for HIT antibodies **(Level of evidence low, recommendation weak)**.

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SECTION 21

Superficial vein thrombosis

General considerations

Prevalence of superficial vein thrombosis

The prevalence of superficial vein thrombosis (SVT) in the general population ranges from 3 to 11%.[1-5] The incidence is 0.05 per 1000 men per year and 0.31 per 1000 women per year during the third decade of life, increasing to 1.8 per 1000 men per year and 2.2 per 1000 women per year during the eighth decade of life.[2] The mean age of presentation is 60 years[3, 6-12] and the older the patient is the fewer risk factors are present.[11, 13] SVT is more common (50-70%) in women.[3, 6, 7, 11, 12, 14-21]

The great saphenous system is involved in 60-80% of the cases, and the small saphenous system in 10-20%.[3, 11, 22, 23] Bilateral SVT is reported in 5-10% of patients.[3, 6, 11, 23, 24]

Development of SVT in patients with varicose veins ranges from 4-59%,[3, 11, 14, 15, 23] and it is confined more frequently to varicose tributaries rather than to the saphenous trunks.[3, 14] Obesity, age and protein-S deficiency have been found as factors associated with SVT episodes in patients with varicose veins.[25]

Risk factors

SVT in patients without varicose veins is found in 5-10% of all cases[11, 12, 26] and the etiology includes: autoimmune disease (Behcet's, Buerger's, and Mondor's disease),[5, 6, 16] malignancy,[5, 6, 16, 27-30] thrombophilia,[4-6, 8, 16, 17, 31-40] mechanical or chemical trauma or injury (venous infusion, catheter introduction),[16] radiation injury[16] and bacterial or fungal infections.[16] Cancer patients with SVT have a poor prognosis, similar to that of patients with cancer-related DVT.[41]

The risk factors are the same as those for DVT[17, 42] including previous thromboembolic events, long-haul flights,[43-45] pregnancy,[46, 47] oral contraceptives, hormone replacement therapy, immobilization,[18, 48] obesity, recent surgery,[18, 49] trauma,[18, 48] and sclerotherapy.[50, 51]

Obesity, as assessed with increased BMI is associated with an increase in prothrombotic factors (fibrinogen, von Willebrand Factor, factor VII and increased blood viscosity)[52] is an independent risk factor not only for VTE,[53-55] but also for SVT.[3, 30, 31, 42]

Association of SVT with VTE

VTE has been reported to coexist with SVT in 6-53% of patients presenting with SVT.[5, 9, 11, 14, 15, 19, 23, 56-67] The most common form is the extension from the great saphenous vein into the femoral vein.[23] SVT of the great saphenous vein above knee is associated with a 17-19% incidence of DVT, while when SVT affects the below knee segment the associated DVT is found only in 4-5% of patients.[10, 42, 58] In a recent systematic review and meta-analysis of the literature involving 21 studies (4358 patients) evaluating the prevalence of DVT and 11 studies (2484 patients) evaluating the prevalence of PE in patients with SVT, the weighted mean prevalence of DVT at SVT diagnosis was found to be 18.1% (95% CI: 13.9% to 23.3%) and that of PE 6.9% (95% CI: 3.9% to 11.8%).[68] Selection of studies including out-patients only gave similar results. Older age, female gender, recent trauma, and pregnancy were associated with the presence of DVT/PE in SVT patients.

Patients with SVT remain at a higher risk of VTE even after initial treatment. In a study of 329 patients, a year after VTE diagnosis, 19 (5.8%) patients had a subsequent diagnosis of DVT or PE.[69]

Clinical course of SVT

As indicated above, DVT may complicate "isolated" SVT in the short term.[5, 11, 12, 70] SVT is a risk factor for the devel-

opment and recurrence of DVT.[3, 5, 11, 22, 71] PE has been observed in 1.5-33% of SVT patients.[5, 7, 11, 12, 19, 23, 63, 66, 72, 73] PE has been reported to occur in 18% of patients when the thrombotic process was in the GSV above the knee and only 4% when in the SSV.[23] PE may complicate "isolated" SVT in the short term (3-4 months after the episode of SVT).[11, 12, 42] It is unclear whether PE associated with SVT arises from extension to deep veins or from thrombus that is located only in the superficial venous system.[3]

In a recent prospective observational study of 1150 patients with objectively confirmed acute isolated SVT who had received in the vast majority two to six weeks of anticoagulant therapy (INSIGHTS-SVT), recurrent or extended SVT developed in 5.8%, DVT in 1.7%, and PE in 0.8% during a three-month follow-up.[74] Complete clinical recovery of SVT was reported in 708 patients (62.4%). In a multivariable analysis factors associated with clinical outcomes included previous SVT (HR: 2.3), age (HR: 0.97 per year), duration of drug treatment per week (HR: 0.92), and thrombus length (HR: 1.03). These conclusions are consistent with those found in other recent studies of similar charcateristics.[75-78]

The development of subsequent VTE was generally found to occur more frequently in patients with malignancy, in those with SVT involving the saphenofemoral and the saphenopopliteal junctions, and in those with SVT not involving varicose veins.[77, 78] Whether SVT is associated with an increased risk of developing subsequent overt malignancy or arterial cardiovascular disorders is controversial, as there are data in support of[76, 79] and against these associations.[80]

SVT and pregnancy

The link between SVT and pregnancy remains unclear.[3, 17, 46, 47, 81-83] The prevalence is very low (0.05-0.1%), but it may be underestimated as only symptomatic patients are included.[46, 47]

SVT and cancer

Patients with SVT have a comparatively high incidence of cancer. In a study of 276 patients the prevalence of malignancy at the time of SVT was 8.7%. In a study of 1270 patients followed for 2 years, the hazard ratios for the risk of VTE in patients with a history of superficial vein thrombosis was 1.94 (95% CI: 1.04 to 3.61) and SVT in non-varicose veins had a stronger association with cancer. Such patients should be screened for malignancies.[84]

Clinical manifestations, pathology and diagnosis

SVT presents with local pain, warmth, erythema, swelling and the superficial vein becomes solid like a cord.[3, 6, 30, 85] SVT that occurs in a healthy vein shows abundant intima proliferation and media fibrosis with non-important thrombosis on histology. These findings are the hallmark of this form which may be associated with a systemic disease. The SVT that occurs in varicose veins is characterized by a large thrombus with a modest inflammatory process localized in the surrounding tissues but not in the vein wall.[86]

Diagnosis should include Duplex ultrasound for confirmation, estimation of thrombus extent, exclusion of DVT in both legs and for follow-up.[5, 6, 9, 10, 20, 23, 28, 56, 59-64, 87]

Treatment

There is great variation in treatment. In a national cross-sectional and prospective epidemiologic cohort study (POST) in France,[11] a total of 634 patients had isolated SVT at inclusion. Information about the treatment they received during the three-month observation period was available for 597 patients. Of these patients, 540 (90.5%) received anticoagulation. Heparin or LMWH was given at therapeutic doses in 374 (62.9%) or at prophylactic doses in 216 (36.7%); 99 (16.8%) received vitamin K antagonists. Elastic compression stockings were used by 584 (97.7%), topical non-steroidal anti-inflammatory drugs (NSAID) by 278 (47.2%), oral NSAID by 48 (8.2%), and 60 patients (10.2%) had venous surgery (stripping or ligation). Fourteen patients were lost to follow-up at three months. Among the remaining 586 patients, thromboembolic complications occurred in 58 (10.2%).

UFH, LMWH and VKA

An open RCT involving 562 patients with SVT associated with varicose veins has shown that **UFH, LMWH or VKA had equal efficacy and were superior to elastic compression or flush ligation combined with elastic compression** regarding SVT extension at three months.[16]

A double-blind RCT involving 427 patients[49] compared **LMWH** (enoxaparin 40 mg and 1.5 mg/kg) with a non-steroidal anti-inflammatory agent (tenoxicam) and placebo for 8-12 days. **Rates of DVT and SVT extension combined as detected by ultrasonography at 12 days were 30.6% in the placebo, 14.9% in the tenoxicam, 6.9% in the enoxaparin 1.5 mg/kg and 8.3% in the enoxaparin 40 mg** ($P<0.01$).

In another open RCT involving 117 patients **LMWH** (nadroparin) was superior to a non-steroidal anti-inflam-

matory agent in reducing symptoms at 6 days (P<0.001) and 8 weeks (P=0.007).[88]

High doses of UFH twice daily (12,500 IU for one week followed by 10,000 IU for three weeks) were superior to prophylactic doses (5000) twice daily in 60 randomized patients. **During the 6-month follow-up, the rate of asymptomatic involvement of the deep veins and/or symptomatic VTE was reduced from 20% in the prophylactic dose to 3.3% in the high dose group** (P=0.05).[89] However, when therapeutic doses of nadroparin were compared with prophylactic doses in another study, progression or VTE occurred in 7.2% and 8.6% of patients respectively (VESALIO Study).[90]

In order to compare the efficacy and safety of different doses and durations of parnaparin for symptomatic lower limb SVT, 664 outpatients with SVT were randomized to receive parnaparin either 8500 IU once daily for 10 days followed by placebo for 20 days (group A) or 8500 IU once daily for 10 days followed by 6400 UI once daily for 20 days (group B) or 4250 IU once daily for 30 days (group C) in a double blind fashion, and were then followed up for an additional month (STEFLUX Study).[91] The primary outcome (composite of symptomatic and asymptomatic VTE and relapse or recurrence of SVT) developed in 15.6%, 1.8% and 7.3% subjects of groups A, B and C, respectively. There were no major bleeds. Therefore, **intermediate dose parnaparin for 30 days was found to be superior to either 30-day prophylactic dose or 10-day intermediate dose for lower limb SVT treatment**.[79]

Fondaparinux

An international double-blind RCT, involving 3002 patients[12] compared **fondaparinux** subcutaneously 2.5 mg once daily for 45 days **with placebo**. Eligible for inclusion were hospitalized or non-hospitalized patients 18 years or older, with acute, symptomatic lower limb SVT at least 5 cm long as confirmed by compression ultrasonography. Exclusion criteria were the interval between the onset of symptoms and planned randomization more than 3 weeks; treatment for cancer within the previous 6 months; presence of symptomatic or asymptomatic DVT; symptomatic documented PE; SVT associated with sclerotherapy or placement of an intravenous catheter; SVT located within 3 cm of the saphenofemoral junction; DVT or PE within the previous 6 months; if the patients with SVT had received an antithrombotic agent (other than aspirin at a dose of ≤325 mg per day) for more than 48 hours or a NSAID for more than 72 hours as treatment for the current episode; if in the investigator's opinion a saphenofemoral junction ligation was required; major surgery within the previous 3 months; if there were conditions that could confer predisposition to bleeding including creatinine clearance <30 mL/min, platelet count <100,000/mm^3; and finally women in childbearing age if they were pregnant. **The primary efficacy outcome** (death from any cause or symptomatic PE, symptomatic DVT, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of DVT at day 47) **occurred in 0.9% of patients in the fondaparinux group and 5.9% in the placebo group (P<0.001). The rate of PE or DVT was 85% lower in the fondaparinux group**. Similar risk reductions were observed by day 77. No difference was observed in major bleeding between the two groups.

Rivaroxaban *vs.* fondaparinux

In an open-label, non-inferiority phase 3b trial (SURPRISE Study), 472 patients with symptomatic SVT were randomly assigned to receive 10 mg rivaroxaban or 2.5 mg fondaparinux once a day for 45 days.[80] **The primary efficacy outcome** (composite of symptomatic VTE, progression or recurrence of SVT and all-cause mortality at 45 days) **developed in 3% in the rivaroxaban group and 2% in the fondaparinux group**. There were no major hemorrhagic events in either group. Therefore, oral rivaroxaban was found non-inferior to subcutaneous fondaparinux.[92]

Surgical therapy

A review of six studies comparing surgical therapy to anticoagulation showed similar rates of SVT progression, but the incidence of VTE and complications was higher with surgery.[93] Surgical treatment combined with elastic stockings was associated with lower VTE rate and SVT progression compared with elastic stockings alone.[92] In another study no difference was seen between surgery and enoxaparin for 4 weeks.[94]

Antibiotics

Antibiotics have no role in the management of SVT[30, 95] except in cases of infection secondary to indwelling intravenous catheters.

Hirudoids

Hirudoids have some effect in alleviating pain and local inflammatory signs and in some countries, topical agents (hirudoid cream, piroxicam cream, piroxicam patch) are available.[96] **Local application of heparinoid cream was better than placebo**.[97, 98] Local application of heparin

was reported to have effects on symptoms comparable to LMWH.[99]

Elastic stockings

Elastic stockings are traditionally used if tolerated as an adjunctive treatment together with anticoagulation[6, 16, 30, 37, 49] In a recent RCT, adding compression stockings for three weeks to LMWH and NSAIDs did not bring significant additional benefit in the treatment of isolated SVT.[100] However, worn for one week, compression stockings stimulated significantly faster thrombus regression.

Systematic review and meta-analysis

A systematic Cochrane review including 33 studies and involving 7296 patients with SVT was published in 2018.[101] Treatment included fondaparinux, rivaroxaban, LMWH, UFH, NSAIDs, compression stockings, and surgical interventions such as thrombectomy or ligation. Based on this analysis, **prophylactic dose fondaparinux** given for 45 days, **intermediate-dose LMWH for at least 30 days** and **prophylactic doses of oral rivaroxaban for 45 days** appear to be valid therapeutic options for SVT of the legs for most patients. Topical treatments improve local symptoms. Surgical treatment combined with elastic stockings is associated with lower rate of VTE and progression of SVT compared with elastic stockings alone. However, the evidence on topical treatment or surgery is too limited and does not inform clinical practice about the effects of these treatments in terms of VTE. Further research is needed to assess the role of rivaroxaban and other direct oral factor-X or thrombin inhibitors, LMWH, and NSAIDs; the optimal doses and duration of treatment in people at various risk of recurrence; and whether a combination therapy may be more effective than single treatment.

Duration of anticoagulation

Although SVT involving the saphenofemoral and saphenopopliteal junctions is generally regarded as an indication for three months of therapeutic dose anticoagulants, a recent enquiry based on data from the RIETE international registry has questioned this approach.[102] There is the need for controlled randomized clinical trials addressing the optimal intensity and duration of anticoagulation, at least in patients with unprovoked or weakly provoked SVT.

Recommendations

All patients with SVT should have bilateral lower extremity duplex scanning to exclude DVT **(Level of evidence low, recommendation strong)**.

Fondaparinux 2.5 mg once daily for at least 45 days is an effective treatment **(Level of evidence high, recommendation strong)**.

LMWH in intermediate doses for at least one month is recommended **(Level of evidence high, recommendation strong)**.

Rivaroxaban 10 mg daily for 45 days can be used as alternative to fondaparinux **(Level of evidence moderate, recommendation moderate)** when approved for this indication.

Surgery is not better than **LMWHs and should not be used as first line therapy (Level of evidence low, recommendation weak)**.

When thrombus is close to saphenofemoral or saphenopopliteal junctions, **therapeutic anticoagulation** or **surgery** (ligation) are both acceptable options depending on the patient's characteristics and the treating physician's preference **(Level of evidence low, recommendation weak)**. However, it must be remembered that surgery carries an increased risk of complications and thus should be performed by experienced surgeons.

For isolated SVT at a below knee location and confined to varicosities, local application of **heparinoids, NSAIDs and elastic stockings** is an acceptable treatment option **(Level of evidence low, recommendation weak)**.

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SECTION 22

Prevention of post-thrombotic syndrome

Introduction

Despite anticoagulation therapy using LMWH for at least 5 days followed by warfarin for DVT, 30-50% of all patients, depending on the anatomical level of the thrombus, will develop the post-thrombotic syndrome (PTS).[1] One study has even shown PTS to develop in up to 70% of patients.[2] Although PTS may occur within two years after DVT, in most patients, symptoms develop within the first six months.[3-5] Established PTS is a significant cause of chronic incapacity and inability to work with considerable consequences for both the patient and the society.[6-10]

PTS is the result of venous hypertension produced by reflux, which is caused by remodeling of the venous wall and/or damaged valves alone or combined with persisting outflow obstruction.[11-15] Venous hypertension is associated with chronic inflammation affecting not only the venous wall, but also the microcirculation. Excessive capillary leakage produces impairment of skin nutrition with skin changes and eventually skin ulceration.[14]

Factors that are associated with the development of PTS include iliofemoral DVT[7, 8] especially if chronic iliofemoral vein obstruction persists,[16-18] increased BMI, older age and female gender,[8, 18] recurrent DVT,[18] which often obstructs part of the collateral circulation, and sub-therapeutic anticoagulant therapy which allows DVT recurrence.[18] Elevated inflammatory biomarkers such as Il-6, ICAM-1 and CRP[19-21] are associated with increased rates of PTS following DVT. A study by Jeraj *et al.*[22] demonstrated that incomplete or absent recanalization is associated with a higher incidence of PTS, because of deteriorated blood flow and increased venous pressure. These findings suggested that early recanalization could improve the outcome of DVT treatment in selected patients.

So far, three risk models have been identified, which have the potential to predict the development of PTS: the SOX PTS model generated from the SOX study,[23, 24] the IDEAL PTS model generated from the IDEAL DVT study,[25, 26] and a Chinese nomogram.[27] They are displayed in Table 22.I, 22.II and Figure 22.1. However, at present the value of these scores for clinical practice remains uncertain.[4, 5]

PTS can be prevented by preventing DVT in the first place and DVT recurrence by extended therapy with LMWH, DOACs or sulodexide. There is emerging evidence that venous recanalization occurs more frequently with LMWH and DOACs that have anti-Xa activity than with VKA. Elastic compression after DVT, and early

Table 22.I.—*SOX PTS score for the prediction of PTS.*

Features	Score
BMI >35 kg/m^2	2
Iliac vein involvement	1
Moderate (score 5-9) Villalta Score at DVT presentation	1
Severe (score >10) Villalta Score at DVT presentation	2
A score ≥ 4 identifies patients at a higher risk of PTS.	

Table 22.II.—*IDEAL PTS score for the prediction of PTS.*

Features	Baseline score	Score at six months
Age >56	2	1
BMI >30 kg/m^2	2	1
Varicose veins	4	3
Smoking	1	1
Residual vein thrombosis	--	1
Female gender	1	--
Ilio-femoral DVT	1	--
Provoked DVT	1	--
Previous DVT	1	--
Baseline model: 0-2 points: 10%; 3-4 points: 20%; >5 points: 40%. After six months: 0-2 points: 25%; 3-4 points: 45%; >5 points: 60%.		

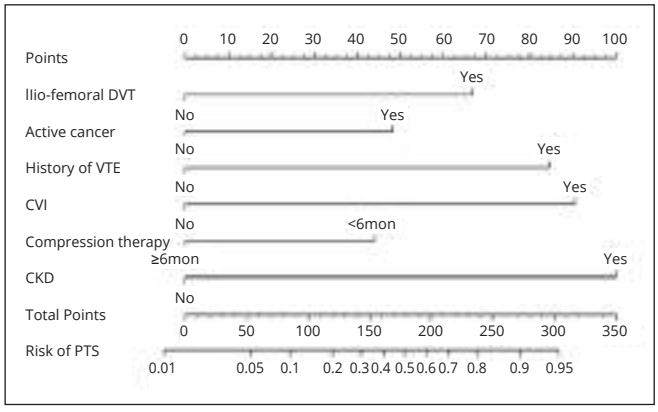

Figure 22.1.—CHINESE nomogram for estimation of PTS in patients with acute DVT.

thrombus removal after iliofemoral DVT are also associated with a reduced incidence of PTS or reduction in the severity of PTS symptoms. The evidence for the above is presented below.

Prevention of primary DVT

Prevention of DVT should also prevent the development of PTS. The evidence and guidelines for primary prevention in surgical and medical patients have been summarized in Sections 3-14. Early thrombus removal either by thrombectomy or catheter directed thrombolysis is also associated with a reduction in PTS (see Section 19). Guidelines aiming to reduce PTS and leg ulcers by 50% have been published.[4, 5, 28]

Prevention of recurrent DVT (secondary prevention)

Recurrence of DVT after completion of conventional oral anticoagulation therapy is high. For patients with unprovoked DVT the incidence of recurrence is 11% at one year, 30% at 5 years and 40% at 10 years. For patients with provoked DVT the recurrence rate is approximately half.[29] As indicated above, recurrence of DVT may result in severe post-thrombotic syndrome and reduced quality of life. RCTs with DOACs and antithrombotic medications, which have resulted in several strategies that can reduce the incidence of DVT recurrence are presented below.

For efficacy of anticoagulation methods in the prevention of VTE recurrence please see "Secondary Prevention of VTE" in Section 16 on "Anticoagulation Therapy."

For Strategies to identify patients at increased risk of DVT recurrence and bleeding risk please see also Section 16 on "Anticoagulation Therapy."

Assessment of risk of recurrence *vs.* risk of bleeding with adjustment of anticoagulation

It is now established that the risk of recurrence of VTE and risk of bleeding are not the same in every patient. As indicated in Section 16, methods that can assess these risks which have met with moderate success are now available.[30] In addition, as indicated in the review of secondary prophylactic anticoagulation, therapies are now available with very low risk of bleeding (low-dose apixaban, low-dose rivaroxaban, sulodexide). Therefore, recommendations for secondary (extended) prophylaxis should be based on calculations for the risk of recurrence *vs.* risk of bleeding with appropriate drug selection.

Thus, based on the available medications and knowledge of risk of recurrence *vs.* risk of bleeding a health-care provider can make up a plan or algorithm for extended prophylaxis after the initial treatment for 3-6 months. An example is given below.[31]

A. Patients at high or intermediate risk of VTE recurrence

There are different risks of bleeding:

- ***low risk of bleeding*** **–** any anticoagulant can be given (VKA, rivaroxaban, apixaban, edoxaban);
- ***intermediate risk of bleeding*** **–** *apixaban* or rivaroxaban;
- ***high risk of bleeding*** **–** low dose apixaban, low dose rivaroxaban, sulodexide.

B. Patients at low risk of recurrence

Anticoagulants can be omitted, but if the patient prefers to continue with prophylaxis, then sulodexide may be chosen.

The efficacy of such plans needs to be validated in prospective studies.

Compression stockings for prevention of PTS

Effective compression has been shown to reduce venous hypertension, edema and minimize the damage to the microcirculation.[32, 33] Four RCTs involving 745 patients have demonstrated that in patients with proximal DVT, **knee-length compression stockings used for 2 years reduce the incidence of PTS from 39% to 19% (RR: 0.49, 95% CI: 0.38 to 0.62)**.[34-37] A Bayesian meta-analysis concluded that there is a 95% probability of some reduction in the risk of PTS of any severity and 72% probability that some reduction in the risk of severe PTS can be seen wearing compression stockings.[38]

One study has shown no difference between knee and thigh length compression stockings.[39]

Based on the above it appears that treatment with LMWH combined with early ambulation and elastic compression prevent further the development of PTS.[40, 41] However, in contradiction to previous publications, a large multicenter placebo controlled RCT involving 794 patients with a first DVT (SOX Trial) casted doubt on the effectiveness of compression in the prevention of PTS.[42] Indeed, after two years of follow-up there was no difference at all between the two study groups (each of them including approximately 400 patients) in terms of PTS development, as assessed with the Ginsberg Index and with the Villalta Scale. It should be noted that use of Villalta Scale for defining PTS may misclassify 42.3% of patients with primary CVD as having PTS.[43] In addition, we now realize that the so-called sham stocking had a pressure of 8 mm in the calf and below 5 mm at the ankle which represented an antigraduated stocking. Mosti and Partsch have demonstrated that low pressure antigraduated stockings can be as effective as higher pressure graduated stockings in decreasing leg volume compared to conventional graduated compression hose.[44] A number of problems with this study have been described, especially the unexpectedly low compliance (lower than 50%).[45] Although the conclusions of this study have generally been criticized, most international guidelines no longer recommend the routine use of compression stockings besides conventional anticoagulation in patients with proximal DVT.[4, 46] This study which contradicts previous publications has stimulated several groups to publish reviews and meta-analyses on this subject, all with the conclusion that further studies will be needed to achieve clear recommendations.

Following the publication of the OCTAVIA study, which failed to show the non-inferiority of a 1-year over a 2-year course of compression stockings,[47] a meta-analysis of nine available controlled studies involving 1694 patients, published in 2023, indicated a statistically significant reduction in the overall PTS favoring the use of stockings (RR: 0.73, 95% CI: 0.53 to 1.00; P=0.05).[48] A further analysis on four high quality studies involving 1409 patients in the same publication still indicated a statistically significant reduction in the overall PTS rate (RR: 0.66, 95% CI: 0.44 to 0.99; P=0.05). The optimal duration of elastic stockings after an episode of proximal DVT was addressed by two studies. In a prospective, controlled, randomized clinical trial Aschwanden *et al.* showed that prolonging their use for up to two years does not improve the rate of PTS development over a 6-month period.[37] In a large Dutch-Italian clinical trial (IDEAL), where a fixed 2-year period was compared with an individualized strategy (patients with a Villalta Score <4 were instructed to stop using the stockings after the first six months or later during their subsequent follow-up), the latter was found not inferior to the standard 2-year duration of elastic stockings.[49]

Early thrombus removal for prevention of PTS

For thrombectomy, catheter directed thrombolysis, and mechanical and aspiration thrombectomy see Section 19.

Extended therapy with LMWH, DOACs and sulodexide for prevention of PTS

A. Effect of long-term anticoagulation with LMWH on development of PTS

Standard treatment of DVT (initial LMWH for at least 5 days followed by VKA) prevents thrombus extension and embolization but does not directly lyse the thrombus, which often results in partial recanalization. Several studies have compared **long-term treatment with LMWH** *vs.* standard therapy,[50-54] and demonstrated **better recanalization in the long-term LMWH groups**. A meta-analysis on 5 studies that reported on total recanalization demonstrated a risk ratio of 0.66 (95% CI: 0.57 to 0.77; P<0.0001) in favor of long term LMWH.[55] In a large multicenter study involving 480 patients there was a **reduction of the incidence of PTS with long-term LMWH compared with standard therapy (RR: 0.77; P=0.001)**.[56] Pooled analyses of two studies reporting on the **long-term development of leg ulcers as part of PTS**,[56, 57] **demonstrated an 87% risk reduction for venous ulcers when long-term LMWH was used instead of standard therapy (P=0.019)**.[56]

B. The effect of direct oral anticoagulants on development of PTS

Anecdotal reports of marked early vein recanalization in patients treated with rivaroxaban[58, 59] and a small study involving 102 patients with iliofemoral DVT[60] suggested that rivaroxaban was associated with rapid recanalization during the first 2 weeks of therapy. In this study, patients were divided into three groups. In group one 38 patients received standard therapy with LMWH (enoxaparin) followed by warfarin combined with diosmin 600 mg once daily. In group two 33 patients received rivaroxaban at a dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily. In group three, 31 patients were also given rivaroxaban in the above-described standard regimen in

combination with diosmin 600 mg once daily. The results indicated that rivaroxaban "from the first day of the disease made it possible to considerably improve and accelerate the processes of restoration of patency of deep veins of lower extremities as compared with the patients taking warfarin." In patients receiving rivaroxaban, there were no cases of residual thrombotic occlusions of the major veins, and recanalization in three fourths of patients was assessed as good and in the remaining third as moderate. In the warfarin group, occlusion in the iliac veins was noted to persist in 13% of patients, with good recanalization observed only in half of the patients. In addition, a combination of diosmin with rivaroxaban was more efficient than a combination of diosmin with warfarin.

A *post-hoc* subgroup analysis of the EINSTEIN DVT trial was performed to assess the efficacy of rivaroxaban on the development of the PTS.[61] They included 336 patients of which 162 received rivaroxaban and 174 enoxaparin/VKA. **At 5 years the hazard ratio of PTS development for rivaroxaban was 0.76 (95% CI: 0.51 to 1.13)**. The authors concluded that rivaroxaban was associated with a numerically lower but statistically non-significant reduction in risk of PTS compared with enoxaparin/VKA treatment.

In a prospective study, 100 consecutive patients treated for DVT were included, of which 39 were treated with enoxaparin/warfarin and 61 with rivaroxaban.[22] The authors assessed symptoms and signs of PTS and calculated the Villalta Score at 23 months (median) after acute DVT diagnosis. **Patients in the rivaroxaban group had a lower prevalence of PTS than those treated with warfarin (25% *vs*. 49%, P=0.013)**. Logistic regression showed an odds ratio of 2.9 (95% CI 1.2 to 6.8; P=0.014) for PTS development in the warfarin group compared with the rivaroxaban group. When adjusted for other variables, the OR was 3.5 (95% CI 1.1 to 11.0; P=0.035). The authors concluded that treatment of DVT with rivaroxaban might be associated with a lower risk for PTS development and that a larger randomized trial would be needed for stronger evidence.

In a subsequent study, 309 patients with an objectively confirmed DVT diagnosed between 2011 and 2014 and treated with either rivaroxaban (N.=161) or warfarin (N.=148) were assessed at 24±6 months after DVT diagnosis using the patient reported Villalta Scale.[62] **The incidence of PTS was 45% (95% CI: 37% to 52%) in the rivaroxaban group and 59% (95% CI: 51% to 66%) in the warfarin group**. Absolute risk difference was 14% (95% CI: 3% to 25% with an OR of 0.6 (P=0.01). The adjusted OR for development of PTS in those treated with rivaroxaban was 0.50 (95% CI: 0.30 to 0.80; P=0.01). Health related quality of life was better in the rivaroxaban treated patients as measured by WQ-VAS (P=0.002) and VEINES-QOL/Sym (P=0.005/ P=0.003). The authors pointed out that these results should be interpreted with caution due to the limitation imposed by the study.

In the most recent publication, the relative hazard of PTS in patients with VTE treated with rivaroxaban or warfarin in routine US clinical practice was assessed using MarketScan claims data (IBM Corp., Armonk, NY, USA) from January 2012 to June 2015.[63] Adults with a primary diagnosis code for VTE during a hospitalization/ emergency department visit, ≥6 months of insurance coverage prior to the index event and newly started on rivaroxaban or warfarin within 30 days of the index VTE were identified. Differences in baseline characteristics between rivaroxaban and warfarin users were adjusted for using inverse probability of treatment weights based on propensity scores. In total, 10,463 rivaroxaban and 26,494 warfarin users were followed for a mean of 16±9 (range, 4-39) months. Duration of anticoagulation was similar between cohorts (median = 6 months). **Rivaroxaban was associated with 23% (95% CI: 16 to 30) reduced hazard of PTS *vs.* warfarin**.

Among factors associated with an increased risk of PTS development, the inadequacy of vitamin K antagonist (VKA) treatment has consistently been found to play a key role in the development of PTS.[18, 64] DOACs have now become commercially available worldwide. Because of their predictable pharmacokinetics, they can be used in a fixed dose, without laboratory monitoring, and result in a much more stable anticoagulation than that induced by VKAs.[65] In addition, they have recently been found to restore the vein patency more rapidly than VKA.[66] Recently, the results of a prospective multicenter Italian study have been published. The rate of PTS over a 2-year follow-up was calculated in more than 300 patients who had been treated with DOACs (mostly rivaroxaban) and was compared with that found in a historical cohort of more than 1000 patients who had been treated with VKAs and had been followed-up over time using an identical approach.[66] After adjusting for several unavoidable differences between the two cohorts, **DOACs were found to decrease the risk of overall and severe PTS by more than 50% compared with VKAs**.

A meta-analysis of seven comparative studies (2364) found that **rivaroxaban treatment was associated with**

a lower risk of PTS compared with conventional VKAs (pooled unadjusted OR 0.53, 95% CI: 0.43 to 0.65; P<0.00001).[67] This effect was maintained after adjustment of potential confounders (pooled adjusted OR: 0.44, 95% CI: 0.35 to 0.56; P<0.00001). Furthermore, rivaroxaban therapy was found to be associated with reduced risk of mild PTS (OR: 0.64, 95% CI: 0.50 to 0.82; P=0.0005), moderate PTS (OR: 0.64, 95% CI: 0.45 to 0.91; P=0.01), and severe PTS (OR: 0.52, 95% CI: 0.33 to 0.82; P=0.005). There was also a similar but non-significant trend of reduced incidence of venous ulceration (OR: 0.41, 95% CI: 0.15 to 1.08; P=0.07). The authors concluded that in comparison to VKAs, the use of rivaroxaban for treating DVT has the potential to reduce PTS events. However, well-designed studies with larger sample sizes are needed to corroborate these findings.

Recommendations

Adherence to the guidelines for the **prevention of primary DVT** in hospitalized patients is essential. In patients who present with DVT, every effort should be made to **reduce recurrence rates**. This can be achieved by using anticoagulation of **adequate intensity and duration according to the guidelines (Level of evidence high, recommendation strong)**.

Early and more extensive recanalization, and a reduction in the incidence of PTS occurs when DVT is treated with **anticoagulants such as LMWH or the DOAC rivaroxaban compared with VKA (Level of evidence moderate, recommendation moderate)**.

DVT **recurrence is reduced** by extended therapy using **rivaroxaban, apixaban, edoxaban, dabigatran or sulodexide (Level of evidence high, recommendation strong)** (see Section 16).

The incidence of PTS is reduced by extended therapy using rivaroxaban or sulodexide **(Level of evidence low, recommendation weak)** due to lack of large randomized controlled trials.

Due to the lack of RCTs with PTS occurrence as a study endpoint, the possible influence of dabigatran, edoxaban and apixaban on the PTS prevention needs to be investigated.

Strategies to determine the need and type of extended prophylaxis based on the balance of risk of DVT recurrence and risk of bleeding are available **(Level of evidence low, recommendation weak)**.

Compression therapy using below knee elastic stockings for at least 6 months after DVT is associated with reduction of symptoms **(Level of evidence moderate, recommendation strong)** and incidence of PTS **(Level of evidence moderate, recommendation strong)**.

Surgical thrombectomy is also associated with reduction in the incidence of PTS **(Level of evidence high, recommendation moderate)** (see Section 19).

In patients with **iliofemoral DVT** catheter directed thrombolysis is associated with reduction in the incidence of PTS and improved QoL, **but** is associated with **increased risk of bleeding (Level of evidence moderate, recommendation moderate)** (see Section 19).

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SECTION 23

Periprocedural management of patients on chronic oral anticoagulant therapy and use of heparin bridging

General considerations

The periprocedural management of patients requiring temporary interruption of chronic oral anticoagulants (OAC) such as warfarin or more recently DOACs such as rivaroxaban, apixaban, edoxaban, and dabigatran due to an elective invasive procedure or elective surgery is a common clinical problem.[1] Approximately 15-20% of patients on chronic OAC will require surgery or procedure each year,[2, 3] which translates in North America alone to an annual estimate of 250,000 patients on chronic OAC being assessed in periprocedural situations.[4] Management of these patients is difficult due to the risk of bleeding when antithrombotic therapy is administered near an invasive procedure or surgery *vs.* the risk of thromboembolism if antithrombotic therapy were interrupted. A careful bleeding and thrombotic risk assessment should be performed for the individual patient undergoing a specific procedure to determine: 1) if interruption of anticoagulant therapy is needed in the periprocedural period; 2) if more aggressive strategies such as heparin bridging anticoagulation is needed among those patients requiring temporary interruption of anticoagulant therapy; and 3) the optimal timing of anticoagulant interruption and resumption.

Bridging anticoagulation can be defined as the use of short-acting parenteral anticoagulants such as UFH or LMWH (usually in therapeutic doses) in the pre- and post-procedural period to maintain an anticoagulant effect, especially during temporary interruption of VKA when the INR is subtherapeutic. Any perioperative interruption and resumption of anticoagulant therapy should be based on assessment of procedural bleed risk as well as relevant pharmacokinetic parameters of a particular agent (including patient renal status, when appropriate) (Table 23.I).[5]

TABLE 23.I.—*Pharmacologic properties of anticoagulant drugs pertinent to perioperative management.*

Drug type	Half-life elimination ($t_{1/2}$), hours	Peak action (t_{max}), hours	Renal clearance %	Residual DOAC level in low/moderate-bleed-risk procedure**	Residual DOAC level in high-bleed-risk procedure***
VKA					
Warfarin	36-42	>120	minimal	-	-
Acenocoumarol	8-11	>120	minimal	-	-
Phenprocoumon	96-104	>120	minimal	-	-
DOAC					
Apixaban	9-11	2-4	25	12.9% at >50 ng/mL 17.8% at 30-50 ng/mL	2.1% at >50 ng/mL 4.8% at 30-50 ng/mL
Dabigatran	12-14*	2-4	75-80	7.1% at >50 ng/mL 9.9% at 30-50 ng/mL	0.55% at >50 ng/mL 0.55% at 30-50 ng/mL
Edoxaban	10-14	2-4	50	n/a	n/a
Rivaroxaban	9-11	2-4	33	4.5% at >50 ng/mL 21.9% at 30-50 ng/mL	0.64% at >50 ng/mL 14.0% at 30-50 ng/mL
LMWH	3-4	3-4	80	-	-
UFH	0.5-1	4-24	<5	-	-

VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin; USH: unfractionated heparin.
*18-24 hours in patients with creatinine clearance <50 mL/min; **36-42 hours between last DOAC dose and DOAC level; ***60-70 hours between last DOAC dose and DOAC level.

The impact of major bleeding in the periprocedural period is greater than previously thought and may be associated with significant morbidity and a case-fatality rate of up to 9%.[6] Moreover, postoperative bleeding delays resumption of antithrombotic therapy, thereby placing patients at risk for thromboembolism.[7] Bleeding risk assessment involves considerations of both patient and procedure-related risk factors for bleeding. For the patient, factors such as a history of prior bleeding, especially prior periprocedural bleeding, or the use of multiple antithrombotic drugs may place that patient at higher risk for bleeding. Although there is no validated procedure-related bleeding risk score, it is helpful to empirically characterize procedures into a three-tiered risk scheme of high, moderate/low, and minimal bleed risk in developing a periprocedural management strategy (Table 23.II).[8]

High bleeding risk procedures include most major operations lasting more than 45 minutes, vascular procedures, major orthopedic procedures, cardiothoracic procedures, extensive cancer surgery, and prostate or bladder surgery which require sufficient preprocedural anticoagulant interruption (usually 4-5 drug half-lives) so there is minimal-to-no residual anticoagulant effect at the time of the surgery/procedure, and delayed postprocedural anticoagulant resumption, to account for the longer time required for surgical site hemostasis.[9] In addition, invasive proce-

TABLE 23.II.—*Suggested Risk Stratification for Procedural Bleed Risk, based on International Society on Thrombosis and Haemostasis Guidance Statements.*[8]

	Major surgery with extensive tissue injury
High-bleed-risk surgery/ procedure* (30-day risk of major bleed ≥2%)	Cancer surgery, especially solid tumor resection (lung, esophagus, gastric, colon, hepatobiliary, pancreatic)
	Major orthopedic surgery, including shoulder replacement surgery
	Reconstructive plastic surgery
	Major thoracic surgery
	Urologic or Gastrointestinal surgery, especially anastomosis surgery
	Transurethral prostate resection, bladder resection or tumor ablation
	Nephrectomy, kidney biopsy
	Colonic polyp resection
	Bowel resection
	PEG placement, ERCP
	Surgery in highly vascular organs (kidneys, liver, spleen)
	Cardiac, intracranial, or spinal surgery
	Any major operation (procedure duration >45 minutes)
	Neuraxial anesthesia†
	Epidural injections
Low/moderate-bleed-risk surgery/ procedure** (30-day risk of major bleed 0-2%)	Arthroscopy
	Cutaneous/lymph node biopsies
	Foot/hand surgery
	Coronary angiography††
	Gastrointestinal endoscopy ±biopsy
	Colonoscopy ± biopsy
	Abdominal hysterectomy
	Laparoscopic cholecystectomy
	Abdominal hernia repair
	Hemorrhoidal surgery
	Bronchoscopy ± biopsy
Minimal-bleed-risk surgery/ procedure*** (30-day risk of major bleed ~0%)	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi)
	Ophthalmological (cataract) procedures
	Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings
	Pacemaker or cardioverter-defibrillator device implantation

PEG: percutaneous endoscopic gastrotomy; ERCP: endoscopic retrograde cholangiopancreatography.
*No residual anticoagulant effect at time of procedure (*i.e.*, 4-5 drug half-life interruption preprocedure); **some residual anticoagulant effect allowed (*i.e.*, 2-3 drug half-life interruption preprocedure); ***procedure can be safely done under full dose anticoagulation (may consider holding DOAC dose day of procedure to avoid peak anticoagulant effects); †includes spinal and epidural anesthesia or any other neuraxial (*e.g.*, pain management) intervention; consider not only absolute risk for major bleeding but potentially devastating consequences of epidural bleeding and associated lower limb paralysis; ††radial approach may be considered minimal bleed risk compared to femoral approach.

dures such as resection of colonic polyps, prostate, liver, or kidney biopsy, or neuraxial interventions may place the patient at increased risk of bleeding or significant epidural hematomas.[10, 11]

Moderate-to-low bleed risk procedures such as arthroscopies, coronary angiography, and abdominal laparoscopy can be undertaken with some residual anticoagulant effect at the time of the surgery/procedure and usually require a 2-3 drug half-life interruption of anticoagulant therapy.

Minimal bleed risk procedures by definition can safely be undertaken without anticoagulant interruption and include minor invasive procedures such as gastrointestinal diagnostic procedures, cardiac device (pacemaker or cardioverter-defibrillator) implantation, and dermatological, dental or ophthalmologic procedures.[12]

Thrombotic risk assessment should account for the estimated patient-related risk of arterial thromboembolism (ATE) or VTE and include procedural-related risks. An empiric thrombotic risk assessment derived from studies in non-operative settings and based on the three most common indications for VKA therapy (mechanical heart valve, atrial fibrillation or VTE), classifies patients into high, moderate, and low-thrombotic risk groups based on annualized ATE rates and monthly VTE rates (Table 23.III).[13]

High thrombotic risk groups include patients with mitral position valves and stroke risk factors or older-generation mechanical valves, patients with atrial fibrillation with high CHA_2DS_2VASc (≥7) or CHA_2DS_2 (5 or 6) scores, and patients with a recent VTE (<3 and especially 1 month) or VTE associated with severe thrombophilia. Although an increased risk of VTE in the postoperative setting has been well documented, there are emerging data suggesting an up to a 10-fold increased risk of arterial thromboembolism (compared with the risk derived from mathematical modelling) in the perioperative setting, especially among patients undergoing major surgery.[14-17]

Periprocedural management of patients on chronic oral anticoagulation undergoing minimal bleed risk procedures

Minor dental, dermatological or ophthalmological procedures comprise approximately 20% of procedures in patients receiving OACs.[9] Randomized trials and prospective cohort studies indicate that patients who continue VKA during dental extraction, especially with co-administration of antifibrinolytic drugs such as tranexamic acid mouthwash, had similar rates of major and clinically significant non-major bleeding (<5%) and rare thromboembolic events (<1%), as did patients who discontinued VKA.[18-20] Partial interruption of VKA 2-3 days prior to a dental procedure has also been associated with low bleed risk.[21] In addition, prospective cohort studies in patients undergoing

TABLE 23.III.—*Suggested risk stratification for patient-specific periprocedural thromboembolism, based on 2022 American College of Chest Physician Guidelines.*[13]

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10%/year risk of ATE or >10%/month risk of VTE)	Bileaflet mitral valve with risk factors for stroke[b]	CHA_2DS_2VASc Score ≥7 or $CHADS_2$ Score of 5 or 6	Recent (<3 months and especially 1 month) VTE
	Caged ball or tilting disc valve in mitral/aortic position	Recent (<3 month) stroke or TIA	Severe thrombophilia (deficiency of protein C, protein S or antithrombin, homozygous factor V Leiden or prothrombin gene *G20210A* mutation or double heterozygous for each mutation, multiple thrombophilias)
	Recent (<3 month) stroke or TIA	Rheumatic valvular heart disease	Antiphospholipid syndrome
			Active cancer associated with high VTE risk[c]
Moderate (4-10%/year risk of ATE or 4-10%/month risk of VTE)	Bileaflet mitral valve without risk factors for stroke[b]	CHA_2DS_2VASc Score of 5 or 6 or $CHADS_2$ Score of 3 or 4	VTE within past 3-12 months
			Recurrent VTE
	Bileaflet aortic valve with risk factors for stroke[b]		Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene *G20210A* mutation)
			Active cancer or recent history of cancer
Low (<4%/year risk of ATE or <2%/month risk of VTE)	Bileaflet aortic valve without risk factors for stroke[b]	CHA_2DS_2VASc Score of 1-4 or $CHADS_2$ Score of 0-2 (and no prior stroke or TIA	VTE >12 months ago

ATE: arterial thromboembolism; VTE: venous thromboembolism; TIA: transient ischemic attack; $CHADS_2$: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, or transient ischemic attack; CHA_2DS_2VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease history, age ≥65 years, female sex.
[a]Empiric risk stratification that is a starting point for assessing perioperative thromboembolism risk; should be combined with clinical judgement that incorporates individual patient- and surgery/procedure-related factors; [b]AF, prior stroke/TIA during anticoagulant interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, congestive heart failure, age ≥75 years; [c]pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

dermatological and ophthalmological procedures (specifically cataract extraction) showed a low incidence of major bleeding and support the notion that VKA can be continued around the time of certain minor procedures.[22-24] More recent evidence from RCTs including the BRUISE-CONTROL and COMPARE trials and meta-analyses of observational studies consistently reported significantly less major bleeding including pocket hematomas with continuation of VKA *vs.* VKA interruption and heparin bridging anticoagulation in patients undergoing cardiac device and other procedures including implantation of a pacemaker or cardioverter-defibrillator.[25-28]

With regards to DOACs and minimal bleed risk procedures, evidence from a large meta-analysis of randomized trials reported significantly less major bleeding from a strategy of uninterrupted DOAC *vs.* warfarin in patients with atrial fibrillation in procedural settings (RR: 0.62, 95% CI: 0.47 to 0.82).[29] In addition, an RCT (RE-CURCUIT AF) comparing uninterrupted dabigatran *vs.* warfarin in cardiac ablation procedures reported a significant 78% risk reduction of major bleeding with dabigatran.[30]

Periprocedural management of patients on chronic oral anticoagulation undergoing low/moderate and high bleed risk procedures requiring temporary interruption

Interruption of VKA and heparin bridging anticoagulation

Basic principles for patients receiving VKA who undergo low/moderate or high bleed risk procedures and require temporary periprocedural interruption of VKA and basic principles for the use of heparin bridging anticoagulation are as follows:

• for patients undergoing a high bleeding risk procedure or surgery where there is intent to minimize the anticoagulant effect of VKA in the preprocedural period, approximately five days of interruption of warfarin is needed, based on a half-life of approximately 36-42 hours.[21] In elderly patients or patients on a longer-lasting VKA such as the less widely used phenprocoumon (with a half-life of 96-140 hours), longer periods of interruption may be necessary;[31]

• there appears to be a detectable residual anticoagulant effect, as measured by anti-Xa ≥0.10 IU/mL, if therapeutic-dose LMWH is given within 12 hours of the start of the procedure;[32]

• preoperative administration of low-dose vitamin K orally (1-2.5 mg) in patients with an elevated INR (≥1.5) does not appear to be associated with resistance to re-anticoagulation when VKA is resumed after surgery, although uncertainty remains as to the routine use of preoperative vitamin K;[33]

• current global coagulation tests such as the activated partial thromboplastin time (aPTT), prothrombin time (PT), and heparin anti-Xa level are likely to be inadequate to measure the dual anticoagulant effects of both VKA and heparin in the periprocedural period, while other tests such as the thrombin generation (TG) assay may have improved sensitivity in detecting the global anticoagulant effects of both LMWH and VKA, although they are not widely available or standardized;[34]

• in the postprocedural period, administration of heparin bridging therapy at close proximity to the procedure or at therapeutic doses may increase the bleeding risk. Therefore, in low/moderate bleed risk procedures delaying resumption of bridging therapy approximately 24 hours after the procedure while in high bleeding risk procedures, delaying resumption of bridging therapy for approximately 48-72 hours after the procedure, or avoiding postprocedure bridging anticoagulation may decrease the risk of bleeding;[35]

• periprocedural discontinuation and re-initiation of VKA and use of heparin bridging therapy should be based on an explicit, evidence-based, and standardized protocol with careful consideration of patient and procedural risk factors for thrombosis and bleeding;[36]

• there are substantial cost savings with the use of LMWH as bridging therapy due to facilitation of management in an outpatient setting compared with intravenous UFH used in-hospital.[37]

Bridging anticoagulation in patients with a mechanical heart valve (MHV), AF or VTE receiving VKA in periprocedural settings

Older prospective cohort studies in which heparin bridging anticoagulation was assessed in patients on VKA with a MHV included patients with aortic, mitral, or dual position MHVs, as well as a minority of patients with older, caged ball MHVs. Most of these studies included therapeutic-dose LMWH regimens (*i.e.*, enoxaparin 1mg/kg twice daily or 1.5 mg/kg once daily, dalteparin 100 IU/kg twice daily or 200 IU/kg once daily) and none had control groups without bridging therapy. The pooled perioperative arterial thromboembolism event rate was low (~1%), with no reported episodes of MHV thrombosis, and the overall rate of major bleeding was ~3%.[7, 38-41] A study of 1777 patients who underwent mechanical valve replacement and who received either therapeutic or prophylactic dose heparin bridging anticoagulation found a 2.5 to 3-fold increase

in major bleeding with therapeutic heparin bridging (OR: 3.23, 95% CI: 1.58 to 6.62; P=0.001) and similar risk of thromboembolic complications.[42]

In an observational study assessing bridging *vs.* no bridging management in VKA-treated patients which included patients with a mechanical heart valve, those who received perioperative bridging had an increased risk for major bleeding (3.6% *vs.* 1.2%; P=0.0007).[43]

In a large meta-analysis of 12,278 patients on chronic VKA with multiple indications (24% of whom had a mechanical heart valve) that compared bridging *vs.* no bridging, there was no significant difference in the risk of ATE in bridged and non-bridged groups (OR: 0.80, 95% CI: 0.42-1.54), but bridging conferred an increased risk of major bleeding (OR: 3.60, 95% CI: 1.52-8.50).[44]

Lastly, a recent RCT of periprocedural heparin bridging that included 304 patients on chronic VKA with a mechanical heart valve (PERIOP-2) – all of whom received preoperative LMWH bridging while postoperatively were randomized to therapeutic-dose LMWH for low bleed risk and fixed dose LMWH for high bleed risk procedures *vs.* placebo, reported no significant difference in the no bridging and bridging groups for major bleeding (1.96% *vs.* 0.67%; P=0.62) or major thromboembolism (0% *vs.* 0.67%; P=0.67).[45]

There are prospective cohort studies in which mostly therapeutic-dose LMWH bridging anticoagulation was assessed in patients with AF undergoing elective procedures or surgery.[7, 35, 39, 40, 46] The pooled risk of perioperative arterial thromboembolism was ~1%. Most patients described in such studies had at least one additional stroke risk factor as per $CHADS_2$ criteria.

More recent large periprocedural cohort studies in patients with AF on chronic VKA that included heparin bridging with no bridging comparators found higher rates of major bleeding and paradoxically trends towards higher postprocedural thromboembolic events in bridged groups.[43, 47]

Two large double-blind placebo-controlled RCTs assessed the efficacy and safety of periprocedural heparin bridging therapy in patients with AF on chronic VKA with at least one stroke risk factor – the landmark BRIDGE trial and the PERIOP-2 trial.[45, 48] The BRIDGE trial showed that in patients with AF receiving chronic warfarin therapy who needed treatment interruption for an elective procedure/surgery, foregoing a strategy of bridging with therapeutic dose LMWH resulted in no significant difference in the rate of ATE (0.3% *vs.* 0.4%; P=0.01 for non-inferiority) between the bridging and no bridging groups and was associated with a significantly lower risk of major bleeding (1.3% *vs.* 3.2%, P=0.005).[48, 49] In the PERIOP-2 trial, there was no significant difference between the bridging (N.=670) and no bridging (N.=497) arms in the AF subgroup for the outcomes of major thromboembolism (0.75% *vs.* 1.41%) and major bleeding (1.64% *vs.* 2.62%).[45, 50, 51]

Multiple cohort studies in periprocedural settings have evaluated bridging anticoagulation with therapeutic-, intermediate- or low-dose bridging regimens of various LMWHs in patients with VTE on chronic VKA.[35, 39, 46, 52-57] The pooled risk for recurrent symptomatic VTE was low (<1%), however, many studies found an increased risk of major bleeding with heparin bridging. A retrospective cohort study of 1,178 patients on chronic warfarin with VTE indications in periprocedural settings found a markedly increased risk of clinically relevant bleeding with heparin bridging (HR: 17.2, 95% CI: 3.9 to 75.1) and no significant difference in the rate of recurrent VTE (0 *vs.* 3; P=0.56).[58]

In an observational study of 755 patients on VKA who required a procedure or surgery that assessed a bridging (N.=214) *vs.* no bridging (N.=514) approach, there was no significant difference in recurrent VTE or bleeding outcomes in the two groups.[59]

In a systematic review totaling 6195 VKA-treated patients with VTE who required elective surgery, heparin bridging *vs.* no bridging was associated with a higher incidence of any bleeding: 3.9% (95% CI: 2.0 to 7.4) *vs.* 0.4% (95% CI: 0.1 to 1.7) and no difference in recurrent VTE: 0.7% (95% CI: 0.4 to 1.2) *vs.* 0.5% (95% CI: 0.3 to 0.8).[60]

Interruption of DOACs

The periprocedural interruption of DOACs including apixaban, rivaroxaban, edoxaban, and dabigatran should be based on a careful assessment of surgical/procedural bleeding risk (Table 23.II), patient renal function, and pharmacokinetic parameters (Table 23.I).[5] Given DOAC half-lives of 9-14 hours, withholding DOACs for 2 full days before surgery/procedure, which corresponds to four to five half-lives from the last DOAC dose until the surgery, should result in minimal to no residual anticoagulant effect at the time of surgery.[61-64] This approach can be used for patients having a high-bleed-risk surgery/procedure, whereas for patients having a low-to-moderate-bleed-risk surgery/procedure, withholding DOACs for one full day before the procedure, which corresponds to approximately three half-lives, should result in a residual anticoagulant effect which is clinically acceptable for these procedures.[64, 65] Exceptions to these basic DOAC periprocedural management principles includes: 1) patients with

renal impairment (CrCl <50mL/min) on dabigatran, where a 3-4-day interruption is required for drug clearance due to the mostly renal elimination of the drug; and 2) other select patients with hepatic dysfunction or taking drugs that inhibit CYP3A4 or P-glycoprotein pathways that may interfere with DOAC clearance.[66]

A laboratory-based approach for the periprocedural management of DOACs in non-urgent surgery or procedures has been proposed,[67] which includes DOAC-calibrated anti-Xa levels for apixaban, edoxaban, and rivaroxaban, and the dilute thrombin time or ecarin clotting time for dabigatran, given the fact that routine coagulation assays are insensitive to exclude a preoperative DOAC effect.[67, 68] However, questions regarding both optimal level cut-offs and the clinical utility of this approach remain as advantages of laboratory testing have not been validated in prospective studies.[5] Lastly, multiple studies including a review of DOAC trials have revealed that heparin bridging during periprocedural DOAC interruption leads to a multifold increased risk of major bleeding (OR: 3.68, 95% CI: 2.24 to 6.04; P <0.001) and OR: 5.00, 95% CI: 1.2 to 20.4; P=0.023) without a reduction in the risk of stroke or systemic embolism (OR: 1.82, 95% CI: 0.37 to 9.05; P=0.463).[47, 69]

Multiple retrospective cohort studies including a recent large meta-analysis of >19,000 patients comparing periprocedural outcomes during interruption of DOAC-treated *vs.* warfarin treated patients found similar rates of major thromboembolism (<1.0%) and major bleeding (~1.0%).[2, 3, 29, 70] The meta-analysis revealed lower rates of major bleeding with DOACs *vs.* warfarin when interruption occurred within one day prior to the procedure (RR: 0.43, 95% CI: 0.23 to 0.82).[29]

As periprocedural RCTs of DOACs could not be conducted due to inability to define an acceptable comparator, two large prospective studies using a standardized pharmacokinetic-based approach assessing periprocedural DOAC outcomes have been published.[71, 72] In a prospective management study of 541 dabigatran-treated patients with atrial fibrillation who required temporary interruption for an elective surgery/procedure; 1-2 day dabigatran interruption intervals were used for low- and high-bleed-risk surgery/procedures, respectively, with longer interruptions of 2-4 days for those patients with CrCl >30 and ≤50 mL/min.[71] This approach was associated with low 30-day postoperative rates of ATE (0.2%, 95% CI: 0 to 0.5) and major bleeding (1.8%, 95% CI: 0.7-3.0). The largest periprocedural DOAC study to date, PAUSE, was a prospective management study of 3007 patients with atrial fibrillation taking a DOAC (apixaban, dabigatran, or rivaroxaban) who required an elective surgery/procedure and received standardized perioperative management.[72] DOACs were interrupted for 1 day before and 1 day after for a low-to-moderate-bleed-risk surgery/procedure and for 2 days before and 2 days after for a high-bleed-risk surgery/procedure. An exception to this management occurred in a small proportion of patients 2.7% (80 of 3007) who were receiving dabigatran and had a CrCl<50 mL/min, in whom the interruption interval was extended by 1 or 2 days depending on the procedural bleed risk. Although both global and DOAC-specific coagulation assays were collected preprocedurally, the investigators were blinded as to their results, which did not inform interruption times. With this management approach, the 30-day postoperative incidences of ATE and major bleeding, respectively, were: 0.16% (95% CI: 0 to 0.48) and 1.35% (95% CI: 0 to 2.0) in the apixaban cohort (N.=1257); 0.60% (95% CI: 0 to 1.33) and 0.9% (95% CI: 0 to 1.73) in the dabigatran cohort (N.=668); and 0.37% (95% CI: 0 to 0.82) and 1.85% (95% CI: 0 to 2.65) in the rivaroxaban cohort (N.=1082). For high bleed risk surgeries/procedures, 98.9% of DOAC-treated patients had levels <50 ng/mL.[72]

Recommendations

In VKA-treated patients undergoing minimal bleed risk procedures/surgery including minor dermatological, ophthalmological, and dental procedures (specifically cataract extraction), **continuing VKA** around the time of the procedure should be considered **(Level of evidence low, recommendation weak)**.

For dental procedures, consider co-administration of an oral prohemostatic agent (tranexamic acid) while **continuing VKAs (Level of evidence low, recommendation weak)**. Another option in patients undergoing dental procedures includes stopping VKA 2-3 days before the procedure **(Level of evidence low, recommendation weak)**.

For cardiac device procedures (pacemaker and ICD implantation) continuation of VKA should be considered over stopping VKA and bridging with heparin **(Level of evidence high, recommendation: strong)**.

In VKA-treated patients undergoing low/moderate or high-bleeding risk procedures or surgery that requires temporary interruption of VKA, discontinuation of VKA (warfarin) approximately five days earlier to allow adequate time for the INR to normalize is indicated **(Level of evidence low, recommendation weak)**. A longer interruption time is needed for phenprocoumon, whereas a shorter interruption is needed for acenocoumarol which is

used in some countries **(Level of evidence low, recommendation weak)**.

In patients on VKA who are receiving therapeutic-dose or intermediate dose, LMWH as bridging therapy, the last dose should be administered 24 hours before the procedure or surgery at approximately half the total daily dose **(Level of evidence low, recommendation weak)**. For **intravenous UFH**, we suggest **stopping approximately four hours** prior to the procedure or surgery **(Level of evidence low, recommendation weak)**. In patients whose INR is still elevated 1-2 days before the procedure (INR:≥1.5), avoid routine administration of low-dose (1.0-2.5 mg) oral vitamin K but consider administering of oral vitamin K if the INR needs rapid normalization to acceptable levels **(Level of evidence low, recommendation weak)**.

In VKA-treated patients undergoing low/moderate bleed risk procedures or surgery and receiving bridging anticoagulation, bridging anticoagulation with LMWH should be resumed at approximately 24 hours after the procedure if there is adequate hemostasis **(Level of evidence moderate, recommendation moderate)**.

In VKA-treated patients undergoing high-bleeding risk procedures/surgery and receiving bridging anticoagulation, consider one of three options: 1) delay LMWH bridging for approximately 48-72 hours after surgery until hemostasis is achieved; 2) administer prophylactic low-dose LMWH (usually within 24 hours after a procedure); or 3) avoid postprocedural bridging therapy altogether **(Level of evidence moderate, recommendation moderate)**.

LMWH should be used in the outpatient setting as bridging therapy over in-hospital **UFH** to avoid hospitalization **(Level of evidence low, recommendation weak)**. Routine use of standardized laboratory tests to guide periprocedural management of heparin bridging therapy should be avoided **(Level of evidence low, recommendation weak)**.

In VKA-treated patients with MHV or AF at high arterial thromboembolic risk or patients with VTE at high VTE risk, bridging therapy with LMWH or UFH in the periprocedural period during temporary interruption of VKA should be considered **(Level of evidence low, recommendation weak)**. LMWH should be preferred over UFH **(Level of evidence low, recommendation weak)**. Assessment of individual patients and surgery related factors should be considered using a standardized approach of bridging therapy **(Level of evidence low, recommendation weak)**.

In patients with AF at moderate or low arterial thromboembolic risk, no bridging over bridging therapy should be considered during temporary interruption of VKA **(Level of evidence high, recommendation strong)**.

In patients with MHV at moderate or low arterial thromboembolic risk, no bridging over bridging therapy should be considered during temporary interruption of VKA **(Level of evidence moderate, recommendation moderate)**. In patients with VTE at moderate or low VTE risk, no bridging over bridging therapy should be considered during temporary interruption of VKA **(Level of evidence low, recommendation weak)**.

In all patients undergoing major procedures or operations for which there are international guideline recommendations for VTE prevention in the postoperative period, an appropriate prophylactic agent should be used during re-initiation of VKA if postoperative heparin bridging is not used **(Level of evidence moderate, recommendation strong)**.

In patients on a DOAC (rivaroxaban, apixaban, edoxaban, dabigatran) undergoing minimal bleed risk procedures/surgery including minor dermatological, ophthalmological, dental procedures (specifically cataract extraction), **continuing the DOAC** around the time of procedure should be considered **(Level of evidence low, recommendation weak)**. For cardiac device procedures (pacemaker and ICD implantation) continuation of the DOAC around the time of the procedure should be considered **(Level of evidence moderate, recommendation moderate)**.

In DOAC-treated patients undergoing low/moderate bleeding risk procedures or surgery, the DOAC (rivaroxaban, apixaban, edoxaban, dabigatran with patient CrCl≥50 mL/min) should be **interrupted for one day before the procedure/surgery** and for dabigatran with patient CrCl≥30 mL/min to <50 mL/min, **2 days before the procedure/surgery (Level of evidence moderate, recommendation moderate)**.

In DOAC-treated patients undergoing high bleeding risk procedures or surgeries, the DOAC (rivaroxaban, apixaban, edoxaban, dabigatran with patient CrCl≥50mL/min) should **be interrupted for two days before the procedure/surgery** and for dabigatran with patient CrCl ≥30mL/min to <50 mL/min, **4 days before procedure/surgery (Level of evidence moderate, recommendation moderate)**.

In DOAC-treated patients undergoing low/moderate bleed risk procedures, the DOAC should be resumed at approximately 1 day after the procedure/surgery

provided that adequate hemostasis is achieved **(Level of evidence moderate, recommendation moderate)**.

In DOAC-treated patients undergoing high bleed risk procedures, the DOAC should be resumed at approximately 2-3 days after the procedure/surgery provided that adequate hemostasis is achieved **(Level of evidence moderate, recommendation moderate)**.

Consider LMWH or UFH at prophylactic doses for DVT prevention if the patient is unable to tolerate oral medications until DOAC resumption based on extrapolation for the need for thromboprophylaxis in major surgery **(Level of evidence low, recommendation strong)**.

Avoid heparin bridging during perioperative DOAC interruption **(Level of evidence low, recommendation moderate)**.

Avoid routine DOAC laboratory measurements (either global coagulation assays such as the aPTT or DOAC-specific assays (*i.e.*, DOAC-specific anti-Xa for rivaroxaban, apixaban, edoxaban and dilute thrombin time or ecarin clotting time for dabigatran) to guide periprocedural DOAC strategies **(Level of evidence low, recommendation moderate)**.

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SECTION 24

Antiphospholipid syndrome

General considerations

Antiphospholipid syndrome (APS) is one of the most prevalent acquired causes of venous and arterial thrombosis in all age groups, as well as of obstetric complications, and is considered the best model of immunothrombosis. The prevalence of APS is 50 per 100,000 individuals and its incidence ranges from 7.1 to 13.7 per 100,000 person-years.[1-3]

APS can occur in the absence of any other rheumatic disease, until recently called primary, or it may be associated with other autoimmune diseases such as SLE, Sjogren syndrome or Rheumatoid arthritis (secondary as it used to be known).[4]

This syndrome is characterized by the presence of antiphospholipid antibodies in the blood, which lead to activation of blood coagulation, and endothelial cells, causing micro and macro-thrombosis leading to impairment of various organs and tissues, including the placenta. The conventional-basic antiphospholipid antibodies are anticardiolipin (aCL), the anti-β2 glycoprotein-I antibodies (aβ2GPI), and the lupus anticoagulant (LA). A panel of secondary – nonconventional antibodies (*i.e.*, antiprothrombin antibodies, antiphosphatidylethanolamine, antiphosphatidylserine, antiannexin V antibodies, antibodies to vimentin/CL complex, antibodies to phosphatidic acid etc.) is under clinical evaluation. The triple-positivity of the conventional autoantibodies (aCL, aβ2GPI and LA) is associated with a higher risk of relapse and obstetrical complications.[5]

The catastrophic APS is a rare, life-threatening subgroup of APS that multiple thromboses of small, medium, and large-size vessels occur over days (further discussed below and elsewhere).

Diagnosis

The diagnosis of APS is based on the Sapporo criteria published in 1999 and revised in 2006 (Sapporo criteria; Table 24.I). However, recently the American Rheumatological Society and EULAR have published newer diagnostic criteria (Figure 24.1).[6, 7]

The revised Sapporo criteria for APS require clinical features: thrombosis or pregnancy morbidity and laboratory tests for lupus anticoagulant (LAC), IgG/IgM anticardiolipin antibodies (aCL), and/or IgG/IgM anti–β2-glycoprotein I antibodies (anti-β2GPI) with at least 2 aPL tests performed at least 12 weeks apart (Table 24.I).[6]

The newer diagnostic criteria of the European League against Rheumatism (EULAR) incorporate microvascular features, and cardiac, renal, pulmonary, and skin manifestations, blood alterations and also specific placental pathology.[7] These criteria include an entry criterion of at least one positive antiphospholipid antibody (aPL) test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (lupus anticoagulant functional coagulation assays and solid-phase enzyme-linked immunosorbent assays for IgG/IgM anticardiolipin and/or IgG/IgM anti-β2GPI antibodies). Patients accumulating at least 3 points each from the clinical and laboratory domains are classified as having APS.[7] In the validation cohort, the new APS criteria, *vs.* the 2006 revised Sapporo classification criteria, had a specificity of 99% *vs.* 86%, and a sensitivity of 84% *vs.* 99%.[7]

TABLE 24.I.—*The Sapporo clinical and laboratory criteria for the diagnosis of the antiphospholipid syndrome.*

Clinical criteria
1. Vascular thrombosis
One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus;
OR
b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: 1) eclampsia or severe preeclampsia defined according to standard definitions, or 2) recognized features of placental insufficiency;
OR
c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria
Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (*i.e.* >40 IgG phospholipid units (GPL) or IgM phospholipid units (MPL), or >the 99th percentile, or > mean + 3SD of 40 healthy controls), on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA).
Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies).
Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma, present on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay, according to recommended procedures.
Definite APS is present if at least one of the clinical criteria and one 3 of the laboratory criteria are met, with the first measurement of the laboratory test performed at least 12 weeks from the clinical manifestation.

Primary prevention

APS may be present in 5% of a healthy population, with unknown significance.

Although a few randomized trials on primary prophylaxis in APL carriers did not show a significant benefit,[8] a meta-analysis proposed that the risk of a first thrombotic event is significantly decreased by low-dose aspirin among asymptomatic aPL individuals, patients with SLE or obstetric APS.[9, 10]

EULAR 2019 Guidelines recommend low-dose aspirin (LDA) for asymptomatic aPL carriers, patients with systemic lupus erythematosus without prior thrombotic or obstetric APS, and non-pregnant women with a history of obstetric APS only, all with high-risk aPL profiles (double, or triple positivity).[11]

Clopidogrel may be useful in patients allergic to aspirin or severe asthma or with G-6-Pd deficiency, but randomized studies are not available.

Specifically in patients with systemic lupus erythematosus (SLE), or Sjogren disease, hydroxychloroquine, which shows intrinsic antithrombotic properties, may be also helpful.[11]

Statins, especially in patients with hyperlipidemia may also be protective. EULAR guidelines, citing a lack of studies of cardiovascular risk management in patients with APS, recommend managing hyperlipidemia and hypertension in these patients.[11]

Treatment of thrombotic APS

During the acute phase of VTE in the thrombotic APS the antithrombotic treatment aims to prevent extension of thrombosis and to contribute to vein recanalization.

In the chronic phase of VTE in patients with APS, the risk of recurrence increases by about 20 times after the cessation of the antithrombotic treatment independently of the interval from the thrombotic episode. Long-term secondary thromboprophylaxis at therapeutic doses is the unique evidence-based antithrombotic strategy for secondary prevention of VTE. The duration of the antithrombotic treatment in patients with documented APS could be compromised only by the presence of comorbidities that substantially increase the risk of bleeding.

First-line treatment of secondary prevention of VTE in patients with APS includes LMWH at therapeutic doses followed by long-term anticoagulants with a VKA, usually warfarin. The target for the international normalized ratio (INR) is 2.0-3.0, as a RCT has shown no advantage of higher intensity INR target ranges in this population[12] However, when a patient on VKA has an recurrent thrombotic event, an increased INR of 3.0-4.0 should be aimed for.

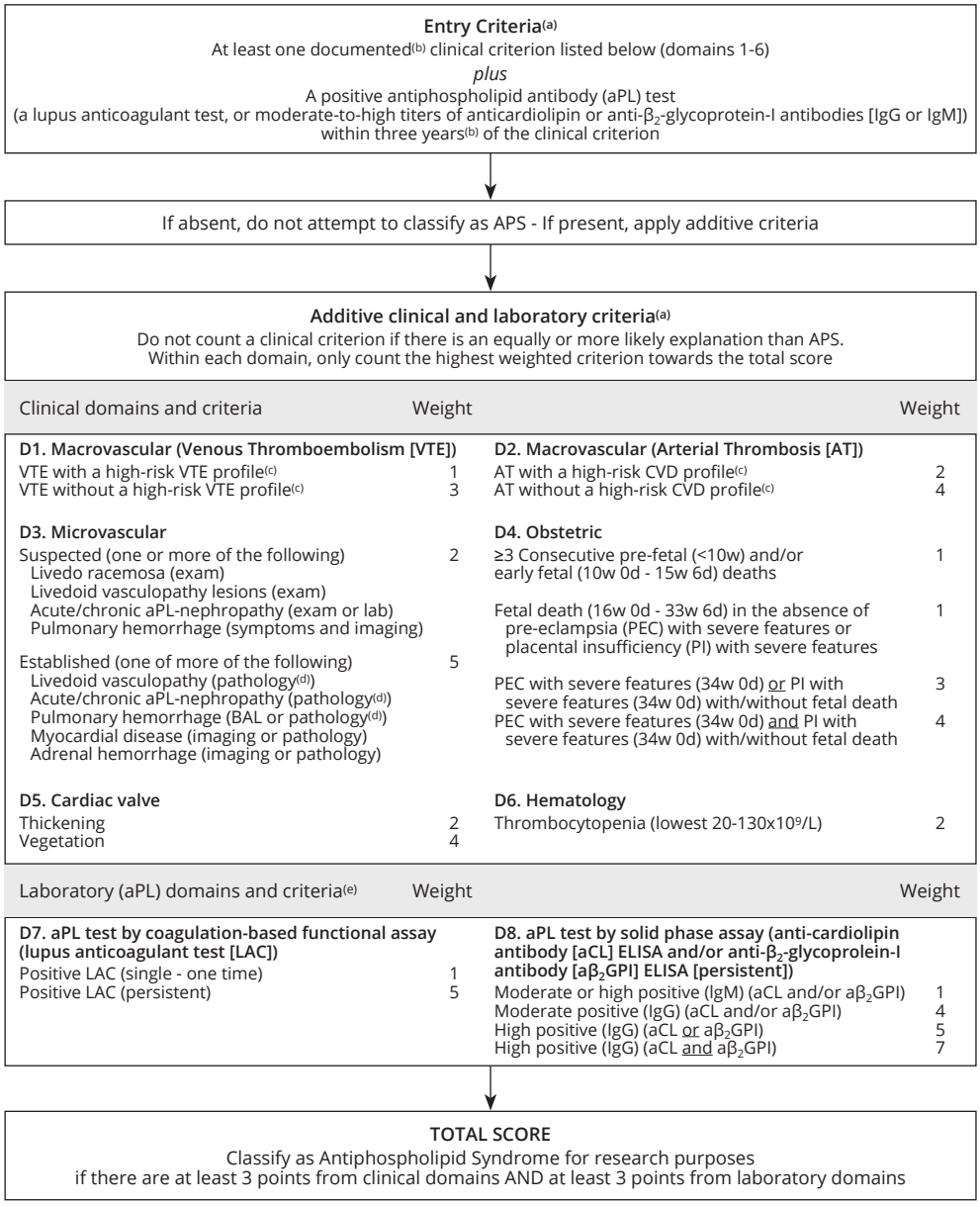

Figure 24.1.—Clinical and laboratory criteria for the diagnosis of the antiphospholipid syndrome according to the American Rheumatological Society and EULAR 2023.

A cohort study in 176 APS patients followed for a median of 51 months reported an increased risk of recurrent thromboembolic events and recurrent VTE alone in patients receiving DOAC compared with those receiving warfarin.[13] No differences were found between rivaroxaban and apixaban or among single-positive, double-positive, and triple-positive APS.[13] RCTs investigated the use of direct oral anticoagulants -DOACs in APS patients, the majority with negative results, except for the Rivaroxaban for Antiphospholipid Syndrome (RAPS) phase II/III non-inferiority trial from UK.[14] In this trial which involved 116 APS patients – the percentage change in endogenous thrombin potential at 42 days for rivaroxaban 20mg was inferior to that of warfarin targeted to an INR range of 2-3.[14] However, because no thromboembolic events occurred over the 210-day follow-up in either group, the investigators concluded that rivaroxaban might be an effective and safe alternative in patients with APS and previous VTE.[14] Limitations of this study were the relatively small number of patients, the short period of follow-up and the

fact that the majority of patients included in the trial had single or double APL positivity and only a few patients were high risk triple positive APL.

The phase III Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS) trial which included high-risk APS patients triple-positive for lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I antibodies compared rivaroxaban 20 mg to warfarin targeted to an INR of 2.5.[15] The trial was terminated prematurely after the enrollment of 120 patients because of an excess rate of arterial thromboembolic events in patients on rivaroxaban: 12% (3 myocardial infarctions and 4 ischemic strokes) *vs.* 0% in patients on warfarin, after 569-day follow-up.

A third randomized non-inferiority trial of 190 adults comparing rivaroxaban 20 mg or 15 mg daily according to renal function to dose-adjusted VKAs (target INR 2.0-3.0, or 3.1-4.0 in patients with a history of recurrent thrombosis) found a non-statistically significant near doubling of the risk for recurrent thrombosis (especially stroke) in the rivaroxaban treated patient group.[16]

A smaller RCT which involved 48 patients compared apixaban (first at 2.5 mg twice daily, then at 5 mg twice daily after protocol changes) to dose-adjusted warfarin targeted to an INR of 2-3. There was an increased risk of recurrent thrombosis (especially stroke) in the apixaban treated patients.[17]

Finally, the recent meta-analysis of 2023 showed that patients with thrombotic antiphospholipid syndrome randomized to DOACs compared with VKAs appear to have a significant increased risk for arterial thrombosis (*e.g.*, 6-12%/year compared to 0-3%).[18] No significant differences were observed between patients randomized to DOACs *vs.* VKAs in the risk of subsequent VTE or major bleeding.

In May 2019, the European Medicines Agency (EMA) issued a guidance statement recommending against the use of DOAC (including rivaroxaban, apixaban, edoxaban, and dabigatran etexilate) for patients with a history of thrombosis who are diagnosed with APS, in particular those who have triple positivity (lupus anticoagulant, anti-β2 GPI and anticardiolipin antibodies).[19]

Management of APS in pregnancy

There are two types of APS that may complicate pregnancy *e.g.* the thrombotic APS in a pregnant woman and the obstetric-only type of APS.

In general, in women with all APS types, prophylaxis during pregnancy is provided with LMWH and low-dose aspirin (75-150 mg).[20]

Women with thrombotic APS who became pregnant, already on VKA, should change to therapeutic dose LMWH with the first positive test. Warfarin is contraindicated in pregnancy; it may be used only in APS women with severe allergy to all LMWH or fondaparinux. After labor, APS breastfeeding women may use either LMWH or warfarin.

Previous studies reveal that women with obstetric APS that are not on long-term anticoagulation, may benefit by starting a prophylactic dose of LMWH and low dose aspirin (75-150 mg) with the first positive test.[9, 11] LMWH should be given for at least 6 weeks *postpartum*. Currently, there are no RCTs regarding the management of women with obstetric APS after the discontinuation of LMWH 6-12 weeks *postpartum*.[11] In women with persistent high positive APL, especially with double or triple positivity, or with other thrombotic risk factors, EULAR proposed that they may have aspirin as primary prophylaxis.[11] Aspirin can be given to breastfeeding women if the newborns have normal G-6-PD levels.

Despite conventional treatment, 20% to 30% of APS pregnancies still present complications.[21, 22] Retrospective clinical and animal model studies suggest that treatment with hydroxychloroquine may help prevent pregnancy complications in women with aPL and APS[23-25] and this strategy is currently being studied in a RCT.[26, 27] Immunoglobulins and anticomplement drugs are also under investigation.

Catastrophic antiphospholipid syndrome

The catastrophic antiphospholipid syndrome (CAPS) is a rare (1%), life-threatening, manifestation of antiphospholipid syndrome.[28] It is usually, but not always, associated with another rheumatic or chronic inflammatory disease, or triggered by inflammation, infection, or surgery.

It is characterized by:

- the simultaneous and rapid attack of multiple organs;
- histopathological findings of multiple diffuse thromboses in small vessels;
- laboratory confirmation of the presence of antiphospholipid antibodies, usually at high titers.

The condition is too rare to support clinical trials, but improved mortality has been referred with triple therapy consisting of anticoagulation, corticosteroids, and plasma exchange and/or intravenous immunoglobulin.[28] In addition, attention should be paid to associated disorders (*e.g.*, infection, SLE).

Cyclophosphamide has been used in cases associated with SLE, but during pregnancy its use in first trimester increases the risk of fetal loss. In refractory or relapsing

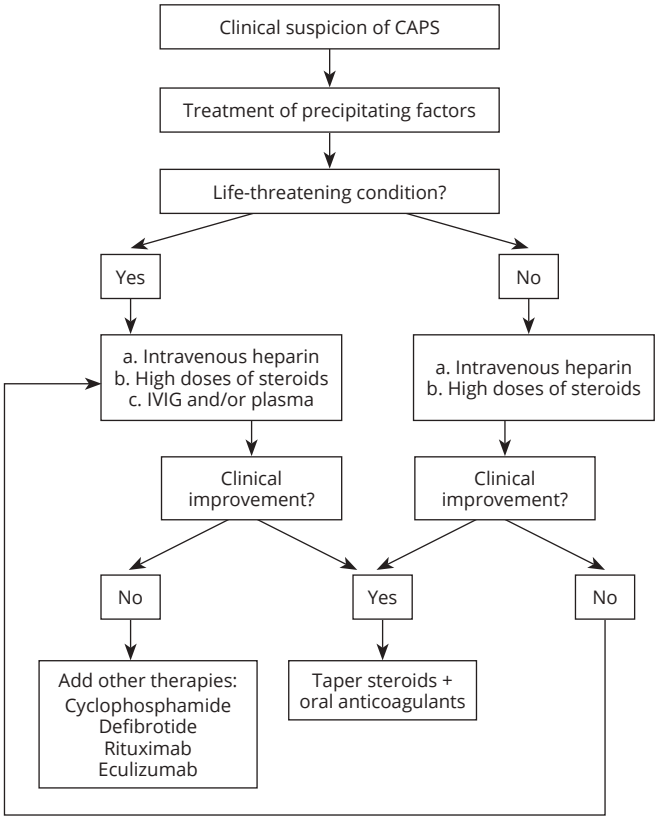

Figure 24.2.—Algorithm for current CAPS management.

cases, rituximab and eculizumab have been used and are under evaluation.[29, 30] Figure 24.2 summarizes the algorithm for current CAPS management.

Recommendations

Primary prevention

For primary prevention:

• asymptomatic carriers of antibodies related to APL should be advised for lifestyle modification and control of cardiovascular risk factors (*i.e.*, hypertension, diabetes hyperlipidemia) aiming reduction of the risk of vascular complications **(Level of evidence weak, recommendation strong)**;

• asymptomatic individuals with transient APL or presence of a low title of one type of APL antibodies should not receive routine primary thromboprophylaxis **(Level of evidence weak, recommendation strong)**;

• asymptomatic carriers of antibodies related to double or triple APL positivity suffering with rheumatic disorders may benefit from low dose aspirin **(Level of evidence weak, recommendation moderate)**.

APS in women/pregnancy

Regarding APS in women/pregnancy:

• women with thrombotic APS already on VKA, should change to therapeutic dose LMWH with the first positive pregnancy test. *Postpartum* breast-feeding women may use either LMWH or switch to VKA **(Level of evidence weak, recommendation strong)**;

• women with obstetric APS should start a prophylactic dose of LMWH and low dose aspirin (75-150mg) with the first positive test. LMWH should be given for at least 6 weeks *postpartum* **(Level of evidence weak, recommendation strong)**;

• women with obstetric APS, with no personal history of thrombosis and persistent positive APL after 6- 12 weeks of gestation may benefit from low dose aspirin **(Level of evidence weak, recommendation moderate)**;

• women with persistent positive APL antibodies should be advised against the use of estrogen treatment for oral contraception or hormone replacement therapy **(Level of evidence weak, recommendation moderate)**.

Treatment of thrombotic APS

For treatment of thrombotic APS:

• administration of therapeutic dose of antithrombotic treatment is recommended for patients with confirmed thrombotic APS (according to the Saporo criteria) **(Level of evidence moderate, recommendation strong)**;

• therapeutic dose of LMWH (as per package insert) bridging to VKA antagonists at doses targeting an INR range of 2-3 is first line treatment for the acute phase of treatment of thrombosis in patients with thrombotic APS **(Level of evidence strong, recommendation strong)**. This is especially important for APS patients with triple APS positivity and those who present with arterial thromboembolism **(Level of evidence strong, recommendation strong)**;

• DOACs should not be first-line therapy in APS patients, especially with double or triple APL positivity or arterial thrombosis **(Level of evidence strong, recommendation strong)**;

• DOACs may be considered in patients with VTE who are intolerant or allergic to VKA or have poor anticoagulant control, or refuse to take VKA **(Level of evidence moderate, recommendation moderate)**;

• patients with confirmed thrombotic APS should be treated with long term anticoagulation with VKA to an INR range of 2-3 **(Level of evidence moderate, recommendation strong)**;

• patients with thrombotic APS and very high-risk fea-

tures, or who have failed antithrombotic therapy, or with uncontrolled INR or intolerance to VKA are recommended to receive consultation in a specialized center **(Level of evidence weak, recommendation strong)**. Patient education in those with thrombotic APS is encouraged as an important component of their care.

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SECTION 25

Cost-effectiveness of prevention and treatment of VTE

Cost-effectiveness of primary prevention

General considerations

An extensive literature has been published so far concerning the cost-effectiveness of approaches commonly used for primary prevention of VTE.[1-55]

In selecting and evaluating studies for this section, we considered only those where data for comparative effectiveness of approaches were based on RCTs and/or systematic reviews of such trials. All the studies had to report a solid methodology for the comparisons (*e.g.*, direct or indirect treatment comparisons, network meta-analyses) and follow established guidelines for valid cost-effectiveness analysis.[55-59]

In this section, the perspective of analysis is that of the government health system or private insurance payer unless stated otherwise. In general, an approach is cost-effective if it is associated with an incremental cost per Quality-Adjusted-Life-Year (QALY) of less than $ 50,000, or £20,000-30,000, which are thresholds commonly used to determine the society's willingness-to-pay for healthcare interventions.[60-62]

In medium and high-risk patients, the evidence establishes unequivocally that primary prevention with antithrombotic drugs or intermittent pneumatic compression is cost-effective compared with "no prophylaxis."[1-16, 18, 27, 28]

Primary prevention is also cost-effective compared with case-finding (screening) for DVT.[2] Case-finding does not prevent development of DVT and therefore does not reduce morbidity from PTS and its associated costs. However, case-finding is indicated in selected patients with contraindications to anticoagulant prophylaxis (*e.g.*, major trauma, see below).

Data are not available for low-risk patients concerning cost-effectiveness for currently used prophylactic methods.

Total hip and knee replacement

VKA and LMWH in primary prevention

Several studies have evaluated the cost-effectiveness of primary prophylaxis using different anticoagulant drugs in patients having hip or knee replacement surgery or surgery for fractured hip.[12, 13, 19, 33, 34] Two studies based on the US healthcare system,[12, 19] and one study based on the Norwegian system,[13] found that prophylaxis using fondaparinux was marginally less expensive than prophylaxis using enoxaparin. The Norwegian study found that the conclusions were sensitive to the price difference between the drugs and the type of surgery.

DOACs in primary prevention

Before the development of DOACs, heparin and VKA were the main treatment options for postoperative thromboprophylaxis. However, they had drawbacks. Heparin had to be given parenterally and had the risk of HIT. VKA needed regular monitoring, had a narrow therapeutic range and several food and drug interactions. In contrast, DOACs have overcome these issues. DOACs have shown promising results in Phase III clinical trials for postoperative VTE prophylaxis.[42]

A study based on the UK National Health Service found dabigatran etexilate to be cost saving compared with enoxaparin (40 mg once daily) in patients having total hip or knee replacement.[34] The cost of prophylaxis for each patient, including drugs and administration costs, was estimated at £137 for dabigatran etexilate and £237 for enoxaparin. From the perspective of the UK National Health Service, thromboprophylaxis with dabigatran was cost saving compared with enoxaparin 40 mg once daily, with comparable efficacy and safety profiles.

In another study based on the Irish healthcare, where

both rivaroxaban and dabigatran were compared with enoxaparin, rivaroxaban was the less costly and more effective option after THR and TKR. Probabilistic sensitivity analysis indicated that rivaroxaban was the most cost-effective strategy at a cost-effectiveness threshold of euro 45,000 per QALY. A study from the perspective of the Canadian health system confirmed that rivaroxaban was a cost-effective alternative to enoxaparin.[39] Thus, the available evidence from studies in three different health systems indicates that both dabigatran and rivaroxaban are cost-effective alternatives to enoxaparin.[33, 34, 39]

A subsequent study showed that rivaroxaban may be cost saving against enoxaparin or dabigatran in Italian, Spanish and French settings.[43]

A recent meta-analysis of eight studies involving 5700 patients undergoing total knee arthroplasty (TKA) and 7684 undergoing total hip arthroplasty (THA) found that rivaroxaban was associated with lower rates of VTE and DVT when compared with enoxaparin without any significant difference in any complications. Cost analysis revealed that rivaroxaban was superior to enoxaparin with the medication cost needed to prevent one DVT being $1081 and $432 less with rivaroxaban for THA and TKA respectively in the Australian healthcare setting.[63]

A Canadian study[44] evaluated the cost-effectiveness of apixaban (2.5 mg twice daily) compared with enoxaparin (40 mg once daily or 30 mg twice daily) as VTE preventive therapy in patients undergoing elective total hip arthroplasty and total knee arthroplasty. The decision model considered VTE, bleeding, and mortality incidence that occurred in patients within 90 days after operation using data from the ADVANCE trials. The model provided the option to simulate events that may occur over the long term, such as recurrent VTE and PTS occurring at 5 years. There were fewer occurrences of VTE, bleeding events, recurrent VTE, and PTS events in the TKA population with apixaban therapy. Similar results were seen in patients undergoing THA, except for bleeding events, which were more common with apixaban treatment. Savings of $180 to $270 per patient are expected with apixaban treatment compared with enoxaparin treatment.

A similar study conducted in the Chinese context was performed using data on THR from two RCT (ADVANCE3 and RECORD1).[45] Thromboprophylaxis with apixaban was estimated to have a higher cost (US $178.70) and more health benefits (0.0025 QALYs) than thromboprophylaxis with enoxaparin over a 5-year time horizon, which resulted in an incremental cost-effectiveness ratio (ICER) of US $71,244 per QALY gained and was more than three times the GDP per capita of China in 2014 (US $22,140). Owing to the higher cost and lower generated QALYs, rivaroxaban was inferior to enoxaparin among post-THR patients. The sensitivity analyses confirmed these results.

In a UK study for primary prevention of VTE following hip surgery,[46] expected clinical benefits were similar for rivaroxaban and LMWH, whereas the lower costs of intervention with rivaroxaban meant that it was the most cost-effective intervention at the usual NICE thresholds; for primary prevention of VTE following knee surgery, rivaroxaban and LMWH were considered similarly cost-effective.

Extended duration of prophylaxis

The cost-effectiveness of an extended duration of prophylaxis (28 to 35 days) after hip arthroplasty or surgery for hip fracture has been evaluated in multiple studies.[20, 24, 31, 36, 38]

Two Canadian studies evaluated extended prophylaxis with LMWH compared with warfarin or no extended prophylaxis.[24, 31] Dranitsaris *et al.*[31] reported the incremental cost of 35 days of prophylaxis with dalteparin was Cdn $ 31,200-40,100 per QALY, whereas Skedgel *et al.*[24] found an incremental cost of Cdn $ 106,454 per QALY for extended LMWH prophylaxis. The difference in these analyses may be explained by the proportion of patients requiring home-nursing services. The study by Dranitsaris appeared to assume no use of home nursing services[31] and Skedgel *et al.* found extended prophylaxis with LMWH met the cost-effective threshold of Cdn $ 50,000 per QALY when less than 10% of patients require home nursing services.[24]

Two studies, one from Sweden,[20] and the other one from Italy,[36] both using a five-year time horizon, suggest that fondaparinux is a cost-effective alternative to enoxaparin for extended prophylaxis, and may be cost-saving at five years. The Canadian study which found rivaroxaban to be cost-effective relative to enoxaparin in hip arthroplasty patients included a duration of prophylaxis of 35 days.[39]

In the UK perspective, for elective total hip arthroplasty, LMWH for 10 days followed by aspirin for 28 days was shown to be the most cost-effective VTE prophylaxis strategy; for elective total knee arthroplasty, the results were highly uncertain, but foot pump appeared to be the most cost-effective strategy, followed closely by low dose aspirin.[47]

Mechanical vs. *pharmacological prophylaxis*

A comparative cost-effectiveness analysis of mechanical and pharmacological VTE prophylaxis after lower limb arthroplasty in the Australian setting was performed.[48] This was based on a stratified meta-analysis of IPC of lower

limbs to prevent VTE in hospital patients.[49] It involved a total of 16,164 hospitalized patients from 70 trials. IPC was more effective than no IPC prophylaxis in reducing DVT from 16.7% to 7.3% (RR: 0.43, 95% CI: 0.36 to 0.52; P<0.01) and PE from 2.8% to 1.2% (RR: 0.48, 95% CI: 0.33 to 0.69); P<0.01). IPC was also more effective than thromboembolic deterrent stockings in reducing DVT and appeared to be as effective as pharmacological thromboprophylaxis but with a reduced risk of bleeding (RR: 0.41, 95% CI: 0.25 to 0.65); P<0.01). Adding pharmacological thromboprophylaxis to IPC further reduced the risk of DVT (RR: 0.54, 95% CI: 0.32-to 0.91; P=0.02) compared with IPC alone. Based on the above data and Australian health care costs for apixaban, IPC or a sequential/simultaneous combination of both were found to be the most cost-effective VTE prophylaxis regimens. The authors suggested that the choice between them is best guided by the relative VTE and bleeding risks of individual patients.

A limitation of applying these cost-effectiveness analyses is that they do not incorporate differences in values and preferences which may exist between surgeons or patients to avoid bleeding relative to preventing thromboembolism. Thus, an approach which increases bleeding, such as fondaparinux, even if found to be cost-effective or even cost-saving, may not be accepted by surgeons or patients whose preferences are weighted to avoiding bleeding complications.

Major trauma

In patients with major trauma, although a regimen of the LMWH enoxaparin is more effective than unfractionated heparin for preventing DVT, an increase in major bleeding cannot be confidently excluded based on the results of the randomized trial comparing these approaches.[64] Cost-effectiveness modelling in this clinical scenario indicates that although enoxaparin appears to be a cost-effective alternative when considering the outcome of DVT averted, it is not cost-effective for the outcome of life-years gained, because of the potential increase in major bleeding.[21] In patients with major trauma considered to have a contraindication to anticoagulant prophylaxis, combined short-term (two weeks) intermittent pneumatic compression and case-finding with serial Doppler ultrasonography for the duration of hospitalization is more cost-effective than prophylactic placement of an inferior vena cava filter.[30]

Non-orthopedic surgery

UFH and LMWH in primary prevention

Using the perspective of US Medicare reimbursement, Heerey *et al.*[14] evaluated the cost-effectiveness of two regimens of LMWH (dalteparin 5000 U or 2500 U once daily) compared with UFH for primary prevention in patients undergoing abdominal surgery. The base-case analysis suggested that both dalteparin regimens were cost-effective using an incremental cost-effectiveness threshold of $ 50,000 per QALY gained.[14] However, sensitivity analysis indicated that there was substantial uncertainty in the cost-effectiveness results, in part due to the influence of patient age and gender. In the base analysis, unit costs for the dalteparin 2500 U and 5000 U regimens were more than 10 and 20 times that of unfractionated heparin.[14] Sensitivity analysis showed that reducing the cost of dalteparin by 50% would result in the 2500 U regimen being the more cost-effective, and the 5000 U regimen would be cost-effective by comparison to either the 2500 U dalteparin or unfractionated heparin. Thus, in healthcare systems in which the cost of LMWH is much lower relative to unfractionated heparin than in the US, primary prevention using LMWH in patients having abdominal surgery may have acceptable incremental cost-effectiveness or may even be the most cost-effective, depending on the regimen.

In non-orthopedic surgery patients, thromboprophylaxis with enoxaparin was found to be highly cost-effective compared with no prevention in patients with Caprini Risk Score ≥3 in the Chinese setting.[50]

DOACs in primary prevention

The context of thromboprophylaxis for the prevention of VTE in surgical women with gynecologic cancer in US has been studied by Glickman *et al.*[51] who reported that apixaban (28 days) is more cost-effective than enoxaparin (28 days).

A cost-benefit analysis was performed for patients having abdominal surgery based on the incidence of symptomatic DVT and PE from literature reports in patients not on prophylaxis and a meta-analysis of 11 RCTs of studies comparing IPC or IPC+GEC with no prophylaxis.[28] Using the costs of US Medicare reimbursement schedule, the cost of investigating symptomatic patients with suspected VTE (72 with symptoms suggestive of DVT and 32 with suspected PE out of 1000 patients without prophylaxis) and treating those with confirmed VTE was $263,779 ($263 per surgical patient). The cost of prophylaxis with IPC plus GEC in 1000 patients plus the cost of investigation and therapy of the reduced number of patients with clinically suspected DVT and PE would be $150,344. Thus, compared with the group not receiving prophylaxis, there would be a saving of $133,435 ($133 per surgical patient). Sensitivity analysis using the range of costs pro-

vided, demonstrated that a marked saving persists. This study demonstrated that investing in prophylaxis using IPC reduces not only VTE events, but also produces a significant financial saving.

Medical patients

UFH and LMWH in primary prevention

The cost-effectiveness of primary prevention in hospitalized medical patients using LMWH or UFH has been evaluated in five studies.[10, 18, 22, 27, 52] The health system was in the US in three of these studies,[10, 22, 27] in Germany in one study[18] and in Canada in another one.[52] The results of all five studies were consistent indicating that prophylaxis with LMWH was more effective and less costly than with unfractionated heparin. The same results were reported for the group of critically ill medical-surgical patients in a US study.[53]

DOACs in primary prevention

In the US, Guy *et al.*[54] showed that a 35-42-day regimen with betrixaban, from hospitalization through posthospital discharge, was a dominant strategy (higher QALYs and lower cost) compared with a 6-14-day prophylaxis with the LMWH enoxaparin, due to a reduced incidence of thromboembolic events and lower associated costs, for nonsurgical patients with acute medical illness at risk of VTE. The analyses were based on the APEX trial.[55] Lastly, adjusted postindex hospitalization costs in a US medically ill population identified as candidates for extended postdischarge thromboprophylaxis revealed cost savings of US $32,623 per patient by preventing a VTE event in the immediate postdischarge period (P<0.001).[65]

Pregnancy

The cost-effectiveness of primary prevention of VTE during pregnancy using once daily LMWH in women with a single previous episode of VTE has been evaluated.[15] The results indicate that primary prevention is cost-effective for "high risk" women with a prior idiopathic VTE or a known thrombophilic condition if the risk of bleeding is 1% or lower.

Cost-effectiveness of secondary prevention (treatment to prevent recurrent VTE)

General considerations

The criteria for selecting studies to evaluate the comparative cost-effectiveness of alternative strategies for secondary prevention included RCTs and/or systematic reviews of such trials and studies reporting a solid methodology for the comparisons (*e.g.*, direct, or indirect treatment comparisons, network meta-analyses). The studies had to follow established guidelines for cost-effectiveness.[56-59] However, in some cases studies have not used the QALY as the measure of effectiveness, and conclusions from these studies were based on cost-per-event of recurrent VTE.

Acute DVT

Prior to the development of DOACs, the standard care for most patients with established DVT or PE was anticoagulation consisting of initial treatment with either LMWH or intravenous UFH, followed by long-term treatment with a vitamin-K antagonist (*e.g.*, warfarin). The cost-effectiveness of anticoagulant therapy has been formally evaluated by several studies.[66-69] For the treatment of cancer associated VTE in the US context, Connell *et al.* found that warfarin was a more cost-effective strategy compared with LMWH from the social care perspective.[70]

Two studies have compared the cost-effectiveness of intravenous UFH with subcutaneous LMWH for the initial treatment of patients with DVT.[66, 67] The findings were consistent and indicated that LMWH was cost-effective. Hospitalization was the major driver for cost. LMWH was an effective approach to treat DVT out of hospital.[71, 72] LMWH for initial therapy was a cost saving approach if 8% or more patients were treated entirely as outpatients, or 13% or more had a reduced hospital stay.[66]

Thrombolysis and early thrombus removal

The cost-effectiveness of other approaches such as catheter-directed thrombolysis (CDT) and/or mechanical thrombus removal, venous stenting or insertion of a vena cava filter has not been extensively evaluated; these approaches have usually been reserved for specific indications in selected patients.

The cost-effectiveness of CDT compared with standard treatment alone in patients with iliofemoral DVT and a low risk of bleeding was estimated using the CaVenT data.[73] The model captured the development of PTS, recurrent VTE and treatment-related adverse events within a lifetime horizon and the perspective of a third-party payer. Direct medical costs were $64,709 for additional CDT and $51,866 for standard treatment. The incremental cost-effectiveness ratio (ICER) was $20,429/QALY gained.

In patients with acute DVT, pharmaco-mechanical catheter-directed thrombolysis (PCDT) in conjunction with anticoagulation therapy emerged as an approach for

preventing PTS. Nevertheless, Magnuson *et al.*[74] showed that in US, that PCDT plus anticoagulation had an ICER >$200,000/QALY compared with anticoagulation alone and indicated that PCDT may be of intermediate value in patients with iliofemoral DVT.

Another study[75] estimated a cost per QALY gained of US $233,698 for the placement of vena cava filters to prevent symptomatic pulmonary embolism compared with standard care in a cohort with contraindications to anticoagulant prophylaxis within 3 days of admission; the same study suggested the use of vena cava filters in a subgroup who could not be anticoagulated within 7 days (ICUR $22,250/QALY).

Extended therapy

VKA and LMWH in the prevention of recurrent VTE

Long-term anticoagulation is required in patients with DVT or PE to prevent recurrent VTE. The standard approach prior to the development of DOACs had been treatment with a VKA, with the dose adjusted according to laboratory monitoring of the anticoagulant effect. Long-term therapy with a VKA was cost-effective compared with inadequate long-term therapy.[69] However, the need for laboratory monitoring was associated with significant costs[68, 69] and was a burden which influenced Quality of Life in many patients. Approaches to improve the effectiveness, safety, and efficiency of oral VKA therapy included specialized anticoagulation clinics, and patient self-monitoring. The data on cost-effectiveness of these approaches in patients with VTE was limited, since the studies had included a mixed population with various indications for long-term therapy (*e.g.*, heart valves, atrial fibrillation, etc.). The UK Health Technology Assessment Programme concluded that patient self-monitoring was unlikely to be more cost-effective than specialized anticoagulation clinics, using a threshold of £30,000 per QALY,[68] although patient self-monitoring might improve Quality of Life for some patients who travel frequently or have difficulty travelling to the clinic.

LMWH given in fixed doses without anticoagulant monitoring is an effective and safe approach to treat VTE for three to six months[76-78] but the cost-effectiveness of three to six months therapy with LMWH has not been formally evaluated. Prior to the development of DOACs, LMWH was preferred in patients with VTE in the presence of active cancer because it was markedly more effective than VKA treatment (NNT to prevent one recurrent VTE of approximately 13).[76, 77] LMWH was also effective in the broad spectrum of VTE patients without cancer, and in such patients, it was associated with improvement in the patient's perceived Quality of Life.[78]

DOACs for the prevention of recurrent VTE

For the prevention of recurrent VTE, rivaroxaban showed a better cost-effectiveness profile *vs.* placebo in the US context considering a threshold of $50,000/QALY.[79] However, Sterne *et al.*[46] suggested that in the UK setting it is not cost-effective to prescribe DOACs or warfarin for secondary prevention of VTE considering a willingness-to-pay threshold up to £40,000 per QALY.

From a societal perspective, dabigatran demonstrated to be a cost-effective or even cost-saving option for treatment and secondary prevention of VTE compared with VKAs in the Netherlands.[80]

Edoxaban has been shown to be cost-effective compared with dalteparin from the societal perspective in the US for the management of patients with cancer who had acute symptomatic or incidental VTE.[81] Another study regarding patients with cancer showed that DOACs are more cost-effective compared with LMWH in treating VTE from the Spanish healthcare system perspective.[82]

A comprehensive evaluation of the cost-effectiveness profiles of LMWH/VKA, UFH/VKA, fondaparinux/VKA, apixaban, rivaroxaban, dabigatran and edoxaban for secondary prevention of VTE has been performed by NICE.[83] This study, based on a network meta-analysis, concluded that for prevention of DVT and PE recurrence in the UK context, apixaban is the strategy that produces the most QALYs and an ICER lower than £2000/QALY compared with LMWH/VKA.

Thrombophilia

The role of laboratory screening for thrombophilia in guiding clinical decisions about an extended or indefinite duration of anticoagulant therapy has generated much debate. The UK Health Technology Assessment Programme concluded that scenarios were found where such an approach is cost-effective using a threshold of £ 20,000 per QALY, but the results are subject to significant uncertainty because of a lack of randomized trials or definitive data on the magnitude of increased risk of recurrence for different categories of thrombophilia.[84] The relative cost-effectiveness of routine screening for thrombophilia *vs.* targeted screening based on patient and family history requires further studies.

A recent meta-analysis[85] indicates that patients with a first episode of unprovoked VTE who completed at least three months of anticoagulant treatment, have a risk of re-

current VTE of 10% in the first year after treatment, 16% at two years, 25% at five years, and 36% at 10 years, with 4% of recurrent VTE events resulting in death. These estimates should inform future cost-effectiveness analysis and clinical practice guidelines to guide decision making about long term management of unprovoked VTE.

Stenting in patients with PTS

A study, conducted from the Italian Healthcare Service perspective, showed that stenting in patients with venous outflow obstruction and ulceration (CEAP clinical class C6) is a cost-effective (incremental cost-utility ratio €12,388/QALY) or dominant option *vs.* compression therapy, according to in-patient or day-hospital settings, respectively. Increasing use of stenting over standard medical therapy, in the next 5 years, is expected to yield additional costs of 39.5 million euros (in-patient) or savings of 5.1 million euros (day-hospital).[86]

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SECTION 26

Key questions to be answered by new research

Statements and recommendations made in this document are based on a literature review using clearly defined levels of evidence. This process has revealed several key questions that require to be addressed by future studies. They are summarized in this final section.

Patient populations

Although VTE is an appealing target for maximally effective prevention, there is still a low rate of appropriate prophylaxis worldwide, particularly for acute medically ill patients. Continuing efforts to educate combined with hospital-wide protocols, local audits for VTE prevention, electronic alerts, use of advanced informatics with clinical decision support tools, and use of clinical nurse specialists have been shown to result in a marked increase in appropriate application of guidelines.

Prophylaxis

Section 3: general, vascular, bariatric, plastic, cardiac and thoracic surgery

The thresholds of the Caprini Risk Score that define low, intermediate, and high-risk groups for VTE need to be determined for each operation/procedure in different specialties.

In the 1970s and 1980s, when the efficacy of electrical calf muscle stimulation was assessed, the equipment used produced painful stimuli so that it could be used only during general anesthesia. Modern equipment, now commercially available, produces muscle contractions as a result of electrical impulses that are painless and can be tolerated by patients throughout the day.

The efficacy of such modern equipment used not only during surgery but also during the postoperative period should be determined in adequately powered RCTs, since:

- RCTs are needed to determine the optimal thromboprophylactic regimen of different modalities in patients having laparoscopic surgery;
- RCTs are needed to determine the optimal thromboprophylactic regimen of different modalities in patients having bariatric surgery;
- RCTs are needed to determine the optimal thromboprophylactic regimen of different modalities in patients having cardiac surgery;
- RCTs are needed to determine the optimal thromboprophylactic regimen of different modalities in patients having thoracic surgery;
- RCTs are needed to determine the optimal duration of thromboprophylaxis in vascular surgery;
- RCTs are needed in plastic surgery patients so that eventually an international guideline, based on plastic surgery data, using a validated risk assessment model, which combines the surgical risk with the patient related risk.

Section 4: urologic surgery

RCTs are needed to determine the efficacy and adverse effects of LMWH, fondaparinux, IPC and DOACs in patients having urologic surgery.

Section 5: gynecologic surgery

RCTs are required to determine the efficacy and adverse effects of DOACs in patients having gynecologic surgery.

Section 6: obstetrics

RCTs are needed to determine the efficacy of currently used thromboprophylaxis in pregnant women with different VTE risk factors. As sufficiently large trials are unlikely to be funded, secondary data analyses based on high quality registry data are important.

Section 7: orthopedic patients

RCTs are needed before recommendations can be made for thromboprophylaxis beyond 35 days in patients having hip and knee arthroplasty. The optimal duration of prophylaxis is currently unknown.

RCTs are necessary to determine the efficacy of IVC filters in patients with trauma in the presence of contraindications to LMWH.

RCTs are essential to determine the efficacy and safety of antiplatelet agents in preventing VTE in patients undergoing spinal surgery.

RCTs are required to determine the efficacy and safety of prophylactic methods in preventing VTE in patients with spinal cord injury.

RCTs are needed to determine the efficacy and safety of mechanical thrombectomy followed by DOACs compared with DOACs only in preventing VTE in patients undergoing spinal surgery.

RCTs are useful to further explore the benefit/risk profile as well as the optimal duration of the forthcoming inhibitors of factor XI and factor XIa in patients undergoing major orthopedic surgery.

Prophylaxis for patients in plaster casts requires further study, in particular establishing those at risk and delivering prophylaxis for an adequate duration in a safe, cost effective and pragmatic way. New oral agents should be studied in this group.

Section 8: burns

RCTs are needed to establish the efficacy of DOACs in patients with thermal injury.

Section 9: neurosurgery

RCTs that directly compare the timing of the first dose of LMWH prophylaxis and a possible association with bleeding are needed.

Section 10: medical patients

RCTS are significant to further refine efficacy and safety of extended postdischarge thromboprophylaxis in medical inpatients, including patients with active cancer.

The efficacy of GEC varies in different populations. Their relative efficacy needs to be determined by further RCTs and/or systematic reviews of published studies.

There is a need for further studies to assess the efficacy of IPC in medical patients other than those with stroke.

The medical patient populations that benefit most from extended pharmacological thromboprophylaxis with DOAC should be identified.

There is a need for studies addressing the value of the forthcoming inhibitors of factor XI and factor XIa for prevention of catheter induced DVT in patients with cancer.

Section 12: combined modalities

Studies are essential to define the patients at high risk that should have combined modalities for thromboprophylaxis using the most recent tools and validated criteria.

Possible differences in the efficacy of mechanical devices of different design need to be determined such as thigh length *vs.* knee length stockings and pneumatic sleeves, and sequential gradient *versus* uniform pressure sleeves.

Section 14: COVID-19

The potential benefit of sulodexide on endothelial protection (one of the components of Virchow's triad) needs to be explored in future RCTs in high-risk patients not only with COVID-19 but also in other surgical and medical conditions.

RCTs are needed using combined modalities acting on all three arms of Virchow's triad (*e.g.*, LMWH, IPC, GEC and sulodexide) in high-risk patients.

RCTs are necessary to further refine efficacy and safety of extended postdischarge thromboprophylaxis in high risk hospitalized COVID-19 patients.

When COVID-19 presented as a novel pandemic, the bodily response was entirely different from what had ever been seen with other diseases. The mortality and thrombosis rates were high due to exaggerated immune response (cytokine surge). As the population develops some innate immunity, the influence of the immune response is likely to differ in subsequent waves and the thrombotic risk may decrease. With widespread immunization and the development of herd immunity, current guidelines may become invalid when applied to new patients admitted with covid. Vigilance on the rates of VTE in future waves of COVID-19 is required which may indicate the need for further RCTs.

Therapy

Section 16: anticoagulation

RCTs are important to support interventions in order to prevent PTS in patients with isolated calf DVT and to confirm that extension therapy with sulodexide in patients with DVT reduces the incidence of PTS.

It is fundamental to have studies addressing the value of the forthcoming inhibitors of factor XI and factor XIa for the treatment of VTE in patients with end-stage renal failure.

Section 17: treatment in patients with cancer

RCTs are essential to evaluate the efficacy and safety of anticoagulation beyond 6 months in patients with cancer (long term strategy); these RCTs should be able to better define the anticoagulation choice related with the cancer location.

RCTs are also useful to evaluate the benefit/risk profile of the forthcoming inhibitors of factor XI and factor XIa for the initial and long-term treatment of VTE in patients with cancer.

Section 19: thrombectomy and thrombolytic therapy

RCTs with 2 to 5-year follow-up are needed to compare the efficacy of CDT followed by DOACs with DOACs only in preventing DVT recurrence and PTS in patients with iliofemoral DVT.

RCTs with 2 to 5-year follow-up are needed to compare the efficacy of mechanical thrombectomy followed by DOACs with DOACs only in preventing DVT recurrence and PTS in patients with iliofemoral DVT.

Section 20: HIT

There is a need for clinical trials for the management of patients with confirmed HIT using fondaparinux, the DOACs including dabigatran, and the new treatment option of FXIa inhibitors. In such studies, it would be important to understand the safety and efficacy of the drug in the various phases of HIT including the acute phase (severe thrombocytopenia both with and without thrombosis), patients in recovery from the acute phase, and patients with moderate thrombocytopenia without thrombosis who are given prophylactic treatment. These studies can also incorporate duration of therapy.

Section 21: superficial vein thrombosis (SVT)

Further RCTs are needed to assess the value, optimal dose, and duration of anticoagulation with LMWH, fondaparinux and DOACs in patients with SVT, particularly in obstetrics.

There is a need for RCTs addressing the optimal intensity and duration of anticoagulation in patients with unprovoked or weakly provoked SVT.

Section 22: prevention of PTS

Further RCTs are required to value the compression and its optimal duration in preventing PTS in patients with DVT.

The possible effect of dabigatran, edoxaban and apixaban on PTS prevention needs to be investigated (see also Section 19 above).

Section 23: periprocedural management of patients on chronic OACs and heparin bridging

Further RCTs are necessary to assess periprocedural heparin bridging for patients with mechanical heart valves.

Optimal periprocedural management of DOACs in patients undergoing neuraxial anesthesia need to be addressed.

Periprocedural management of patients undergoing urgent or emergency procedures or surgeries, including use of target specific reversal agents, are needed.