

VOLUME 32 · APRIL 2013 · No. 2

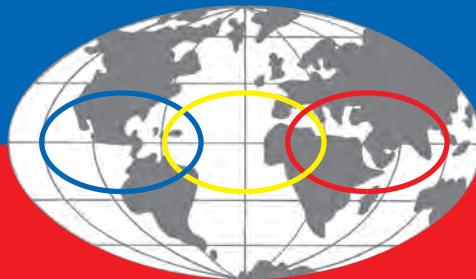
# International Angiology

The Journal of Vascular Biology, Medicine, Surgery and Phlebology

OFFICIAL JOURNAL OF



**UNION  
INTERNATIONALE  
DE PHEBOLOGIE**



**INTERNATIONAL UNION OF ANGIOLOGY**



**CENTRAL  
EUROPEAN  
VASCULAR FORUM**

**PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM  
International Consensus Statement**

E D I Z I O N I M I N E R V A M E D I C A

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# **PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM**

**International Consensus Statement**  
(Guidelines according to scientific evidence)

*Under the auspices of the  
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2013

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## ACKNOWLEDGEMENTS

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.<sup>1</sup> 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.<sup>2</sup> The latter was updated at the IUA European Congress in Rhodes in May 1999 and was published in “International Angiology” in 2001.<sup>3</sup> Subsequent work by the editorial committee and faculty reconvened at Windsor (UK) in January 2005 produced the publication of 2006.<sup>4</sup> The current version has been updated by the faculty at a special meeting at the Royal Society of Medicine, London, UK in July 2011 and subsequent meetings in Chicago and Prague in July 2012.

We are grateful to the following companies for their educational grants towards the meetings of the faculty over the years 1991 to 2012: Abbott Laboratories, Advanced Technology Laboratories, AstraZeneca, Aventis, Bayer, Behringwerke/Hoechst AG, Boehringer Ingelheim Ltd, Braun, Covidien, Italfarmaco Spa, Kendall UK, Kendall HealthCare Inc, Knoll AG, Leo Pharmaceutical Products, Lilly Industries Ltd, Novamedix, Novartis, Novo Nordisk Pharmaceutical Ltd, N V Organon, Pentapharm, Pfizer, Pharmacia AB, Porton Products Ltd, Sanofi-Synthelabo, SanofiAventis, Tyco Healthcare, and Wyeth-Ayerst Laboratories.

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Due to the evolving field of medicine, new research may, in due course, modify the recommendations presented in this document. At the time of publication, every attempt has been made to ensure that the information provided is up to date and accurate. It is the responsibility of the treating physician to determine best treatment for the patient. The authors, committee members, editors, and publishers cannot be held responsible for any legal issues that may arise from citation of this statement or any updated versions printed or in electronic form.

## GLOSSARY

APTC: antiplatelet trialists collaboration  
COC: combined oral contraceptives  
CVD: chronic venous disease  
CVI: chronic venous insufficiency  
DVT: deep vein thrombosis  
EMA: European Medicines Agency  
FIT: foot impulse technology  
FUT: fibrinogen uptake test  
GEC: graduated elastic compression  
HIT: heparin induced thrombocytopenia  
HRT: hormone replacement therapy  
IPC: intermittent pneumatic compression  
LDUH: low dose unfractionated heparin  
LMWH: low molecular weight heparin  
OR: odds ratio  
PE: pulmonary embolism  
Proximal DVT: DVT in popliteal or more proximal veins  
PTS: post-thrombotic syndrome  
QOL: quality of Life  
RCT: randomised controlled trial(s)  
RCOG: Royal College of Obstetricians and Gynaecologists  
RR: relative risk  
THR: total hip replacement  
TKR: total knee replacement  
UFH: unfractionated heparin  
VTE: venous thromboembolism  
WHO: world health organization

## POTENTIAL CONFLICTS OF INTEREST

D. Bergqvist: honoraria for lecturing from Pfizer and Leo Pharma; J. Bonnar: research support and lecture honoraria from Leo Pharma and Sanofi-Aventis; J.A. Caprini: consultant for Sanofi, Teleflex and GSK; C. Carter: works for a company that receives funding from the pharmaceutical industry and during the period of his involvement with the guidelines, projects from Janssen Scientific Affairs were awarded; A.J. Comerota: NIH research grants, honoraria from Covidien and consultant for BMS; J. Conard: None; B. Eklof: none; I. Elalamy: lecture fees from Bayer Healthcare, Boehringer-Ingelheim, Bristol Myers-Squibb/Pfizer, Daiichi Sankyo, Amiteis; J. Fareed: member of advisory board of Asahi Kissei USA, consultant to Polymedix Inc. and Grant from Mitsubishi; J. Fletcher: none; G. Gerotziakas: none; G. Geroulakos: none; A. Giannoukas: participated in the CALISTO study funded by GSK and he is a member of the Hellenic Advisory Board for Bayer; S.Z. Goldhaber: research grants from Daiichi Sankyo, Eisai, EKOS, J&J, Sanofi Aventis and consultant to Baxter, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Merck, Pfizer, Portola, Sanofi Aventis; I. Greer: honoraria for lectures and advisory board contributions for Leo Pharma and Sanofi-Aventis; M. Griffin: none; R. Hull: research support from Leo Pharma and Sanofi, consultant to Bayer, Leo Pharma, Pfizer, GSK, Wyeth Pharma and Portola Pharmaceuticals; A.K. Kakkar: consultant to Adventrx Pharmaceuticals, Bayer Healthcare, Boehringer-Ingelheim Pharmaceuticals, Bristol-Myers-Squibb, Daiichi Sankyo Inc., Eisai Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Inc, Sanofi-Aventis Pharmaceuticals, Shire Pharmaceuticals; S. Kakkos: research grant from Sanofi Aventis and honorarium for lectures from Covidien; E. Kalodiki: none; M.R. Lassen consultant to Bayer, Jansen, BMS, Pfizer, Eisai, Astellas, Portola, Stryker, Depuy-Synthes, Besst-Test, Serono-Merck and Astra-Tech; G.D.O. Lowe: none; A. Markel: none; A. Nicolaides: Honoraria for lectures from Bayer and Covidien; P. Prandoni: honoraria from Bayer, Boehringer Ingelheim, Pfizer, Sanofi-Aventis, Bristol-Myers and Rovi Pharmaceuticos; G. Raskob: consultant and/or Steering Committee and/or Advisory Boards of Bayer, BMS, Daiichi-Sankyo, Johnson and Johnson, Janssen, Pfizer, Portola, Sanofi-Aventis, Takeda Research and Development, National Blood Clot Alliance, and honoraria or Speaker's Bureau from Bayer, BMS, Pfizer; M. Samama: Consultant for Bayer, ScheringPharma AG, Sanofi Aventis, Eli Lilly and Daiichi Sankyo, Member of advisory board/steering committee for MNS, Pfizer, Johnson & Johnson, and honoraria for lectures by Sanofi Aventis, GSK, Bayer, Shering Pharma AG, Boehringer Ingelheim, Rory Laboratory and TEM; A.C. Spyropoulos: consultant to Bayer, Jansen, BMS, Pfizer, Eisai, Astellas, Portola, Daiichi-Sankyo, Boehringer-Ingelheim; A.G. Turpie: consultant to Bayer, Astellas, Portola, Eisai, Jansen and BI; J. Walenga: none; D. Warwick: honoraria for consultancy and lectures from Orthofix, Novamedix, Bayer, Boehringer-Ingelheim, Sanofi-Aventis, GSK and Covidien.

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First published in 2013  
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# INTRODUCTION

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## **Aims**

The aim of this document is to provide a clear and concise account of the evidence regarding efficacy or harm for various methods available to prevent and manage venous thromboembolism (VTE).

## **Methodology**

This is the fifth revision of this document which was last published in 2006. A literature search performed from 2005 through June 2011 was made available to the faculty which met in July 2011. This was repeated again through August 2012. Both literature searches were performed by an independent agency (Pharmaceutical Strategic Initiatives, North Carolina, USA) by searching Medline and Pub-Med using standard key terms such as venous thrombosis, upper extremity deep vein thrombosis, venous thromboembolism, pulmonary embolism 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 chapter. Similar terms were used to search the Cochrane library. Randomized controlled trials (RCT) 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 were used. Studies in which the diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) was only clinical without confirmation by an objective test were excluded. Abstracts that have not been subsequently published as full papers were also excluded.

For each section of the document, members of the faculty were provided with the references and documentation as well as the opportunity to provide additional data to update it. The updated section was presented to the whole faculty for discussion and comment. Most changes were made on the spot with the agreement of the whole 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 was in agreement.

The final draft produced by the faculty was subsequently sent to the corresponding faculty for comments and additional input. Any further changes or corrections were made with the agreement of the whole faculty.

## **Levels of evidence**

Discrepancies regarding the significance or level of evidence were resolved by discussion involving all members of the faculty. The following

method for determination of levels of evidence was consistently used.

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

Historically, RCT of thromboprophylaxis were of an active agent against placebo or no prophylaxis. Following acceptance of routine thromboprophylaxis in moderate and high risk patients, recent trials have compared new agents with established prophylactic measures (*e.g.*, enoxaparin in patients undergoing hip or knee surgery). Likewise, recent trials have compared new anticoagulants with established treatments for VTE, *e.g.*, heparins followed by vitamin K antagonists (VKA). 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 considered to be provided by RCT with less consistent results, limited power or other methodological problems, which were directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients.

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

Review of the literature using the levels of evidence as defined above has revealed areas of lack of evidence or low level evidence and a number of key questions that require to be addressed by future studies. They are stated throughout the document and are summarised in the final section (Chapter 24).

## Costs

Because 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 summarises available cost-effectiveness evidence for primary prevention and treatment of VTE (Chapter 23) 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.

The relationship between asymptomatic and symptomatic VTE including PE has been known for some time.<sup>4-6</sup> Reduction in the incidence of asymptomatic DVT has been shown to be associated with a reduction of symptomatic DVT and PE.<sup>7-9</sup> Large studies, such as the international multicenter trial, that were powered to study efficacy on fatal PE have demonstrated that reduction in silent DVT is accompanied by reduction in clinical DVT, clinical PE and fatal PE.<sup>10</sup> Another example is the meta-analysis of VKA in orthopedic surgery,<sup>11</sup> 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 low molecular weight heparin (LMWH) in preventing total 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, orthopaedic and

medical patients as a result of different methods of prophylaxis is not constant, but this is not a valid argument to discard the endpoint of silent 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 VTE. The same applies to the current opinion of regulatory bodies and authorities that favours weighting recommendations for effectiveness of prophylaxis or treatment based on symptomatic VTE and mortality. Treating symptomatic DVT (it would be unethical not to treat) suppresses the true effect on mortality. Relatively few PE occur in patients with symptomatic DVT. 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.

Demonstration that asymptomatic below knee DVT is associated with subsequent development of the PTS,<sup>12, 13</sup> that 20% of asymptomatic calf DVT extend proximal to the knee if untreated<sup>14</sup> and that 18% of symptomatic calf DVT are associated with proximal extension or recurrence<sup>15</sup> also validates adoption of such endpoints for efficacy evaluation. Because the PTS results in a marked reduction of quality of life (QOL) and suffering 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, we have devoted a separate section to it (Chapter 21).

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 mortality as an endpoint), which results in a large number of recommendations based on high level of evidence for preventing DVT, PE or recurrent VTE. Such an ap-

proach provides clinically important distinctions to guide clinicians concerning prophylactic and treatment regimens.

This document presents the evidence in a concise format and 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. Information on safety (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 from morbidity.

### **Low molecular weight heparins**

Regulatory bodies in Europe and North America consider the various LMWHs (both originator and generics) 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 have been shown to be equally effective and because they have been grouped together in the majority of 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 are pending review or are under review, while some have been approved by individual regulatory affairs agencies. The Food and Drug Administration (FDA) in the USA has approved a generic LMWH under the generic pathway of approval. On the other hand, the European Medicines Agency (EMA) and Canadian Regulatory authorities require approval by the biosimilar pathway which may include clinical trial evidence. Neither the EMA nor the Canadian Regulatory authorities have approved any generic LMWH. Other jurisdictions such as Central America, South America and India have approved generic heparins without clinical trials.

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# THE PROBLEM AND THE NEED FOR PREVENTION

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DVT and PE are major health problems with potential serious outcomes. Acute PE may be fatal. Pulmonary hypertension can develop in the long term from recurrent PE. Often overlooked is post-thrombotic chronic venous disease (CVD) occurring as a result of DVT causing deep venous reflux or obstruction, with skin changes and ulceration causing an adverse impact on quality of life and escalation of health care costs. In North America and Europe, the annual incidence is approximately 160 per 100,000 for DVT, 20 per 100,000 for symptomatic non-fatal PE and 5 per 100,000 for fatal autopsy-detected PE.<sup>1-6</sup> The prevalence of venous ulceration is at least 300 per 100 000 and approximately 25% are due to DVT.<sup>7, 8</sup> Estimates of the overall annual costs of CVI vary from 600-900 million €\* (US\$ 720 million-1 billion) in Western European countries,<sup>9, 10</sup> representing 1-2% of the total health care budget, to 2.5 billion € (US\$ 3 billion) in the USA.<sup>11</sup>

Virchow's triad of factors that predispose to VTE are venous stasis, alterations in blood constituents, and changes in the endothelium; these are as true today as when postulated in the 19<sup>th</sup> century. Principal clinical predisposing factors are immobilization, trauma, surgery, malignancy and previous history of venous thrombosis.<sup>12</sup> Other predisposing factors are age, obesity, infection, the postpartum period, varicose veins, dehydration and hormone therapy.<sup>6, 13-22</sup> In the background for all of these is predisposition due to thrombophilia.<sup>23</sup>

Patients admitted to hospital, surgical or medical, are particularly at risk for VTE and the

problem continues after discharge.<sup>24-28</sup> 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.<sup>29</sup>

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.<sup>30-32</sup> Continuing efforts to educate combined with hospital-wide protocols,<sup>33</sup> local audits for VTE prevention,<sup>34</sup> electronic alerts<sup>28, 35</sup> and use of clinical nurse specialists have been shown to result in a marked increase in appropriate application of guidelines. The use of electronic medical alerts is particularly effective.

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# GENERAL, VASCULAR, BARIATRIC AND PLASTIC SURGICAL PATIENTS

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## The risk

Patients who undergo general and vascular surgical procedures are at risk of developing VTE.<sup>1-6</sup> In the absence of prophylaxis, the risk of silent DVT is 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 reconstruction (Table 3.I). In a meta-analysis of 32 studies involving 5091 general surgical patients without prophylaxis, the frequency of clinical PE was 1.6% (95% CI 1.3% to 2.0%) and that of fatal PE 0.8% (95% CI 0.62% to 1.1%).<sup>3</sup>

Contrary to the belief that the incidence of postoperative DVT is rare in Asian patients, recent studies have demonstrated that this is not the case. The incidence of DVT was found to be 12.4% (95% CI 10% to 15%) in Asians using the fibrinogen uptake test (FUT) in five studies.<sup>7-11</sup> In a meta-analysis of four studies, the overall adjusted incidence of PE and fatal PE was 1% (95% CI 0 to 2) and 0.4% (95% CI 0% to 1%), respectively.<sup>12</sup> A multicenter study performed in Japan in 2006 using routine venography demonstrated that in the absence of prophylaxis, the incidence of postoperative DVT was close to that found in Caucasians (24%).<sup>13</sup>

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 therapy and pregnancy.<sup>14-18</sup>

Known clinical risk factors allow for classification of patients into high, moderate and low risk of developing VTE (Tables 3.II and 3.III). Another approach is to use a scoring system based on weighting risk factors according to their tendency to be associated with a thrombotic event.<sup>19-23</sup> These studies in nearly 10000 patients demonstrate a linear association between the risk score and development of symptomatic thrombosis up to 60 days after operation. Scores >8 were associated with 6.5% incidence of clinical events at 30 days and 11.3% incidence at 60 days.

Studies in patients having abdominal or pelvic surgery demonstrate that the risk continues after discharge from hospital.<sup>24-26</sup> This finding has implications for the duration of thromboprophylaxis. Patients having operations for cancer have been shown to benefit from 30 days of LMWH (for evidence, see section on cancer).

Despite the use of intraoperative heparin or other perioperative antithrombotic agents, vascular surgical patients are at moderate risk. In the absence of postoperative prophylaxis, the incidence of asymptomatic DVT is of the order of 18% 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%,<sup>27, 28</sup> 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%.<sup>29</sup> A prospective European registry

TABLE 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).

Patient groups	Number of studies	Patients N.	DVT incidence (weighted mean)	95% CI
<i>General surgery</i>				
Clagett and Reisch, 1988 <sup>3</sup>				
Total	54	4310	1084 (25%)	24% to 26%
<i>General surgery (Asian studies with FUT)</i>				
Cunningham <i>et al.</i> , 1974 <sup>11</sup>		68	8	
Nandi <i>et al.</i> , 1980 <sup>7</sup>		150	4	
Shead <i>et al.</i> , 1980 <sup>8</sup>		50	14	
Inada <i>et al.</i> , 1983 <sup>9</sup>		256	39	
Phornphibulaya <i>et al.</i> , 1984 <sup>10</sup>		74	9	
Total	4	598	74 (12.4%)	10% to 15%
<i>Abdominal vascular surgery</i>				
Hartsuck and Greenfield, 1973 <sup>161</sup>		26	7	
Angelides <i>et al.</i> , 1977 <sup>162</sup>		88	18	
Belch <i>et al.</i> , 1980 <sup>163</sup>		25	6	
Olin <i>et al.</i> , 1993 <sup>27</sup>		50	9	
Killewich <i>et al.</i> , 1997 <sup>164</sup>		48	1	
Hollyoak <i>et al.</i> , 2001 <sup>28</sup>		21	9	
Total	6	258	50 (19%)	15% to 25%
<i>Peripheral vascular reconstruction</i>				
Hamer <i>et al.</i> , 1972 <sup>165</sup>		21	9	
Passman <i>et al.</i> , 2000 <sup>166</sup>		53	1	
Hollyoak <i>et al.</i> , 2001 <sup>28</sup>		28	5	
Total	3	102	15 (15%)	9% to 23%

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.

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.<sup>30</sup> The National Inpatient 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.<sup>31</sup> 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.<sup>32</sup>

The risk of VTE in patients undergoing laparoscopic surgery appears to be low. Two small prospective studies in which no prophylaxis was used showed an incidence of DVT detected by

TABLE II.—The definition of risk categories in general surgical patients using FUT and in hospital pulmonary embolism.

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%

Modified from Salzman and Hirsh, 1982.<sup>167</sup> Although based on old studies the percentages shown in this table are still used to define the category of risk.

TABLE III.—Risk categories according to clinical risk factors in general surgical patients.

Risk category
<i>High</i>
— Major General Surgery, age >60
— Major General Surgery, age 40-60 & cancer or history of DVT/PE or other risk factors including thrombophilia
<i>Moderate</i>
— 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
<i>Low</i>
— Major General Surgery, age <40; No other risk factors*
— Minor surgery, age 40-60; No other risk factors*

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

Duplex ultrasound or venography in the range of 0-2%.<sup>33, 34</sup> Other prospective studies in which some form of prophylaxis was used confirmed the low incidence<sup>35-39</sup> with the exception of one in which 11 of 20 patients developed DVT.<sup>40</sup> Large series from surveys,<sup>41-43</sup> registries,<sup>44-47</sup> a literature review,<sup>48</sup> and a population study<sup>29</sup> 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.

Obesity is an independent risk factor for sudden postoperative fatal PE.<sup>49, 50</sup> Bariatric surgery is associated with clinical 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.<sup>51-57</sup> Risk factors in patients having bariatric surgery also include: BMI >55, venous stasis syndrome,

past history of VTE, obesity hypoventilation syndrome, pulmonary hypertension, cardiomyopathy and obstructive sleep apnea.<sup>58</sup>

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.<sup>59</sup> In a survey involving 10000 abdominoplasties not having prophylaxis the incidence of symptomatic PE was 1%.<sup>60</sup> In a large plastic surgery cohort, Pannucci showed that the 60 day clinically relevant VTE incidence was related to the Caprini score. Those with a score of 5-6 had a 1.3% rate, those with a score of 7-8 had a 2.7% rate and those with a score >8 had an 11.3% rate by 60 days. None of these patients had pharmacologic prophylaxis.

## Prophylactic methods and recommendations

### *General considerations*

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.<sup>61-63</sup> In the International Multi-Center Trial which included 4121 patients randomised to LDUH or no prophylaxis, there was a reduction in fibrinogen uptake test (FUT) detected DVT, clinical DVT, clinical PE, and fatal PE.<sup>62, 63</sup> During the late 1980s, two published meta-analyses concerning prophylaxis with LDUH compared with no prophylaxis or placebo<sup>3, 4</sup> 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). The price was a small increase in bleeding complications from 3.8% to 5.9% (RR 1.56; 95% CI 1.21 to 1.99).

A multi-center study found that **low molecular weight heparin (LMWH)** not only reduced the incidence of fatal PE but also the overall surgical mortality as compared with controls without prophylaxis.<sup>64</sup> Two small randomized placebo-controlled trials in patients having major oncological abdominal surgery<sup>65</sup> and emergency abdominal surgery<sup>66</sup> demonstrated the effect of LMWH in reducing the rate of asymptomatic DVT.

Subsequently, 16 studies<sup>67-82</sup> and nine meta-analyses **compared LMWH with LDUH**.<sup>83-91</sup> Six studies compared different doses of LDUH or LMWH.<sup>72, 92-96</sup> 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.<sup>84, 86-88</sup> 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)<sup>84, 86</sup> and one showed a decrease in symptomatic VTE.<sup>88</sup> 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) than LDUH.<sup>97, 98</sup> 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.<sup>86</sup>

Regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug. Therapeutic interchange among these products is not appropriate.<sup>99</sup>

In a recent double-blind double-dummy randomized study in 2927 patients having high risk major abdominal surgery, **fondaparinux 2.5 mg** once daily was found to be at least as effective as perioperative LMWH (dalteparin 5000 U daily) in preventing venographically detected DVT without any increase in bleeding.<sup>100</sup> 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%) provided fondaparinux was administered at least six hours after operation. 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** including Aspirin in high doses (500-1500 mg per day) reduce DVT by 30% and PE by 50%. In a meta-analysis of 22 RCTs<sup>101</sup> involving 1459 general surgical patients in which

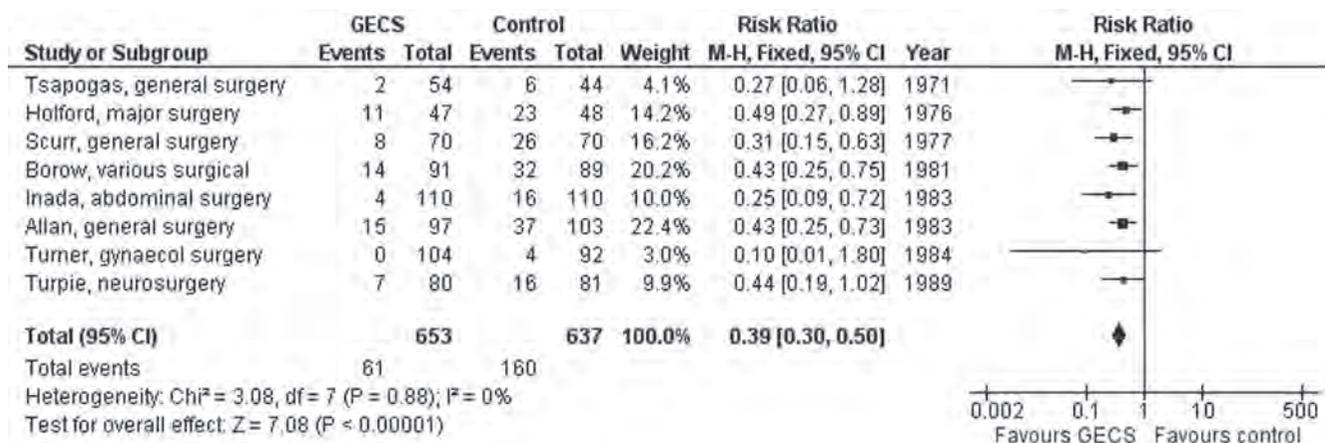


Figure 3.1.—Effect of graduated elastic compression stockings (GEC) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake and/or phlebography) in non-orthopedic surgical randomised controlled studies.<sup>102-108</sup>

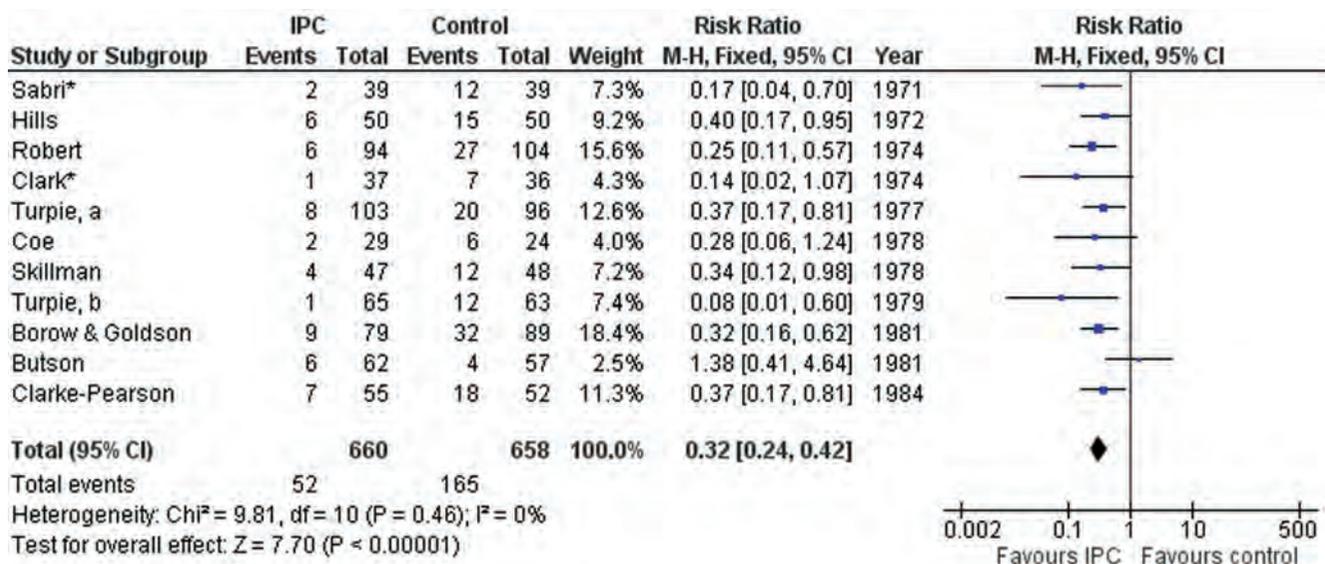


Figure 3.2.—Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test or phlebography) in non-orthopaedic surgical randomized controlled studies (\*Contralateral leg was used as the control).<sup>113-122</sup>

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). However, in view of the availability of more effective methods of prophylaxis and the potential hazards of high dose aspirin, aspirin is not considered as an alternative prophylaxis.

**Graduated elastic compression (GEC)** stockings reduce the incidence of asymptomatic DVT by approximately 50-60% as shown by several studies (Figure 3.1)<sup>9, 102-108</sup> and three systematic reviews,<sup>109-111</sup> but the number of patients studied has been too small to be able to assess the effects on the development of PE. A recent Cochrane systematic review demonstrated that in four studies involving 530 patients the incidence of DVT was reduced from 35.6% in the control group to 15.9% in the compression group.<sup>112</sup> In another five studies involving 848 patients, elastic compression added to a background of addi-

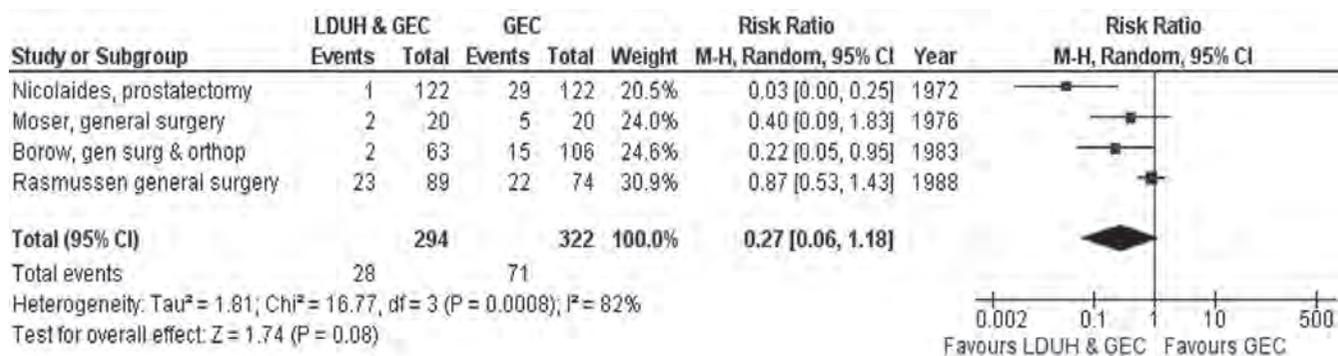


Figure 3.3.—Effect of graduated elastic compression (GEC) stockings versus low dose unfractionated heparin (LDUH) plus GEC in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).<sup>127-130</sup>

tional antithrombotic measures reduced the incidence of DVT from 10.5% in the control group to 1.9% in the compression group.

**Intermittent pneumatic compression (IPC)** tested in 11 RCTs (1318 patients) (Figure 3.2)<sup>105, 113-122</sup> was found to reduce 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).

**IPC or GEC.**—A recent systematic review of 16 RCT of mechanical compression (MC), *i.e.*, GEC or IPC *vs.* subcutaneous heparin (SCH), *i.e.*, LDUH or LMWH demonstrated that the pooled RR for MC compared with SCH 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 reduced risk of postoperative bleeding compared with SCH (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.<sup>123</sup>

**Electrical stimulation.**—Two studies have 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).<sup>124</sup> 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).<sup>125</sup> 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 stimulated group (OR 0.33; 95% CI 0.11 to 0.97).<sup>126</sup> In the 1970s and 1980s when the above studies were performed, the equipment used produced painful stimuli so that electrical calf muscle stimulation 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 post-operative period should be determined in adequately powered RCT before any recommendations can be made.

**Combined modalities.**—RCT show that combinations of prophylactic methods are more effective than using each method singly. They include **LDUH with GEC** (Figure 3.3),<sup>127-130</sup> **GEC with IPC** and **LDUH with IPC** (Figure 3.4).<sup>128-133</sup>

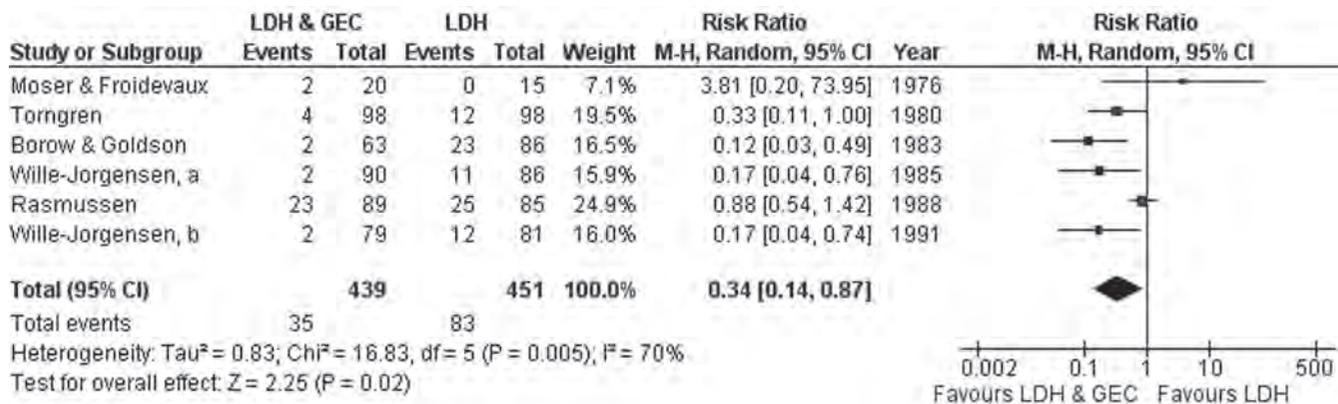


Figure 3.4.—Effect of low dose unfractionated heparin (LDUH) versus LDUH plus graduated elastic compression (GEC) in the prevention of DVT in non-orthopedic surgical patients diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).<sup>128-133</sup>

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). The combination of LDUH with IPC was more effective than LDUH alone. It reduced the incidence of DVT from 26% to 1.5%. 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 to **IPC alone**. 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 bleeds occurred in 1.6% in the combined group and 0.2% in the intermittent pneumatic compression group.<sup>134</sup>

A randomized study involving 2,551 patients undergoing cardiac surgery has 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).<sup>135</sup>

The additive role of mechanical and pharmacological modalities suggests that venous stasis and hypercoagulopathy are independent risk factors. IPC reduces venous stasis by producing active flow enhancement<sup>136, 137</sup> and also increases the plasma levels of tissue factor pathway inhibitor (TFPI)<sup>138</sup> while LDUH and LMWH inhibit factors II and X. The different mechanisms of action are probably responsible for the improved results.

In a survey of members of the American Society for Bariatric Surgery, 95% of surgeons routinely used some form of thromboprophylaxis.<sup>139</sup> Prospective and retrospective non-controlled studies found a low incidence of VTE (less than

1.2%) in patients in patients undergoing bariatric surgery given **LMWH or LDUH**.<sup>140-143</sup> In two consecutive groups of patients, **a higher dose of LMWH (enoxaparin 40 mg 12 hourly) in combination with GEC and IPC** was associated with fewer thrombotic events compared to a lower dose group (enoxaparin 30 mg 12 hourly) in combination with GEC and IPC (0.6% vs. 5.7%; P<0.01).<sup>144</sup> Bleeding was rare occurring in one patient in each group.

In the absence of RCT **in high risk patients having plastic surgery** recommendations are based on extrapolation from general surgery. In high risk patients **LMWH, fondaparinux starting 24 hours after surgery or a combination of LMWH with IPC and GES** are often used.

#### Duration of prophylaxis

In the majority of studies, the duration for prophylaxis was 5-7 days. However, several studies suggested that the risk continues after discharge from hospital.<sup>24, 25, 144-149</sup> Subsequently, RCT have demonstrated that extending prophylaxis from one week to one month reduces asymptomatic DVT by 50-70%.<sup>96, 150-153</sup> In the study by Lausen *et al.*,<sup>96</sup> approximately 70% of patients were operated on for malignancy. The other studies had only pelvic/abdominal malignancies included. In three metaanalyses,<sup>154-156</sup> there was a relative risk reduction for VTE of 60-70%. The number of patients were too small to allow conclusions for an effect on 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 was obtained in a recent study on bemiparin, a second generation LMWH.<sup>157</sup> 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.

Further studies are needed to determine the optimal duration of extended prophylaxis and whether or not 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.<sup>158, 159</sup>

Obese patients undergoing bariatric surgery should also be evaluated for postdischarge VTE risk and considered for extended pharmacological prophylaxis.<sup>160</sup>

## Recommendations

**Low-risk patients** are those without risk factors undergoing minor surgery. The data are insufficient to make any recommendations. On the basis of risk/benefit ratio and extrapolation 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**).

**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) or **LDUH** is recommended (**level of evidence: high**). However, LMWH is the preferred option because it is administered as one injection daily and is associated with a lower incidence of HIT. 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**). LMWH may be added when the risk of bleeding is minimized.

**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**). In the absence of LMWH or fondaparinux, **LDUH 5000 IU** commenced preoperatively and continued twice or three times daily can be used (**level of evidence: high**). Any one of the three may be combined with mechanical methods (**GEC and/or IPC**), particularly in the presence of multiple risk factors (**level of evidence: high**).

Patients undergoing laparoscopic surgery who do not have any additional risk factors should receive **GEC** (**level of evidence: low**). In the presence of additional risk factors they should receive **LDUH, LMWH, fondaparinux or IPC with GEC** (**level of evidence: low**).

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: high**).

Patients undergoing bariatric surgical procedures should receive **LMWH (higher dosage) alone or in combination with GEC and IPC** (**level of evidence: moderate**).

Patients undergoing major vascular procedures should receive **LMWH or fondaparinux** (**level of evidence: low**). In the absence of LMWH or fondaparinux, **LDUH 5000 IU** commenced preoperatively and continued twice or three times daily can be used (**level of evidence: low**).

**High risk patients having plastic surgery** should receive **LMWH, fondaparinux starting 24 hours after surgery or a combination of LMWH with IPC and GES** (**level of evidence: low**). In the absence of LMWH or fondaparinux, **LDUH 5000 IU** commenced pre-operatively and continued twice or 3 times daily can be used (**level of evidence: low**).

**GEC** is contraindicated in patients with peripheral arterial disease because of anecdotal reports of gangrene.

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# UROLOGIC SURGERY

## The risk

In the 1970s, the incidence of DVT in the absence of prophylaxis was 33% in patients having open urologic surgery and 9% in patients having transurethral resection (Table 4.I).<sup>1-11</sup> The incidence of symptomatic VTE is currently in the range of 0.2-5% and PE is the most common cause of postoperative death.<sup>12-16</sup>

A review of 1,653,275 surgical cases entered into the California Patient Discharge Data Set between January 1, 1992, and September 30,

1996, found that the incidence of symptomatic VTE was 3.7% after radical cystectomy,<sup>12</sup> 2% after nephrectomy for malignancy compared with 0.4% in non-cancer patients, and 1.5% after radical prostatectomy. Urologic procedures with a low incidence of VTE included transurethral resection of the prostate (TURP) and incontinence operations.<sup>12</sup>

Similar rates between 0.3-4.8% have been reported for laparoscopic urologic surgery,<sup>17-20</sup> which was shown in a single comparative

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
<i>Open urological operations</i>				
Becker <i>et al.</i> , 1970 <sup>1</sup>		187	39	
Mayo <i>et al.</i> , 1971 <sup>2</sup>		41	21	
Nicolaides <i>et al.</i> , 1972 <sup>3</sup>		25	7	
Hedlund <i>et al.</i> , 1975 <sup>4</sup>		40	18	
Rosenberg <i>et al.</i> , 1975 <sup>5</sup>		32	11	
Sebeseri <i>et al.</i> , 1975 <sup>6</sup>		31	18	
Kutnowski <i>et al.</i> , 1977 <sup>7</sup>		25	12	
Coe <i>et al.</i> , 1978 <sup>8</sup>		8	1	
Bergqvist & Hollböck, 1980 <sup>9</sup>		19	6	
Vandendris <i>et al.</i> , 1980 <sup>10</sup>		33	13	
Hedlund & Blomback, 1981 <sup>11</sup>		28	13	
<b>Total</b>	<b>11</b>	<b>469</b>	<b>159 (33%)</b>	<b>29% to 38%</b>
<i>Transurethral prostatectomy</i>				
Hedlund, 1975 <sup>4</sup>		101	10	
Mayo <i>et al.</i> , 1971 <sup>2</sup>		20	2	
Nicolaides <i>et al.</i> , 1972 <sup>3</sup>		29	2	
<b>Total</b>	<b>3</b>	<b>150</b>	<b>14 (9%)</b>	<b>5% to 15%</b>

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.

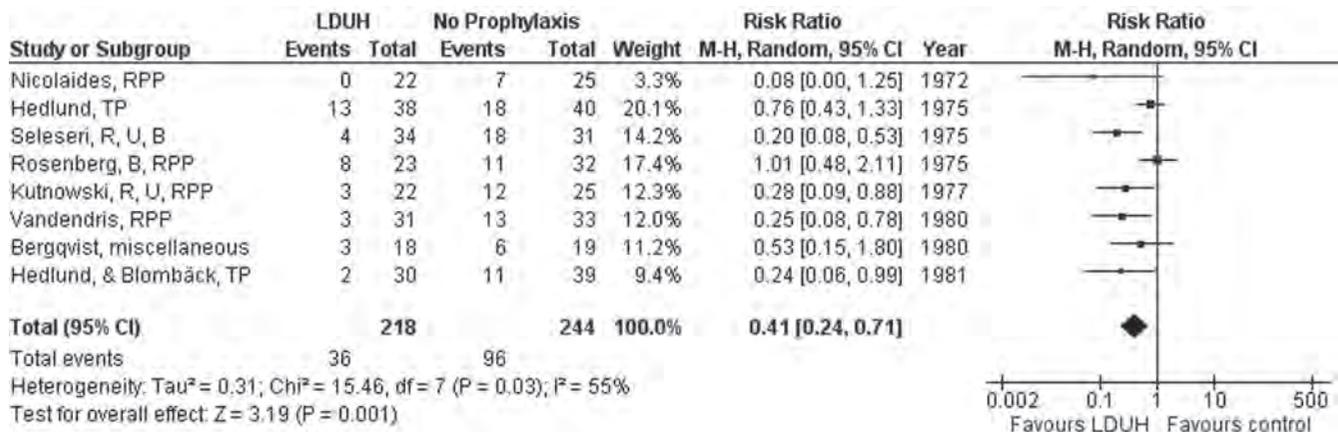


Figure 4.1.—Effect of low dose heparin (LDUH) versus no prophylaxis in the prevention of DVT in patients having urologic surgery diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).<sup>3-7, 9-11</sup>

study to be as hazardous as open urologic surgery.<sup>16</sup>

## Prophylactic methods and recommendations

### General considerations

Two small randomized studies involving 153 patients undergoing open urological procedures compared **IPC** with controls.<sup>8, 21</sup> DVT was reduced from 14.9% to 6.3% (RR; 0.43; 95% CI 0.15 to 1.17) (P=0.085).

**LDUH** was effective in reducing asymptomatic DVT in eight RCT in which the control groups did not have prophylaxis (Figure 4.1).<sup>3, 4, 6, 7, 9-11</sup> The overall incidence of DVT was reduced from 39% to 16% (RR 0.41; 95% CI 0.24 to 0.71).<sup>3, 4, 6-8, 10-22</sup> 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.<sup>23</sup> RCT to study efficacy of LMWH for VTE prevention in patients undergoing urologic surgery have not been performed. Also, RCT using any prophylactic modality in patients having transurethral resection are not available.

### Recommendations

**LDUH is recommended (level of evidence: high) or LMWH** extrapolated from trials in patients having general surgery (**level of evidence:**

**low**). **IPC with GEC** is recommended in patients with increased risk of bleeding, also by extrapolation from trials in patients having general surgery (**level of evidence: low**).

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## Gynecology

### *The risk*

Thromboembolic complications after gynecologic surgery occur with approximately the same frequency as for general surgery (Table 5.I). PE is a leading cause of death following gynecologic cancer surgery<sup>1</sup> and accounts for approximately 20% of perioperative hysterectomy deaths.<sup>2</sup>

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.<sup>3,4</sup> This risk is also affected by the nature and duration of the operation, type of anesthesia, dehydration, sepsis, varicose veins and hormone therapy.<sup>3-7</sup> Known clinical risk factors allow for classification of patients into high, moderate and low risk of developing VTE (Table 5.II).

The incidence of symptomatic VTE appears to be minimal for benign laparoscopic gynecologic surgery,<sup>8</sup> and as high as 16% in surgery for ovarian cancer.<sup>9</sup>

As indicated above, a common additional risk for VTE is estrogen contained in **combined oral contraceptives (COC)**,<sup>10</sup> which had been used by 18% of women in a UK study.<sup>11</sup> The COC increase the risk of VTE.<sup>10</sup> However, the absolute risk is small and represents an increase from 5 to 15-30 per 100,000 women years.<sup>12</sup> The latter is lower than the risk of 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 *versus* non-users in early studies.<sup>13</sup> The absolute excess risk in COC users has to 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 if 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 at least as moderate-risk 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.<sup>14</sup> For other contraceptive preparations, consult the manufacturers' data sheets.

**Hormone replacement therapy (HRT)** should be included as a risk factor for VTE when assessing patients for elective or emergency surgery.<sup>15</sup> HRT does not need to be stopped routinely prior to surgery provided that appropriate thromboprophylaxis is used such as LMWH.<sup>16</sup> An individual assessment is required in each

TABLE 5.I.—The frequency of all DVT in patients having gynaecologic 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 <i>et al.</i> , 1973 <sup>20</sup>		55	15	
Walsh <i>et al.</i> , 1974 <sup>66</sup>		45	16	
Taberner <i>et al.</i> , 1978 <sup>2148</sup>		48	11	
Clarke-Pearson <i>et al.</i> , 1983 <sup>25</sup>		97	12	
Clarke-Pearson <i>et al.</i> , 1984 <sup>32</sup>		52	17	
Clarke-Pearson <i>et al.</i> , 1990 <sup>26</sup>		103	19	
<b>Total</b>	<b>6</b>	<b>400</b>	<b>90 (22.5%)</b>	<b>19% to 27%</b>
Gynecological surgery				
Benign disease				
Ballard <i>et al.</i> , 1973 <sup>20</sup>		55	16	
Bonnar and Walsh, 1972 <sup>67</sup>		140	15	
Taberner <i>et al.</i> , 1978 <sup>21</sup>		48	11	
Walsh <i>et al.</i> , 1974 <sup>66</sup>		217	21	
<b>Total</b>	<b>4</b>	<b>460</b>	<b>63 (14%)</b>	<b>11% to 17%</b>

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 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 and cancer or Major gynecologic surgery, age 40-60 without other risk factors
- Major gynecologic surgery, age 40-60 and cancer or Minor gynecologic surgery, age <40 on estrogen therapy
- Major gynecologic surgery, age 40-60 and cancer or 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\*

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

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.

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.<sup>17</sup>

In assisted reproduction, ovarian stimulation

is used which results in a hyperestrogen 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 pregnancy dosage of LMWH is advised.<sup>18</sup>

*Prophylactic methods and recommendations*

GENERAL CONSIDERATIONS

*Low-risk patients.*—A RCT involving 196 patients<sup>19</sup> demonstrated a lower DVT rate with the use of **GEC** vs. no GEC (0% vs. 4%; P<0.05) in women undergoing major gynecological surgery. On the basis the risk-benefit ratio in this study and extrapolation from data from moderate-risk patients and general surgery, thromboprophylaxis with GEC stockings should be used in addition to early ambulation and adequate hydration.

*Moderate-risk patients.*—Two RCT involving 207 patients having surgery predominantly for benign gynecologic disease showed that **LDUH** (5000 IU, 12 h) reduced DVT.<sup>20, 21</sup> LDUH reduced asymptomatic DVT from 25% to 4.8% (RR 0.19; 95% CI 0.07 to 0.48). **LMWH** (initiated and dosed according to the labeling)<sup>22, 23</sup> is equally effective for preventing DVT. There are no RCT in patients having laparoscopic gynecologic sur-

gery. Patients undergoing complex laparoscopic surgery appear to be at similar VTE risk to those having open procedures.<sup>24</sup>

**High-risk patients.**—In patients having gynecologic surgery for malignancy **LDUH administered 12-hourly** was not effective<sup>25</sup> but **LDUH administered 8-hourly** was effective.<sup>26</sup> 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). Subsequent RCT in patients having gynecologic oncology surgery have shown no difference in efficacy between **LMWH and LDUH given three times a day** for thromboprophylaxis against DVT or PE and no difference in the risk of bleeding.<sup>27-30</sup> The risk of wound hematomas appears to be reduced by avoiding subcutaneous injection near the wound. LMWH has the advantage of once daily injection and is less likely to cause HIT. Extrapolating from general surgery, fondaparinux is an alternative to LMWH.

**IPC** has been shown to be as effective as LDUH or LMWH for preventing DVT when used continuously for five days,<sup>31-33</sup> without any bleeding complications.<sup>33</sup> Thus, in patients with a high risk of bleeding, IPC can be used as an alternative to heparin prophylaxis until the patient is ambulatory.

In a RCT involving 208 patients undergoing gynecologic surgery for malignancy, **LDUH and IPC** provided a similar reduction in the incidence of postoperative DVT, but LDUH was associated with a higher frequency of bleeding complications.<sup>33</sup>

In a RCT involving 332 patients undergoing surgery for abdominal and pelvic malignancy of which 8% were gynaecologic operations, four weeks of prophylaxis with **LMWH** reduced venographic DVT from 12.0% in the one week prophylaxis group to 4.8% in the four week prophylaxis group (RR 0.40; 95% CI 0.18 to 0.88).<sup>34</sup>

### *Recommendations*

**Low-risk patients** should receive **thromboprophylaxis with GEC (Level of evidence: moderate)** in addition to early ambulation and adequate hydration.

**Moderate-risk patients:** **LDUH** (5000 IU, 12 h), **LMWH** (initiated and dosed according to labeling) or **IPC** are recommended (**level of evi-**

**dence: high**). **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**).

**High-risk patients:** **LMWH** (initiated and dosed according to labeling) (**level of evidence: high**), **fondaparinux** (**level of evidence: low**), **LDUH** (5000 IU 8 h) (**level of evidence: high**) or **IPC** (throughout hospital stay) (**level of evidence: moderate**) are recommended. **LMWH or LDUH combined with IPC or GEC** stockings provide optimal prophylaxis (**level of evidence: moderate**). Consideration should be given to continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days especially in patients with cancer (**level of evidence: low**) extrapolated from general surgery.

Until further evidence is available patients undergoing complex laparoscopic surgery should be provided with prophylaxis in accord with risk category similar to patients undergoing open procedures (**level of evidence: low**).

## **Obstetrics**

### *The risk*

Pregnancy is a risk factor for VTE with nearly a five-fold increase compared with the risk for non-pregnant women. The puerperium is the time of greatest risk, with a twenty-fold increase.<sup>35</sup> PE was the leading direct cause of maternal deaths in the UK until 2005. The most recent report "Saving Mothers' Lives" has shown for the first time a sharp fall in the deaths from VTE which is attributed to better recognition of high risk women and more widespread use of thromboprophylaxis.<sup>36, 37</sup> Recent publications have better quantified the magnitude of risk associated with key risk factors in pregnancy.<sup>38, 39</sup> Risk factors for VTE in pregnancy are foremost a history of thrombosis,<sup>40, 41</sup> thrombophilia, immobility, obesity and postpartum hemorrhage.<sup>38</sup> Other risk factors include age over 35 years, Caesarean section, especially as an emergency in labor, coexisting medical problems and surgical procedures during pregnancy and the puerperium.<sup>39, 42</sup> There are significant interactions of risk factors when multiple risk factors are present.

TABLE 5.III.—*Recommended management strategies for various clinical situations. (NB. specialist advice for individualized management of patients is advisable in many of these situations).*

Clinical situation	Recommended management
Single previous VTE (not pregnancy or “pill” related) associated with a transient risk factor and no additional current risk factors, such as obesity.	Antenatal: surveillance or prophylactic doses of LMWH ± GEC stockings. Discuss decision regarding antenatal LMWH with the woman. Postpartum: anticoagulant therapy for at least 6 weeks ± GEC stockings.
Single previous idiopathic VTE or pregnancy or COC related previous VTE or VTE with underlying thrombophilia and not on long-term anticoagulant therapy, or single previous VTE and additional current risk factor(s) (e.g., morbid obesity, nephrotic syndrome).	Antenatal: prophylactic doses of LMWH ± GEC stockings. NB: there is a strong case for more intense LMWH therapy in antithrombin deficiency Postpartum: anticoagulant therapy for at least 6 weeks ± GEC stockings.
More than one previous episode of VTE, with no thrombophilia and not on long-term anticoagulant therapy.	Antenatal: prophylactic doses of LMWH + GEC stockings. Postpartum: anticoagulant therapy for at least 6 weeks + GEC stockings.
Previous episode(s) of VTE in women receiving long-term anticoagulants (e.g., with underlying thrombophilia).	Antenatal: switch from oral anticoagulants to LMWH therapy before 6 weeks gestation + GEC stockings. Postpartum: resume long-term anticoagulants with LMWH overlap until INR in pre-pregnancy therapeutic range + GEC stockings.
Thrombophilia (confirmed laboratory abnormality) but no prior VTE.	Antenatal: surveillance <i>or</i> prophylactic LMWH ± GEC stockings. The indication for LMWH in the antenatal period is stronger in AT deficient, women than the other thrombophilias, in symptomatic kindred compared to asymptomatic kindred and also where additional risk factors are present. Postpartum: anticoagulant therapy for at least 6 weeks ± GEC stockings.
Following caesarean section.	Carry out risk assessment for VTE. If an additional risk factor such as emergency section in labour, age over 35 years, high BMI etc present provide thromboprophylaxis at least until discharge from hospital *
Following vaginal delivery.	Carry out risk assessment for VTE. If two or more additional risk factors such as age over 35 years, high BMI etc present consider thromboprophylaxis ± GEC stockings at least until discharge from hospital*.

\* NB where multiple risk factors are present consider extended prophylaxis after discharge.

Risk assessment for VTE is recommended for all women in early pregnancy and prior to Caesarean section.<sup>36</sup>

### *Prophylactic methods and recommendations*

#### GENERAL CONSIDERATIONS

The Cochrane Review of VTE prophylaxis in pregnancy and the puerperium examined eight trials involving 649 women. It was not possible to assess the effects of interventions because of

the limited number of trials and the small sample sizes.<sup>43</sup> Although large scale randomized trials of currently used interventions are required for evidence based recommendations, practice has evolved based on indirect evidence.

Table 5.III summarizes management strategies for various clinical situations. In the absence of RCT, all recommendations are based on low levels of evidence.

Women at high risk of VTE including those with previous confirmed VTE should be offered pre-pregnancy counselling to agree to a manage-

TABLE 5.IV.—Suggested thromboprophylactic doses for antenatal and postnatal LMWH.

Weight (kg)	Enoxaparin	Dalteparin	Tinzaparin (75u/kg/day)
<50	20mg daily	2,500units daily	3,500 units daily
50-90	40mg daily	5,000 units daily	4,500 units daily
91-130	60mg daily*	7,500 units daily*	7,000 units daily*
131-170	80mg daily*	10,000 units daily*	9,000 units daily*
>170	0.6mg/kg/day*	75 units/kg/day*	75u/kg/day*
High prophylactic (intermediate) dose for women 50-90kg	40mg 12-hourly	5,000 units 12-hourly	4,500 units 12 hourly
Treatment dose	1 mg/kg/12 hourly antenatal; 1.5 mg/kg/daily postnatal	100 u/kg/12hourly or 200u/kg/daily postnatal	175u/kg/daily antenatal and postnatal

\*may be given in two divided doses

ment plan. The thrombotic risk exists from the beginning of pregnancy.<sup>38, 44</sup>

Women with previous VTE or a strong family history of VTE, particularly where familial VTE occurs at a young age (<50 years) should be screened for inherited and acquired thrombophilia before pregnancy (**level of evidence: low**). Ideally, all women should undergo assessment of risk factors for VTE in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to a hospital with complications such as hyperemesis or pre-eclampsia that requires bed rest (**level of evidence: low**).<sup>45, 46</sup> Systematic reviews and retrospective studies have concluded that prophylaxis with **LMWH** is now the method of choice in pregnancy compared to LDUH in view of efficacy and safety<sup>47-51</sup> (**level of evidence: low**). The risks of HIT and osteoporosis during pregnancy are low with LMWH as compared with LDUH.<sup>52, 53</sup>

The overall risk of recurrence of DVT during pregnancy has been reported as high as 10.9% compared with 3.7% outside pregnancy.<sup>54, 55</sup>

Women who have had a previous VTE in association with a temporary risk factor that is no longer present and no known thrombophilia or additional risk factors should be offered antepartum and/or post-partum thromboprophylaxis with LMWH (**level of evidence: low**). GEC stockings during pregnancy should be considered in addition to postpartum prophylaxis (**level of evidence: low**). Women in whom a previous VTE was oestrogen-related (pregnancy or the combined contraceptive pill), or additional risk factors are present such as obesity should be started with thromboprophylaxis

with **LMWH as early as possible in pregnancy and continued for six weeks following delivery (level of evidence: low)**.

Women with thrombophilias have an increased risk of VTE in pregnancy and the risk varies with the specific thrombophilia. Women with previous VTE and certain thrombophilias such as those homozygous for FVL should be offered thromboprophylaxis with LMWH antenatally and throughout the six weeks postpartum (**level of evidence: moderate**).

Women who are on long-term anticoagulant thromboprophylaxis for VTE and women with anti-thrombin deficiency are at very high risk (30%) during pregnancy. Those on vitamin K antagonists (VKA) should be advised to switch to LMWH as soon as pregnancy is confirmed because of the risk of embryopathy from warfarin between the sixth and twelfth week of pregnancy. In both situations, LMWH dosage should be similar to that used for the treatment of VTE (**level of evidence: moderate**).

Table 5.IV shows the most recent Royal College of Obstetricians and Gynaecologists (RCOG 2009) guidelines for recommended **LMWH dosage in pregnancy**. Reports have shown that a once-daily dosage of tinzaparin provides adequate 24 hour cover.<sup>56, 57</sup> A large retrospective audit of tinzaparin use in 1267 pregnancies in 1120 women showed the efficacy and safety compared well with its use in the non-pregnant population.<sup>58</sup>

Women with a previous VTE and a thrombophilia such as protein C deficiency, Factor V Leiden, Prothrombin 20210A or protein S deficiency who are at moderately increased risk of VTE should receive LMWH (e.g., enoxaparin 40 mg daily, dalteparin 5,000 U daily or tinzaparin

4,500 U daily in women of normal body weight) from early pregnancy (**level of evidence: low**).

Women with no personal history of venous thrombosis but who have a thrombophilic defect identified may require thromboprophylaxis. This will depend on the type of thrombophilia, the family history, and the presence of additional risk factors (e.g., obesity, immobilization and hyperemesis). All should be offered anticoagulant prophylaxis following delivery. **The risk of thrombosis should be discussed with the patient antenatally and GEC stockings should be considered (Level of evidence: low).**

Women with **antiphospholipid syndrome** (lupus anticoagulant and/or anticardiolipin antibodies and/or Beta2-glycoprotein antibodies) and previous VTE or adverse pregnancy outcome should receive thromboprophylaxis with **LMWH or LDUH and low dose aspirin (75 mg/day)**<sup>59,60</sup> from the time of diagnosis of pregnancy (**level of evidence: high**). If there is a history of recurrent VTE an intermediate dose (75% of treatment dose) or full treatment dose should be used.<sup>61</sup> Aspirin is discontinued at 36 weeks gestation to allow fetal platelets to recover. Prophylaxis with **LMWH should continue for at least seven days after delivery. In women with antiphospholipid syndrome and previous VTE, postpartum prophylaxis should be continued for six weeks (level of evidence: low).**

#### DELIVERY AND THE PUERPERIUM

*Management of delivery.*—Patients on LMWH antenatally and who wish epidural anesthesia should have heparin prophylaxis discontinued with the onset of labor. 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.<sup>62</sup> 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.<sup>63</sup> **For delivery by elective Caesarean section, the woman should receive a thromboprophylactic dose of LMWH on the day before delivery. On the day of delivery the thromboprophylactic dose of LMWH should be given four hours after operation or four hours after removal of the epidural catheter (level of evidence: low).** There is an increased risk of wound hematoma following

Caesarean section with both LMWH and LDUH. The subcutaneous injections should be given in the flank well away from the incision to minimize wound hematoma.

*Management of the puerperium.*—In addition to previous VTE and thrombophilias, other risk factors should be considered for postpartum prophylaxis: age over 35 years, obesity, Caesarean section (particularly an emergency procedure during labor), gross varicose veins, pre-eclampsia, postpartum hemorrhage (>1000 mL) and immobilization (**level of evidence: low**).

**Postpartum thromboprophylaxis is recommended in women with previous VTE, known thrombophilias and other thrombotic risk factors.** The first postpartum daily dose of s.c. LMWH (enoxaparin 40 mg, dalteparin 5000 U daily or tinzaparin 75 U/kg) should be given 3-4 hours after delivery. Postpartum anticoagulation should be continued for a minimum of six weeks in high-risk patients with previous VTE or thrombophilia. In other patients not at high-risk, prophylaxis should continue for 5-7 days, and the need for prophylaxis should be reviewed if the hospital stay continues beyond seven days (**level of evidence: moderate**).

If a patient does not wish to continue on self-injections of LMWH, **conversion to warfarin should be delayed until at least 5-7 days after delivery** as warfarin will increase the risk of postpartum hemorrhage and perineal hematoma.<sup>61</sup> LMWH can be discontinued when the INR has been within the target range of 2.0-3.0 for two consecutive days. **GEC stockings can be added to LMWH in high-risk patients and should be used where LMWH is contraindicated. Where anticoagulants are contraindicated, GEC stockings should be worn for at least six weeks following delivery (level of evidence: low).**

Patients who develop VTE during pregnancy or the puerperium should be referred for hematological screening to determine if they have underlying thrombophilia and counselled about the increased risk of hormone therapy. Progestogen-only contraception is suitable for these women. They should also be counselled about the need for prophylactic treatment in any future pregnancy.

**Breast feeding is not contraindicated with either LMWH, LDUH or warfarin (level of evidence: low).**<sup>64, 65</sup>

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# ORTHOPEDIC SURGERY AND TRAUMA

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## (A) GENERAL CONSIDERATIONS

### Timing of prophylaxis

VTE prophylaxis involves a balance of risks and benefits. Chemical prophylaxis poses a dilemma: as the closer it is administered to surgery for a given dose, the better the thromboprophylaxis but the greater is the risk of bleeding complications.<sup>1</sup> In Europe, LMWH is given at a lower dose prior to operation providing an anticoagulant effect to counteract the intra-operative activation of coagulation factors and venous stasis. However, 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. In North America, LMWH is given after surgery at a higher dose and more frequently. This should reduce the risk of surgical bleeding, yet intraoperative thrombogenesis is not prevented and thrombi may have already begun forming. The drug is now expected to be therapeutic as well as prophylactic. Therefore, prophylaxis needs to be given close but not too close to surgery.<sup>2, 3</sup>

IPC and 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 LMWH prophylaxis.<sup>4-6</sup>

### Spinal and epidural anesthesia

Meta-analyses show that **spinal and epidural** anesthesia reduce both thromboembolism and perhaps mortality in hip fractures surgery<sup>7, 8</sup> and total knee replacement (TKR).<sup>9-11</sup> 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.<sup>12</sup> However, more recently there have been concerns that a spinal hematoma may develop on rare occasions.<sup>13, 14</sup> Guidelines have been suggested.<sup>15, 16</sup> LMWH (or pentasaccharide) can be given safely four hours after removal of the epidural catheter (see section on pregnancy). However, LMWH or pentasaccharide should be avoided whilst a continuous postoperative neuraxial block is in place. The catheter should not be inserted until serum levels of the chemical agent used are at their lowest. This means that postoperative administration of the agent is generally safer and more predictable than preoperative administration when epidural analgesia is needed.

### Duration of prophylaxis in elective orthopedic surgery

Studies in patients having total hip replacement (THR)<sup>1, 17-25</sup> demonstrate that there is prolonged risk, with 45-80% of all symptomatic events occurring after discharge from hospi-

TABLE 6.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	95% CI Incidence
<i>Elective hip replacement</i>				
Belch <i>et al.</i> , 1982 <sup>42</sup>		36		20
Bergqvist <i>et al.</i> , 1979 <sup>4</sup>		71		45
Dechavanne <i>et al.</i> , 1974 <sup>44</sup>		27		13
Dechavanne <i>et al.</i> , 1975 <sup>45</sup>		20		8
Evarts <i>et al.</i> , 1971 <sup>46</sup>		56		30
Gallus <i>et al.</i> , 1983 <sup>47</sup>		47		25
Hampson <i>et al.</i> , 1974 <sup>48</sup>		52		28
Harris <i>et al.</i> , 1977 <sup>49</sup>		51		23
Hoek <i>et al.</i> , 1992 <sup>50</sup>		99		56
Hull <i>et al.</i> , 1990 <sup>51</sup>		158		77
Ishak and Morley, 1981 <sup>52</sup>		41		22
Kalodiki <i>et al.</i> , 1996 <sup>53</sup>		14		13
Mannucci <i>et al.</i> , 1976 <sup>54</sup>		51		22
Morris <i>et al.</i> , 1974 <sup>55</sup>		32		16
Turpie <i>et al.</i> , 1986 <sup>56</sup>		50		21
VTCSG, 1975 <sup>57</sup>		30		11
Welin-Berger <i>et al.</i> , 1982 <sup>58</sup>		16		5
Total	17	851		435 (51%) 48% to 54%
<i>Multiple trauma</i>				
Freeark <i>et al.</i> , 1967 <sup>59</sup>		124		4
Geerts <i>et al.</i> , 1994 <sup>60</sup>		349		201
Kudsk <i>et al.</i> , 1989 <sup>61</sup>		38		24
Shackford <i>et al.</i> , 1990 <sup>62</sup>		25		1
Total	4	536		270 (50%) 46% to 55%
<i>Total knee replacement</i>				
Hull <i>et al.</i> , 1979 <sup>63</sup>		29		19
Kim, 1990 <sup>64</sup>		244		80
Leclerc <i>et al.</i> , 1996 <sup>65</sup>		57		31
Lynch <i>et al.</i> , 1988 <sup>66</sup>		75		28
Stringer <i>et al.</i> , 1989 <sup>67</sup>		55		31
Stulberg <i>et al.</i> , 1984 <sup>68</sup>		49		41
Wilson <i>et al.</i> , 1992 <sup>69</sup>		32		22
Total	7	541		252 (47%) 42% to 51%
<i>Hip fracture</i>				
Ahlberg <i>et al.</i> , 1968 <sup>70</sup>		45		16
Checketts and Bradley, 1974 <sup>71</sup>		26		13
Darke, 1972 <sup>72</sup>		66		11
Galasko <i>et al.</i> , 1976 <sup>73</sup>		50		23
Gallus <i>et al.</i> , 1973 <sup>74</sup>		23		11
Kakkar <i>et al.</i> , 1972 <sup>75</sup>		50		20
Lahnborg, 1980 <sup>76</sup>		69		28
Montrey <i>et al.</i> , 1985 <sup>77</sup>		81		22
Morris and Mitchell, 1976 <sup>78</sup>		74		50
Morris and Mitchell, 1977 <sup>79</sup>		76		49
Myhre and Hølen, 1969 <sup>80</sup>		55		22
Powers <i>et al.</i> , 1989 <sup>81</sup>		63		29
Rogers <i>et al.</i> , 1978 <sup>82</sup>		37		19
Svend-Hansen <i>et al.</i> , 1981 <sup>83</sup>		65		28
Xabregas <i>et al.</i> , 1978 <sup>84</sup>		25		12
Total	15	805		353 (44%) 40% to 47%
<i>Spinal cord injury</i>				
Bors <i>et al.</i> , 1954 <sup>85</sup>		99		58
Brach <i>et al.</i> , 1977 <sup>86</sup>		10		9
Rossi <i>et al.</i> , 1980 <sup>87</sup>		18		13
Silver, 1974 <sup>88</sup>		32		8
Watson, 1974 <sup>89</sup>		234		42
Frisbie and Sasahara, 1981 <sup>90</sup>		17		1
Merli <i>et al.</i> , 1988 <sup>91</sup>		17		8
Myllynen <i>et al.</i> , 1985 <sup>92</sup>		9		9
Yelnik <i>et al.</i> , 1991 <sup>93</sup>		22		12
Total	9	458		160 (35%) 31% to 39%

TABLE 6.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	95% CI Incidence
<i>Isolated lower limb injuries</i>				
Hjelmstedt and Bergwall, 1968 <sup>94</sup>		76		34
Abelseth <i>et al.</i> , 1996 <sup>95</sup>		82		18
Kujath <i>et al.</i> , 1993 <sup>96</sup>		127		21
Kock <i>et al.</i> , 1995 <sup>97</sup>		163		7
Lassen <i>et al.</i> , 2002 <sup>215</sup>		159		29
Jorgensen <i>et al.</i> , 2002 <sup>99</sup>		77		10
Lapidus <i>et al.</i> , 2007 <sup>100</sup>		96		27
Goel <i>et al.</i> , 2009 <sup>101</sup>		111		14
Total	8	891		160 (18%) 6% to 21%
<i>Elective spinal surgery</i>				
West <i>et al.</i> , 1992 <sup>102</sup>		41		6
Oda <i>et al.</i> , 2000 <sup>103</sup>		110		17
Total	2	151		23 (15%) 10% to 22%
<i>Knee arthroscopy</i>				
Stringer <i>et al.</i> , 1989 <sup>67</sup>		48		2
Demers <i>et al.</i> , 1998 <sup>104</sup>		184		33
Williams <i>et al.</i> , 1995 <sup>105</sup>		85		3
Jaureguito <i>et al.</i> , 1999 <sup>106</sup>		239		5
Delis <i>et al.</i> , 2001 <sup>107</sup>		102		8
Wirth <i>et al.</i> , 2001 <sup>108</sup>		111		5
Michot <i>et al.</i> , 2002 <sup>109</sup>		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.

tal.<sup>19, 26-28</sup> RCT in patients having THR indicate that **prolonged thromboprophylaxis with LMWH** for up to 35 days is safe and effective irrespective of whether in-hospital prophylaxis was with LMWH or warfarin. It decreases the frequency of venographically detected total DVT, proximal DVT and symptomatic VTE after the seventh day by more than 50%.<sup>25, 29-33</sup> One RCT compared warfarin prophylaxis (INR 2-3) for nine 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).<sup>34</sup> 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.<sup>35</sup> The RECORD2 study<sup>36</sup> 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 THR suggested by the RECORD1 study.<sup>37</sup>

Further studies are needed before recommendations can be made for prophylaxis beyond 35 days. The optimal duration of prophylaxis is unknown. Epidemiological 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-morbidity (*e.g.*, rheumatoid arthritis) in which vascular deaths dominate.<sup>38, 39</sup>

## (B) ELECTIVE HIP REPLACEMENT

### The risk

In the absence of prophylaxis, patients undergoing elective major joint replacement and those with hip fracture have a DVT risk of approximately 50% as shown in studies performed in the 1970s, 1980s and 1990s<sup>19, 40, 41</sup> (Table 6.I).<sup>42-91, 67, 92-109</sup> Similar high rates of VTE were found in the

TABLE 6.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 (Imperiale and Speroff, 1994) <sup>112</sup>	25	1436	330* (23%)	20.8% to 25.2%
Total knee replacement (Hull <i>et al.</i> , 1979 <sup>63</sup> Kim, 1990 <sup>64</sup> Leclerc <i>et al.</i> , 1996 <sup>65</sup> Mckenna <i>et al.</i> , 1976 <sup>113</sup> Stringer <i>et al.</i> , 1989 <sup>67</sup> Stulberg <i>et al.</i> , 1984 <sup>68</sup> Wilson <i>et al.</i> , 1992) <sup>69</sup>	7	536	41 (7.6%)	5.5% to 10.1%

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

TABLE 6.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 (Imperiale and Speroff, 1994) <sup>112</sup>	25	1436	57** (4%)	3% to 5.1%
Traumatic orthopaedic surgery (APTC, 1994) <sup>114</sup>	11	494	34 (6.9%)	4.8% to 9.5%

\*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 6.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 (Collins <i>et al.</i> , 1988) <sup>115</sup>	12	485	8 (1.65%)	0.38% to 2.7%
Fractured neck of femur (Lassen and Borris, 1994) <sup>116</sup>	23	1195	48 (4.0%)	3% to 5.3%

\*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.

placebo groups of two recent dose ranging studies for enoxaparin and fondaparinux performed in Japan.<sup>110, 111</sup> The frequencies of proximal DVT (Table 6.II) <sup>63-65, 67-69, 112, 113</sup> and PE (Tables 6.III <sup>112, 114</sup> and 6.IV <sup>115, 116</sup>) are also high, and symptomatic events range from 2-5%.<sup>117</sup> 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.<sup>118</sup> The risk of clinical DVT and PE continues after hospitalisation over a period of approximately three months <sup>19, 20, 117, 119</sup> (Table 6.V).<sup>18, 120-123</sup> Mortality studies have confirmed a reduced survival for 2-3 months following elective surgery with the highest death rate initially early after operation.<sup>38, 124</sup>

There is a high incidence of proximal DVT (18-36%) in patients having THR <sup>47, 50, 51, 53, 56, 125-128</sup> in contrast to patients having TKR in whom the preponderance of thrombosis is distal.<sup>66-68, 129, 130</sup>

Modern THR surgery is performed with a continuing reduction in hospital stay (3-6 days) so that patients are discharged while still at risk. Thus, the majority of clinical events appear after hospital discharge, giving a false impression of a decreasing problem.<sup>20, 119, 131</sup>

A recent meta-analysis of 10 RCTs that used venography in patients having THR 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.<sup>132</sup> The consisten-

TABLE 6.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 <i>et al.</i> 1991 <sup>120</sup>	11600	90 days	93 (1.10%)	0.87 to 1.31%	—	—	Very low
Sheppard <i>et al.</i> 1981 <sup>121</sup>	3016	Inpatient	19 (0.63%)	0.38 to 0.98%	12 (0.40%)	0.20 to 0.70%	20%*
Warwick <i>et al.</i> 1995 <sup>18</sup>	1162**	90 days	15 (1.30%)	0.73 to 2.10%	4 (0.34%)	0.09 to 0.90%	11%*
Wroblewski <i>et al.</i> 1992 <sup>122</sup>	18104	1 year	362 (2.0%)	1.80 to 2.20%	1.27 (0.70%)	0.58 to 0.82%	—
Fender <i>et al.</i> 1997 <sup>123</sup>	2111	42 days	19 (0.91%)	0.05 to 1.42%	4 (0.19%)	0.05 to 0.49%	65%

\*High risk patients received anticoagulation; \*\* All patients wore thigh-length elastic stockings; - Information not available.

TABLE 6.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 orthopaedic surgery) in randomised controlled studies (Antiplatelet Trialists' Collaboration, 1994).<sup>114</sup>

Type of patient	Control groups*			Antiplatelet groups			
	Number of trials with data	Patients N.	DVT(%)	Patients N.	DVT(%)	RR	95%CI
Orthopedic traumatic	10	444	186 (42)	454	163 (36)	0.86	0.73 to 1.0
Orthopaedic 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 6.VII.—Effect of antiplatelet therapy (e.g., aspirin) in the prevention of PE in randomised controlled studies in orthopedic patients (Antiplatelet Trialists' Collaboration, 1994).<sup>114</sup>

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
Orthopedic 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

cy of this finding with previous reports strengthens the belief that asymptomatic DVT is a surrogate for symptomatic DVT.

## Prophylactic methods and recommendations

### General considerations

Prophylactic methods that have been investigated in patients having THR include aspirin, fixed LDUH, LMWH, heparinoid, recombinant hirudin, oral direct -Xa inhibitors, oral direct thrombin inhibitors, fixed mini-dose and adjusted doses of VKA, GEC stockings, IPC and foot impulse technology (FIT). To determine the risk reduction for each prophylactic method, only

randomized studies with systematic screening tests for DVT have been used for the purposes of this analysis (Tables 6.VI-6.VIII<sup>4, 69, 114, 130, 133-139</sup> and Figures 6.1-6.3<sup>1, 47, 51, 63, 65, 140-145</sup>).

**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 randomized controlled studies in patients having elective THR)<sup>115</sup> and was the method of choice in the 1980s.

**LMWH** has been subsequently demonstrated to be superior to LDUH for elective THR surgery, 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).<sup>32, 128, 146-153</sup> Thus, **LDUH** is no longer recommended.

As indicated in the section on "General, Vas-

TABLE 6.VIII.—Effect of prophylaxis using the combination of foot impulse technology (FIT) with graduated elastic compression (GEC) on proximal DVT, in orthopedic patients.

Autors	Diagnostig method	N.	Control		Foot impulse technology plus additional method of prophylaxis	
			Proximal DVT	Method of prophylaxis	N.	Proximal DVT
<i>Hip surgery</i>						
Bradley <i>et al.</i> , 1993 <sup>4</sup> VG	GEC	44	11 (25%)	FIT+GEC	30	2 (6.7%)
Fordyce and Ling 1992 <sup>133</sup> VG	GEC	40	13 (32%)	FIT+GEC	39	2 (5%)
Santori <i>et al.</i> , 1994 <sup>134</sup> US	LDUH	65	13 (20%)	FIT+GEC	67	2 (3%)
Warwick <i>et al.</i> , 1998 <sup>135</sup> VG	LMWH+GEC	138	27 (17.4%)	FIT+GEC	136	12 (9%)
Pitto <i>et al.</i> , 2004 <sup>136</sup> US	LMWH	100	2+4*(6%)	FIT+GEC	100	0+3*(3%)
<i>Knee surgery</i>						
Blanchard <i>et al.</i> , 1999 <sup>137</sup> VG	LMWH	60	2 (3.3%)	FIT only	48	4 (8.3%)
Wilson <i>et al.</i> , 1992 <sup>69</sup> VG	Nil	32	6 (19%)	FIT only	28	0
Westrich <i>et al.</i> , 1996 <sup>130</sup> VG	Aspirin	83	49 (59%)	FIT+Aspirin	81	22 (27%)
Warwick <i>et al.</i> , 2002 <sup>138</sup> VG	LMWH	99	57 (58%)	FIT	98	48 (54%)
<i>Hip fracture</i>						
Stranks <i>et al.</i> , 1992 <sup>139</sup> US	GEC	39	9 (32%)	FIT+GEC	41	0

cular, Bariatric and Plastic Surgical patients”, regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug. Therapeutic interchange among these products is not appropriate.

RCT have shown that **recombinant hirudin** (Desirudin) is more effective than LDUH<sup>154-156</sup> or LMWH.<sup>155</sup> Of 2079 patients studied, 1587 were included in the primary efficacy analysis. Overall, DVT was reduced with hirudin 15 mg b.d. compared with 40 mg enoxaparin from 25.5% to 18.45% (P=0.001; RRR 28%). The safety profile was the same in both groups.<sup>155</sup>

Several randomized controlled trials have compared **VKA** with **LMWH**. LMWH was found to be more effective<sup>1, 142, 157, 158</sup> or at least as effective<sup>143</sup> for preventing 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).<sup>3</sup> Symptomatic DVT was also reduced from 4.4% in the warfarin group to 1.5% in the LMWH group (RR 0.32; 95% CI 0.12 to 0.88). A meta-analysis of VKA in orthopedic surgery<sup>159</sup> 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 total 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).

In a clinical trial for THR,<sup>35</sup> 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% in the LMWH group and in 5.5% in the warfarin group. It appears that reduced bleeding seen initially after surgery due to the slow onset of action for warfarin is offset by long-term increased bleeding. Furthermore, national drug registries have shown warfarin to be a major cause of readmission and fatal bleeding.<sup>160, 161</sup> With these data, and because of the need for monitoring, the small therapeutic window and the risk of drug interactions, some surgeons find it difficult to see an advantage for VKA over 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 anti-thrombin binding to activated factor X, and represents one of many attributes of heparins. The drug is administered by subcutaneous injection

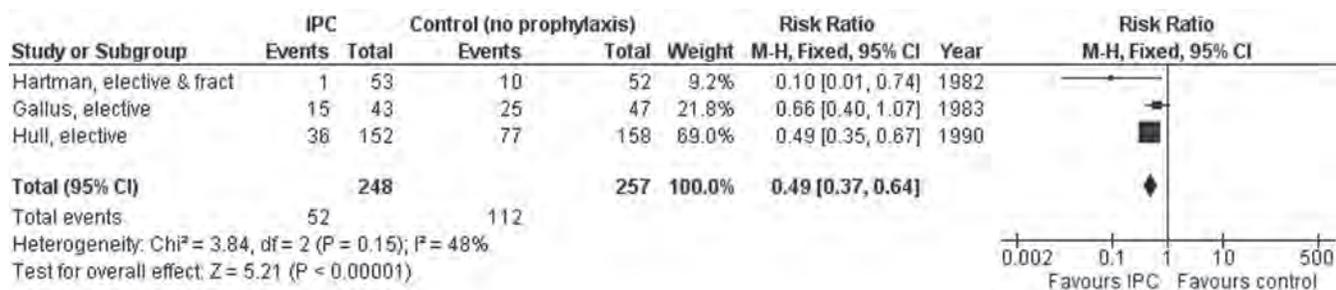


Figure 6.1.—Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with phlebography or duplex ultrasound\* (Fisher *et al.*, 1995)<sup>197</sup> in randomised controlled studies of patients having hip replacement.<sup>47, 51, 140</sup>

once daily. It has been registered internationally for major orthopedic surgery. Two large randomized controlled trials compared fondaparinux to enoxaparin.<sup>98, 162</sup> 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.

A meta-analysis in the early 1990s<sup>114</sup> demonstrated that **antiplatelet therapy** in elective hip surgery is only moderately effective for protection against DVT (RR 0.7; 95% CI 0.61 to 0.82) (Table 6.VI) but the observed reduction in the risk of PE was substantial (RR 0.49; 95% CI 0.26 to 0.92) (Table 6.VII). However, the subsequent PEP study<sup>163, 164</sup> showed that aspirin is not as valuable as the meta-analysis suggested. Over 13000 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 pentasaccharide. The reduced risk of VTE was matched by an increased risk of blood transfusion, gastrointestinal bleeding and wound bleeding. In a supplementary group of 4000 elective hip and knee replacement patients, there was an insignificant difference in symptomatic VTE.<sup>164</sup> The relative weak thromboprophylactic effect of aspirin therefore carries an alternative complication rate and its use might deprive patients of safer or more effective prophylaxis.

The Cochrane database<sup>165</sup> and an earlier meta-analysis<sup>166</sup> show that GEC is effective in re-

ducing DVT in hospitalized patients, but there are few robust studies specific to orthopedic surgery.<sup>52, 167</sup> Because other methods of prevention are more effective, GEC stockings on their own are not recommended.

**IPC** is effective in patients having THR<sup>47, 51, 140</sup> (Figure 6.1) reducing 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.<sup>168</sup> In a recent study involving 392 evaluable patients having THR in which IPC was compared to LMWH, the incidence of postoperative DVT was found to be 3% in both groups.<sup>169</sup>

Three subsequent RCT have compared **combined modalities** with LMWH. In the first study<sup>170</sup> in 131 patients having THR and TKR, the combination of LMWH plus IPC was more effective than LMWH plus GEC stockings (DVT incidence 0% versus 28%). In the second study involving 277 patients, the combination of LMWH plus IPC was more effective than LMWH (DVT incidence 6.6% versus 19.5%).<sup>171</sup> In the third study involving 1803 patients having various orthopedic operations, the combination of LMWH plus IPC was also more effective than LMWH (DVT incidence 0.4% versus 1.7%). In the subgroup of 306 patients having THR the incidence of DVT was 0% in the combined modalities group and 5.2% in the LMWH group (P<0.001)<sup>172</sup> (see section on combined modalities). In another study involving 121 evaluable patients having THR or TKR, in which IPC plus aspirin 100 mg daily

TABLE 6.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 orthopaedic surgery) in randomised controlled studies (Antiplatelet Trialists' Collaboration, 1994).<sup>114</sup>

Type of patient	Control groups*			Antiplatelet groups			
	Number of trials with data	Patients N.	DVT(%)	Patients N.	DVT(%)	RR	95%CI
Orthopedic traumatic	10	444	186 (42)	454	163 (36)	0.86	0.73 to 1.00
Orthopedic 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).

was also compared to LMWH, the incidence of postoperative venographic DVT was found to be 6.6% in the IPC group and 28.3% in the LMWH group (RR 0.23; 95% CI 0.08 to 0.65).<sup>173</sup>

**FIT combined with GEC** is effective in reducing the incidence of proximal DVT in patients having THR or TKR (Table 6.VIII) with less bleeding and swelling. Direct comparisons with chemical prophylaxis are sparse; there is probably superiority to LDUH<sup>134</sup> and equivalence with LMWH for THR<sup>136, 174</sup> but not for TKR.<sup>137</sup>

**IPC and FIT** offer an alternative for patients with contraindications to chemical prophylaxis (Figure 6.1 and Table 6.IX).

**Rivaroxaban** is a new oral direct Xa inhibitor. Two studies (RECORD1 and RECORD2) have compared rivaroxaban with enoxaparin in patients having THR. In RECORD1 study which involved 3153 evaluable patients, both prophylactic regimens were given for 31-39 days. 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 (NS).<sup>37</sup> The RECORD2 study investigated the efficacy of extended thromboprophylaxis (35 days) with rivaroxaban compared with short term enoxaparin (10-14 days) followed by placebo.<sup>36</sup> The incidence of venographic VTE was 9.3% in the enoxaparin group and 2% 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 (NS).

**Apixaban** is another new oral direct Xa inhibitor. In a double blind placebo controlled study

involving 5407 patients having THR, apixaban at a dose of 2.5 mg orally b.d. 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. Prophylaxis was continued for 35 days after surgery, followed by bilateral venographic studies. The incidence of the primary efficacy outcome (asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, 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).<sup>175</sup>

**Edoxaban** is a new oral direct FXa inhibitor that is 10,000-fold more selective for FXa than thrombin.<sup>176</sup> In the randomized, double-blind, double-dummy STARS J-V trial (N.=503), edoxaban (30 mg qd) resulted in significantly fewer VTEs than enoxaparin (2000 IU bid) (2.4% vs. 6.9%; P=0.0157 for superiority). 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).

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

TABLE 6.X.—Effect of antiplatelet therapy (e.g., aspirin) in the prevention of PE in randomised controlled studies (Antiplatelet Trialists' Collaboration, 1994).<sup>114</sup>

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

performed. The primary endpoint of total VTE and all-cause mortality occurred in 8.6%, 6% and 6.7% of the groups respectively ( $P < 0.0001$  for non-inferiority of each group *versus* enoxaparin).<sup>177</sup> In the second study (RE-NOVATE II) 220 mg of dabigatran was compared with 40 mg enoxaparin administered for the same period.<sup>178</sup> The primary endpoint of total VTE and all-cause mortality occurred in 7.7% in the dabigatran and 8.8% in the enoxaparin group ( $P < 0.0001$  for non-inferiority of dabigatran *versus* enoxaparin). There was no significant difference in major bleeding events between the various groups in either study.

#### Recommendations

**LMWH** initiated and dosed according to the manufacturer's recommendations (**level of evidence: high**), **fondaparinux** (**level of evidence: high**), **vitamin K antagonists (VKA)** (**level of evidence: high**), **rivaroxaban** (**level of evidence: high**), **apixaban** (**level of evidence: high**), **dabigatran** (**level of evidence: high**). **IPC or FIT combined with GEC** stockings are an equivalent alternative to LMWH (**level of evidence: high**) for those surgeons or anesthetists concerned about bleeding either in all or in certain patients. 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 five-week period of risk. **Desirudin** is approved for short-term prophylaxis in approximately 20 European countries and the USA and can be used in patients with HIT (**level of evidence: high**).

**LMWH combined with IPC** is more effective than either prophylactic modality used alone and should be considered in all cases (**level of evidence: high**).

**Prophylaxis with LMWH should be initiated either before or after operation depending on the adopted regimen (level of evidence: high). 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) or fondaparinux (level of evidence: low) (extrapolation from a hip fracture trial).**

### (C) ELECTIVE KNEE REPLACEMENT

#### The risk

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

#### Prophylactic methods and recommendations

##### General considerations

IPC is effective in patients having TKR (RR 0.27; 95% CI 0.14 to 0.49) (Table 6.VIII). One small study demonstrated that IPC reduced the incidence of asymptomatic DVT from 65% to 6%.<sup>63</sup> A subsequent study found IPC to be more effective than aspirin.<sup>141</sup> IPC was found to be less effective than coumadin for preventing venographically detected DVT (32% *vs.* 19%).<sup>179</sup> **FIT** was also effective in two studies<sup>69, 130</sup> but showed inferiority when compared to LMWH in two other studies<sup>137, 138</sup> (Table 6.VIII).<sup>180</sup> In a recent study involving 136 patients having THR or TKR, in which a mobile IPC device was also compared to LMWH, the incidence of postoperative venographic DVT was found to be 6.6% in

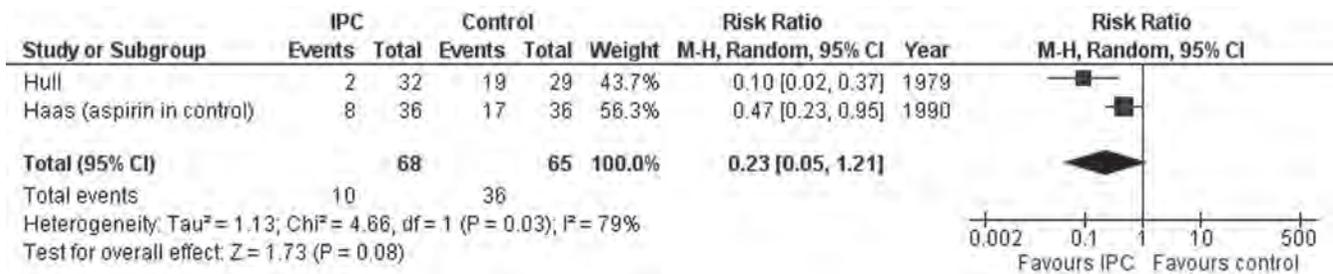


Figure 6.2.—Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with phlebography or duplex ultrasound\* (Fisher *et al.*, 1995)<sup>197</sup> in randomised controlled studies of patients having knee replacement.<sup>63, 141</sup>

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.<sup>173</sup>

A RCT performed in 1992 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).<sup>181</sup> Subsequent studies demonstrated that LMWH was more effective than LDUH (RR 0.75; 95% CI 0.58 to 0.92)<sup>182, 183</sup> or warfarin (RR 0.68; 95% CI 0.62 to 0.76) (Figure 6.3).

**Fondaparinux** (2.5 mg once daily starting 6 h after surgery) was more effective than enoxaparin (30 mg b.d. starting 12-24 h after surgery) in one study.<sup>184</sup> 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. The efficacy of fondaparinux was confirmed in a meta-analysis<sup>185</sup> which included the above study and three other randomized controlled trials comparing fondaparinux with enoxaparin in patients having orthopedic surgery other than TKR.

**Rivaroxaban** is a new oral direct anti-Xa inhibitor. Two studies (RECORD3 and RECORD4) have compared rivaroxaban with enoxaparin in patients having TKR. In RECORD3 study which involved 2531 evaluable patients, both prophylactic regimens were given for 10-14 days. The primary endpoint of total VTE was 18.9% enoxaparin and 9.6% for rivaroxaban, (P<0.001). The incidence of venographic DVT was 2.6% in the

enoxaparin group and 1% in the rivaroxaban group (absolute risk reduction, 1.6%; 95% CI, 0.4 to 2.8; P<0.01 for non-inferiority). There was no significant difference in the incidence of major and non-major clinically relevant bleeding in the two groups.<sup>186</sup> RECORD4 study,<sup>187</sup> compared the efficacy and safety of rivaroxaban with the commonly used North American regimen of enoxaparin 30 b.d. daily until day 11 to 15 when bilateral venography was performed. The incidence of 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** is another new oral direct Xa inhibitor. Two randomized double blind control studies compared apixaban with enoxaparin. In the first study, the overall rate of primary events was much lower than anticipated (primary efficacy outcome 9% with apixaban and 8.8% with enoxaparin) and apixaban did not meet the non-inferiority criteria compared with enoxaparin 30 mg b.d. in the prevention of VTE after TKR.<sup>188</sup> However, in the second study it demonstrated superiority against enoxaparin 40 mg once daily (primary efficacy outcome 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.<sup>189</sup>

**Dabigatran** is a new oral direct inhibitor of thrombin. Two double-blind non-inferiority trials evaluated the efficacy and safety of dabigatran in patients having elective TKR. In the first study (RE-MODEL) there were three groups of patients receiving dabigatran 150 mg, 220 mg or enoxaparin 40 mg for 6-10 days when

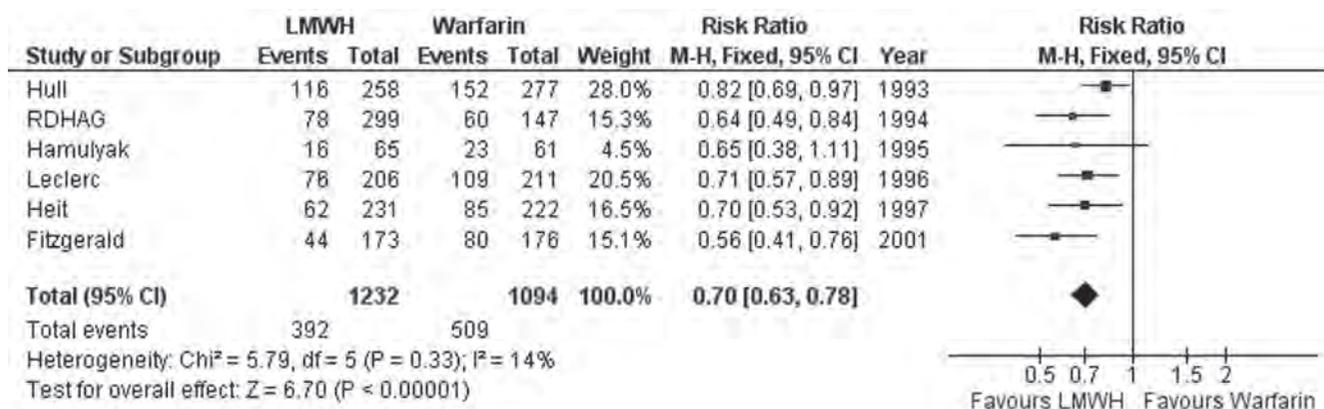


Figure 6.3.—Effect of warfarin *versus* low molecular weight heparin (LMWH) in the prevention of DVT diagnosed by surveillance with phlebography in patients having knee surgery.<sup>1, 65, 142-145</sup>

bilateral venography was performed. The primary 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 *versus* enoxaparin).<sup>190</sup> In the second study (RE-MOBILIZE), there were also three groups of patients receiving dabigatran 150 mg, dabigatran 220 or enoxaparin 30 mg b.d. administered for 12-15 days (median 13 days).<sup>191</sup> 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. Among 1896 patients, dabigatran 220 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 trials have compared combined modalities with LMWH. In the first study<sup>170</sup> in which 131 patients having THR and TKR, the combination of LMWH plus IPC was more effective than LMWH plus GEC stockings. In the subgroup of patients having TKR 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 (DVT incidence 6.6% *versus* 19.5%; P=0.018).<sup>171</sup> In the third study involving 1803 patients having various orthopedic operations the combination of LMWH plus IPC was also more effective than LMWH (DVT incidence 0.4% *versus* 1.7%). In the subgroup of 133 patients having TKR, the incidence of DVT was 3.8% in the combined modalities group and 7.4% in the LMWH group (P<0.038)<sup>172</sup> (see section on combined modalities).

#### DURATION OF PROPHYLAXIS

The effect of extending prophylaxis using LMWH to 30-42 days beyond hospitalization on symptomatic DVT in patients having TKR is less (OR 0.74; 95% CI 0.26 to 2.15; P>0.05) than in patients having THR (OR 0.33; 95% CI 0.19 to 0.56; P<0.05) as shown by a systematic review.<sup>192</sup>

#### Recommendations

**LMWH** (initiated and dosed according to the manufacturer's recommendations) (**level of evidence: high**), **warfarin** (although less effective) (**level of evidence: high**), **rivaroxaban** (**level of evidence: high**), **apixaban** (**level of evidence: high**), **dabigatran** (**level of evidence: high**) and **fondaparinux** (**level of evidence: high**). **IPC** is an alternative option (**level of evidence: moderate due to small study size**). **LMWH combined with IPC** is more effective than LMWH prophylactic modality used alone and should be considered in all cases (**level of evidence: high**).

## (D) HIP FRACTURE SURGERY

### The risk

Patients having hip fracture surgery have the highest rates of DVT (46-60%)<sup>81, 193, 194</sup> and fatal PE (2.5-7.5%)<sup>126, 194, 195</sup> (Tables 6.I, 6.III, and 6.IV). The VTE risk period lasts for 2-3 months after hip fracture surgery in spite of common short-term prophylaxis<sup>20, 117</sup> and the 90-day risk of overall death is 13%.<sup>196</sup> After hip fracture, the risk is greater than the standardized mortality, the majority dying of vascular events despite the fact that most patients receive some form of short-term prophylaxis.<sup>38, 124</sup>

### Prophylactic methods and recommendations

#### General considerations

Because the risks of DVT and PE including fatal PE are high in patients with hip fracture (Tables 6.I, 6.III, and 6.IV), prophylaxis should start as soon as possible after diagnosis and should be the same as that recommended for elective hip surgery.

Reduction in asymptomatic DVT has been demonstrated by **IPC** (RR 0.2; 95% CI 0.07 to 0.55)<sup>140</sup> and **FIT** in combination with **GEC**<sup>139</sup> (RR 0.32; 95% CI 0.32 to 0.67) (Table 6.VIII). In the most recent study,<sup>197</sup> 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.

A meta-analysis<sup>114</sup> 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 6.VI) but the observed reduction in the risk of PE is substantial (RR 0.4; 95% CI 0.22 to 0.71) (Table 6.VII). In a randomized, placebo-controlled trial of patients undergoing surgery for hip fracture (13356 patients) or for elective hip or knee arthroplasty (4088 patients), aspirin in a dose of 160 mg daily started preoperatively was used as the primary prophylactic agent for 35 days. 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 6679 patients assigned aspirin compared with 165 (2.5%) of 6677 patients assigned 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.<sup>163</sup> Since other methods are more effective, aspirin on its own is not recommended for routine thromboprophylaxis.

Several studies performed in the 1970s demonstrated that **LDUH** was effective in reducing asymptomatic DVT, as reported in an overview<sup>115</sup> (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.<sup>115</sup>

**LMWH** has been assessed against placebo,<sup>53, 198</sup> **LDUH**,<sup>199</sup> danaparoid,<sup>200</sup> high dose (40 mg enoxaparin) **LMWH**<sup>201</sup> and fondaparinux.<sup>202</sup> **LMWH** has been found to be equally effective as **LDUH** without increase in hemorrhagic complications.<sup>203</sup>

Three randomized controlled trials have demonstrated that **VKA** are effective in preventing asymptomatic DVT with a 61% RR reduction for DVT and 66% for proximal DVT, compared with no prophylaxis.<sup>81, 204, 205</sup> The increase in hemorrhagic complications reported varied from 0% to 47% without any increased bleeding in the most recent trial.<sup>81</sup>

**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).<sup>202</sup> There was no difference in major bleeding 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.<sup>206</sup> 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.<sup>207-210</sup> The incidence of preoperative DVT as shown by venography can be as high as 62% for all DVT and 14% for proximal DVT when the delay is 48 h or more.<sup>210</sup> Thus, it is strongly recommended that if surgical delay is anticipated, prophylaxis is commenced as close to the fracture as possible. Prophylaxis should be restarted once postoperative hemostasis has been achieved.

None of the new oral anticoagulant regimens shown to be effective in elective hip and knee replacement, have been tested in the hip fracture population.

### *Recommendations*

**LMWH** (initiated and dosed according to the manufacturer's recommendations) (**level of evidence: high**), **fondaparinux** (**level of evidence: high**), **adjusted dose VKA (INR range 2-3)** (**level of evidence: high**) or **LDUH** (**level of evidence: high**). **IPC** or **FIT combined with GEC** should be used when there are contraindications for pharmacological prophylaxis (**level of evidence: low**). **If surgery is likely to be delayed, prophylaxis should be initiated with LMWH or IPC or FIT plus GEC as close to the fracture as possible (level of evidence: low)**. Prophylaxis should be provided for **4-5 weeks after surgery (level of evidence: high)**.

## **(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%.<sup>20</sup> Meta-analysis of six studies<sup>104, 105, 107-109, 211</sup> by Ilahi in 2005 shows that asymptomatic DVT occurs in approximately 9.9%; however there is a very large range: ultrasound demonstrates rates from 6%<sup>212</sup> to 16%<sup>109</sup> and venography from 3.1%<sup>211</sup> to 17.9%.<sup>104</sup>

## **Prophylactic methods and recommendations**

### *General considerations*

In a meta-analysis of four randomized studies in which different **LMWHs** given for 5-7 days,<sup>213</sup> 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. A recent study involving 1,317 patients compared LMWH with GEC.<sup>214</sup> The three-month cumulative incidence of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, 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 clinically relevant bleeding events was 0.3% in the stockings group, 0.9% in the seven day LMWH group (not significant).

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.<sup>67</sup> 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: low**).

### RECOMMENDATION FOR ARTHROSCOPIC SURGERY (E.G., LIGAMENT RECONSTRUCTIONS):

**LMWH** starting before or after surgery (**level of evidence: moderate**) or **IPC** in the presence of contraindications to LMWH are recommended (**level of evidence: low**) 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 6.I) <sup>94-97, 99, 215</sup> and carry a risk of clinical PE in the range of 0.4-2.1%.<sup>196</sup> A recent 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.<sup>216</sup> 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 must be instituted. The risk of compartment syndrome, exacerbated by chemical thromboprophylaxis, must be considered in tibial fractures.

In one study 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 a **LMWH** group.<sup>96</sup> It was reduced from 4% in the control group to zero in the **LMWH** group in another study of 339 patients.<sup>97</sup> Considering both studies the RR was 0.21 (95% CI 0.09 to 0.49)

In patients with lower leg fractures, the five week incidence of venographic DVT was reduced from 18% in the control group to 10% in the **LMWH** group in one study (N.=293),<sup>215</sup> from 13% to 11% in another (N.=150)<sup>99</sup> and from 13% to 9% in a third study (N.=238).<sup>101</sup> In none of the three studies was the effect of LMWH on DVT significant (P>0.05). However, in the subgroups of patients having Achilles tendon repair the incidence of DVT was reduced from 21% to 6% in the first study <sup>215</sup> and from 29% to 10% in the second.<sup>99</sup> However, in a more recent study <sup>100</sup> involving 93 patients LMWH was ineffective (28% vs. 21%). More effective methods are needed in well-defined groups of patients.

A Cochrane review of the 1,490 randomised patients concluded an odds ratio of 0.49 for **LMWH** (95% CI=0.34 to 0.72) which supports a significant risk reduction for patients immobilized in plaster.<sup>217</sup> Furthermore, symptomatic VTE was also significantly reduced (OR 0.16; 95% CI 0.05 to 0.56). Complications were not increased in the LMWH group.

## Recommendations

Currently available data based on a mixture of different types of injury suggest that **routine LMWH prophylaxis** should be considered for isolated limb trauma in the absence of contraindications (**level of evidence: moderate**). The drug will need to be administered in the outpatient setting until the patient is weight bearing.

## (G) MULTIPLE TRAUMA

### The risk

The incidence of DVT in patients who have sustained major trauma is in excess of 50% <sup>60, 61, 218-221</sup> (Table 6.I) and PE is the third leading cause of death in those who survive beyond the first day.<sup>60, 222-224</sup> The risk is particularly high in patients with spinal cord injury, pelvic fracture and those needing surgery.<sup>60, 61, 225-227</sup>

## Prophylactic methods and recommendations

### General considerations

Patients with multiple injuries have a particularly high risk for VTE. The tissue factor released by multiple injuries is potentiated by the likely surgical intervention and the subsequent prolonged immobility<sup>225</sup> which produces marked venous stasis. Routine venography has shown a DVT frequency of 58% in these patients.<sup>60</sup>

Well-designed studies in this area are few and thromboprophylaxis has to be assessed according to the risk for bleeding. However, in the absence of intracranial bleeding and when bleeding is under control, **LMWH** (enoxaparin 30 mg b.d.) started within 36 h of injury has been shown to be more effective than **LDUH** (5 000 IU b.d.).<sup>218</sup> LMWH reduced the incidence of venographic DVT 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.<sup>220, 228</sup> A study comparing nadroparin fixed daily dose *versus* a weight-adjusted dose did not demonstrate any significant difference (0% *vs.* 3% DVT).<sup>229</sup>

Five randomized controlled trials 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 DVT reduction from 11% in the control group to 6% in the **IPC** group was not significant ( $P > 0.05$ ).<sup>197</sup> In the second, which involved 149 patients, **IPC** was compared with **FIT** with an incidence of DVT of 6% and 21%, respectively ( $P < 0.02$ ).<sup>230</sup> **IPC** or **FIT** were compared with enoxaparin 30 mg b.d. in the third study involving 372 patients with an incidence of DVT of 0.8% in the enoxaparin group, 2.5% in the **IPC** group and 5.7% in the **FIT**.<sup>231</sup> The two most recent studies compared **LMWH** with **IPC** in 442 and 120 trauma patients.<sup>232, 233</sup> In these studies the incidence of DVT was 0.5% and 6.6% in the **LMWH** groups with 2.7% and 3.3% in the **IPC** groups, respectively. Thus, mechanical methods are attractive if chemical prophylaxis is contraindicated.

**RCT** of the use of **IVC** filters to prevent **PE** in trauma patients in the absence of DVT have not been performed. A recent systematic review of seven observational studies suggested a potential

reduction in **PE** but an associated 2% to 6% incidence of complications (**IVC** occlusion, filter migration and thrombosis at the insertion site).<sup>234</sup>

### Recommendations

**LMWH** starting as soon as bleeding risk is acceptable (**level of evidence: high**) or **IPC** in the presence of contraindications to **LMWH** (**level of evidence: high**) 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**).

The use of **IVC filter** for primary prevention of **PE** when **LMWH** or **IPC** are contraindicated is not recommended (**level of evidence: low**).

## (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 for different prophylactic methods. The incidence of DVT detected by routine venography in the absence of prophylaxis has been found to be 18% (Table 6.I).<sup>103, 235</sup> A review of studies on complications in patients having spinal fusion reported a 3.7% incidence for symptomatic DVT and 2.2% for **PE**.<sup>236</sup>

## Prophylactic methods and recommendations

### General considerations

Two small randomized controlled studies, one comparing no prophylaxis with **LDUH**<sup>237</sup> and the other with **enoxaparin**<sup>238</sup> demonstrated that prophylaxis reduces the incidence of asymptomatic DVT from 20% and 10% respectively to 0%.

## Recommendations

**Mechanical method: IPC (level of evidence: low); drug: LMWH (level of evidence: low); initiation: before operation for IPC or after operation for LMWH; duration: during hospitalization (level of evidence: low).**

### (I) SPINAL CORD INJURY

#### The risk

In the absence of prophylaxis the incidence of silent DVT is of the order of 35% (Table 6.I). In this group of patients, PE is the third leading cause of death.<sup>239, 240</sup> In a series of 1649 patients undergoing rehabilitation, symptomatic DVT occurred in 10% and PE in 3%.<sup>241</sup>

#### Prophylactic methods and recommendations

##### General considerations

Three studies have compared **LDUH** with placebo.<sup>90, 91, 242</sup> Compared with controls, LDUH was associated with a non-statistically significant reduction in the number of DVT (20% vs. 29.4%; OR 0.55; 95% CI 0.11 to 2.64, P=0.46).<sup>243</sup> Five studies have compared LDUH with **LMWH**.<sup>244-248</sup> A meta-analysis comparing LDUH with LMWH has 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 reduction in the rate of total PE (3.1% vs. 9.2%; OR 0.29; 95% CI 0.09 to 0.95; P=0.04).<sup>243</sup> 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).

When a **combination of LDUH with IPC** was compared with LMWH in a randomized controlled study,<sup>247</sup> results shown by routine venography were equally poor (63% vs. 66%). It appears that patients with spinal cord injury are not only at high risk for VTE but also a highly resistant group to prophylactic measures. Further studies are needed.

## Recommendations

**LMWH and/or LDUH (level of evidence: moderate) and LMWH plus IPC (level of evidence: low); initiation: IPC and GEC on admission and LMWH when bleeding risk is acceptable (level of evidence: low); duration: LMWH and IPC for three months and continuation with GEC indefinitely (level of evidence: low).**

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# 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.<sup>1</sup> Some patients have additional injuries to other organs or comorbid 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 7.I).<sup>2-5</sup> Symptomatic VTE occurs in 0.2% to 7% of patients.<sup>3, 6, 7</sup>

## Prophylactic methods and recommendations

### General considerations

A recent survey carried out in the USA showed that most centers used VTE prophylaxis, mostly in the form of combined mechanical (intermittent pneumatic compression) and LDUH prophylaxis.<sup>8</sup> Faced with the lack of evidence-based data, prophylaxis has to be individually assessed as it is in multiple injured patients. Therefore, recommendations for burned patients are extrapolated from the latter group of patients.

In view of the potential renal impairment associated with burns, a LMWH which is eliminated mainly through the liver (*e.g.*, dalteparin) is preferable.

### Recommendations

**LDUH or LMWH (level of evidence: low) initiated as soon as it is considered safe to**

TABLE 7.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).

Patient groups	Number studies	Patients N.	DVT (weighted mean)	95% CI
<i>Burns</i>				
Wait <i>et al.</i> , 1990 <sup>3</sup>		71	14	
Wahl <i>et al.</i> , 2002 <sup>4</sup>		30	7	
Wibbenmeyer <i>et al.</i> , 2003 <sup>2</sup>		148	9	
Total	3	249	30 (12%)	8.6% to 16%

**do so and continued for as long as the patient remains at risk (level of evidence: low).** For patients at high risk of bleeding, mechanical thromboprophylaxis with **GEC and IPC** is recommended (**level of evidence: low**) if the burns do not involve the lower limbs. FIT is an alternative (**level of evidence: low**).

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# NEUROSURGERY

## The risk

In the absence of prophylaxis, the incidence of asymptomatic DVT in the 1970s and 1980s detected by the fibrinogen uptake test (FUT) was approximately 23%, with proximal thrombosis found in 5% (Table 8.I).<sup>1-9</sup> The prevalence of DVT after neurosurgery is high (13.5%-5/37), even when GEC is used.<sup>10</sup> The risk is particularly high (21-32%) in patients with glioma,<sup>11-15</sup> and persists for a year or more.<sup>11</sup>

## Prophylactic methods and recommendations

### General considerations

In a randomized controlled study involving 161 patients, **IPC** reduced the incidence of silent DVT from 23.5% in the no prophylaxis group to 1.5% in the test group (RR 0.07; 95% CI 0.009 to 0.49).<sup>3</sup> This efficacy was confirmed by a second study involving 95 patients where the incidence of silent DVT was reduced from 25% to 8.3% (RR 0.33; 95% CI 0.11 to 0.94).<sup>1</sup> In a third RCT, **IPC combined with GEC** reduced the incidence of silent DVT from 20% in the control group to 9% in the treatment group (RR 0.45; 95% CI 0.20 to 1.04).<sup>4</sup> In a recent RCT<sup>16</sup> involving 150 patients, the efficacy of calf compression using a new mechanical device plus GEC reduced the incidence of asymptomatic DVT to 4% compared with 18.7% in the control group that had GEC only (RR 0.21; 95% CI 0.05 to 0.75). In addition, it reduced proximal DVT

TABLE 8.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	Number of patients	DVT incidence (weighted mean)	95% CI
<i>Neurosurgery</i>				
Skillman <i>et al.</i> , 1978 <sup>1</sup>		48	11	
Cerrato <i>et al.</i> , 1978 <sup>9</sup>		50	16	
Turpie <i>et al.</i> , 1977 <sup>3</sup>		63	12	
Turpie <i>et al.</i> , 1985 <sup>5</sup>		68	12	
Turpie <i>et al.</i> , 1989 <sup>4</sup>		81	16	
Zelikovski <i>et al.</i> , 1981 <sup>8</sup>		20	10	
Total	6	330	77 (23%)	19% to 28%

from 8% to 2.7% and symptomatic DVT from 2.7% to 0%.

A RCT involving 100 patients compared LDUH with no prophylaxis.<sup>9</sup> 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.<sup>17</sup>

Two large RCT involving 604 evaluable patients compared the effect of **adding LMWH to GEC**.<sup>18, 19</sup> LMWH with GEC was more effective than GEC alone in reducing venographic DVT (17.9% vs. 28.9%) (RR 0.62; 95% CI 0.46 to 0.84), and it also reduced proximal DVT/PE (5.7% vs. 12%) (RR 0.48; 95% CI 0.27 to 0.83). The incidence of major hemorrhage was 3.4% in the

LMWH plus GEC group and 2.0% in the GEC group (RR 1.73; 95% CI 0.64 to 4.71)

In a prospective double-blind clinical trial, 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, but there was a 9.3% incidence of asymptomatic DVT, equal in both groups and mostly confined to the calf.<sup>20</sup>

An early meta-analysis of four randomized controlled studies (827 patients), three of which involved **LMWH** and one **LDUH**, demonstrated reduction in the incidence of all DVT from 29% in the control 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).<sup>21</sup> Major hemorrhage increased from 2.5% to 3.1% (RR 1.23; 95% CI 0.60 to 2.53). Overall bleeding 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.

Another meta-analysis of 18 RCT performed in 2008 showed that **LMWH or IPC** devices were effective in reducing DVT (LMWH: RR 0.60; 95% CI 0.44 to 0.81; IPC: RR 0.41; 95% CI 0.21 to 0.78).<sup>22</sup> However, the pooled rates of intracranial hemorrhage and minor bleeding were higher in the heparin therapy group (2.1% with heparin vs. 1.1% with mechanical methods).

A recent meta-analysis performed in 2011 reported results of six RCT involving 1170 patients undergoing elective cranial neurosurgery.<sup>23</sup> The pooled RR was 0.58 (95% CI 0.45 to 0.75) in favor of heparin. 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 (approximately 35 of which were proximal deep vein thrombosis or pulmonary embolism and 9-18 of which were symptomatic), whereas seven intracranial hemorrhages and 28 more minor bleeds occurred. The authors concluded that heparin prophylaxis for patients undergoing elective cranial neurosurgery 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.

## Recommendations

Recommendations for prophylaxis in this group consist of the use of **IPC in all patients with or without GEC stockings (level of evidence: high)**. Addition of **LMWH** is associated with an increase of efficacy (**level of evidence: high**). However, the use of, and timing of LMWH administration should be individualized because of increased risk of bleeding.

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# MEDICAL PATIENTS

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## The risk

Acute medical conditions such as stroke, congestive heart failure, respiratory disease, infections or myocardial infarction are associated with a high risk of VTE (Table 9.I).<sup>1, 2</sup> Infection, erythropoiesis-stimulating agents and blood transfusion during the 90 days prior to hospitalization for acute VTE are recently identified risk factors not yet included in risk prediction algorithms.<sup>3</sup> The patients' overall risk is affected by reduced mobility, cancer with or without chemotherapy (see below), or by patient-related risk factors such as prior VTE, advancing age, obesity and coagulation disorders which can be either inherited or acquired.<sup>4-9</sup>

The previous oversimplified "silo" thinking about VTE as a venous disease with red thrombus versus coronary artery disease as an entirely separate arterial disease with white thrombus is outmoded. Four years after acute PE, fewer than half of those who initially survive will remain free of myocardial infarction, stroke, peripheral arterial disease, recurrent VTE, cancer, or chronic thromboembolic pulmonary hypertension.<sup>10</sup>

VTE and atherothrombosis share a common pathophysiology, which includes inflammation, hypercoagulability and endothelial injury.<sup>11, 12</sup> 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 risk factors such as cigarette smoking, hypertension, diabetes and obesity, which are often modifiable overlap with risk factors for atherosclerosis.<sup>13</sup> In the Atherosclerosis Risk In Communities (ARIC) Study, C-reactive protein levels (a marker of inflammation) above the 90th percentile were associated

with a marked increase in VTE risk compared with lower percentiles.<sup>14</sup>

A high prevalence of DVT (28% to 33%) has been detected in medical intensive care patients in several studies.<sup>15-17</sup> In three large randomized trials involving acutely ill medical patients, the prevalence of symptomatic VTE ranged from 3.4% to 6.6%.<sup>18-20</sup> In hospitalized medical patients, asymptomatic proximal DVT has been shown to be associated with a higher mortality rate compared with those who have isolated calf DVT.<sup>21</sup>

Fatal PE is the leading cause of sudden death in hospitalized medical patients. Autopsy studies show that approximately 25% of patients dying from PE in general hospitals have had recent surgery and the rest were immobilized patients with medical illnesses.<sup>22</sup> Overall mortality in medical patients admitted to general hospitals is about 10%, and about one in 10 hospital deaths is due to PE.<sup>22, 23</sup> A population based case-cohort study estimated that in the absence of appropriate VTE prophylaxis, one of 20 hospitalized medical patients may suffer a fatal PE.<sup>24</sup>

In the IMPROVE Registry of 15,156 hospitalized medical patients, 45% of the 184 who developed VTE had postdischarge events. An evidence-derived risk assessment model from seven independent risk factors for VTE using this database included previous VTE, known thrombophilia, cancer, age greater than 60 years, lower limb paralysis, immobilization for at least one week or admission to an intensive or coronary care unit.<sup>25</sup> This model has been able to predict patients with a very high risk of VTE and has been validated in the large MAGELLAN database (Table 9.II).

A risk assessment model that may help identify medical patients at high risk of VTE and optimize the preventive strategies is the Padua Prediction Score,<sup>26</sup> which has been validated in

TABLE 9.I.—The frequency of all DVT in medical patients 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
<i>Stroke</i>				
Czechanowski and Heinrich 1981 <sup>79</sup>		41	23	
Dahan <i>et al.</i> , 1986 <sup>32</sup>		27	3	
Elias <i>et al.</i> , 1990 <sup>55</sup>		15	12	
McCarthy <i>et al.</i> , 1977 <sup>80</sup>		16	12	
McCarthy and Turner 1986 <sup>53</sup>		161	117	
Prins <i>et al.</i> , 1989 <sup>56</sup>		30	15	
Sandset <i>et al.</i> , 1990 <sup>57</sup>		50	17	
Turpie <i>et al.</i> , 1987 <sup>54</sup>		25	7	
Warlow <i>et al.</i> , 1972 <sup>81</sup>		30	18	
Total	8	395	224 (56%)	51% to 61%
<i>Patients in ICU</i>				
Moser <i>et al.</i> , 1981 (FUT) <sup>82</sup>		33	4	
Cade, 1982 (FUT) <sup>29</sup>		60	17	
Fraisse <i>et al.</i> , 2000 (Venography) <sup>16</sup>		85	24	
Total	3	178	45 (25%)	19% to 32%
<i>Myocardial infarction</i>				
Emerson and Marks, 1977 <sup>83</sup>		41	14	
Handley, 1972 <sup>84</sup>		24	7	
Nicolaidis <i>et al.</i> , 1971 <sup>85</sup>		51	8	
Warlow <i>et al.</i> , 1973 <sup>86</sup>		64	11	
Total	4	180	40 (22%)	16% to 28%
<i>General medical</i>				
Gallus <i>et al.</i> , 1973 <sup>27</sup>		15	7	
Belch <i>et al.</i> , 1981 <sup>28</sup>		50	13	
Prescott <i>et al.</i> , 1981 <sup>87</sup>		45	4	
Cade, 1982 <sup>29</sup>		67	7	
Dahan <i>et al.</i> , 1986 <sup>32</sup>		131	12	
Schonhofer & Kohler, 1998 <sup>88</sup>		196	21	
Samama <i>et al.</i> , 1999 <sup>18</sup>		288	43	
Oger <i>et al.</i> , 2002 <sup>89</sup>		234	14	
Total	8	1026	121 (12%)	10% to 14%
<i>Geriatric (&gt;65 years)</i>				
Dahan <i>et al.</i> , 1986 <sup>32</sup>	1	131	12 (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.

a large cohort of consecutive patients and has received a degree of acceptance (Table 9.III).

### Prophylactic methods and recommendations

#### General considerations

**Acutely ill medical patients.**—Three RCT performed in the 1970s and early 1980s, demonstrated that **LDUH** was effective in preventing asymptomatic DVT when compared with no prophylaxis.<sup>27-29</sup> 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.<sup>30, 31</sup> Subsequently, two randomized controlled studies demonstrated that LMWH was effective in preventing asymptomatic DVT when compared with no prophylaxis.<sup>18, 32</sup> 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.<sup>33</sup>

An international, multicenter, double-blind RCT using important VTE outcomes (combination of symptomatic DVT, symptomatic PE, asympto-

TABLE 9.II.—*IMPROVE* risk model with risk score in medical patients.\*

Score	Patients, % (N.)	3-month expected VTE risk <sup>a</sup> , %	Observed VTE rate <sup>b</sup> , % (number of VTE events)	Observed PE rate <sup>b</sup> , % (number of PEs)
0	27 (4029)	0.4	0.4 (14)	0.3 (11)
1	42 (6350)	0.6	0.6 (33)	0.3 (19)
2	16 (2420)	1.0	1.5 (31)	0.6 (13)
3	9 (1335)	1.7	1.6 (18)	0.8 (9)
4	5 (729)	2.9	4.8 (30)	2.8 (17)
5–10	2 (262)	7.2	8.1 (17)	3.8 (7)

\*Patients with a score of  $\geq 4$  have a symptomatic VTE event rate of 5.7%.

TABLE 9.III.—*Padua Prediction Score* (high risk of VTE:  $\geq 4$ ).

Baseline features	Score
1. Active cancer*	3
2. Previous VTE (with the exclusion of superficial vein thrombosis)	3
3. Reduced mobility <sup>o</sup>	3
4. Already known thrombophilic condition <sup>^</sup>	3
5. Recent ( $\leq 1$ month) trauma and/or surgery	2
6. Elderly age ( $\geq 70$ 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 $\geq 30$ )	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; <sup>o</sup>bedrest with bathroom privileges (either due to patients limitations or on physicians order) for at least three days; <sup>^</sup> carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

matic 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). 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).<sup>19</sup>

Four randomized controlled trials performed in the years 1996-2003, compared **one daily dose of LMWH with 12 or 8 hourly LDUH**.<sup>33-36</sup> Although none of the studies showed any advantage for LMWH for asymptomatic DVT on its own, a small advantage was apparent when the results were combined (4.24% vs. 5.77%) (RR 0.73; 95% CI 0.56 to 0.97).

A meta-analysis of seven trials performed in the year 2000, comparing prophylactic heparin treatment with a control (15095 patients) demon-

strated a significant decrease in symptomatic DVT and PE with risk reductions of 56% and 58%, respectively and without any significant difference in the incidence of major bleeding or death.<sup>39</sup> In the same paper, 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).<sup>37</sup>

The LIFENOX study was a large (8307 patients) multicenter study 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; 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).<sup>38</sup>

In a randomized double-blind trial<sup>20</sup> in 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). Symptomatic VTE occurred in five patients in the placebo group and none in the fondaparinux group (P=0.029). There were no PE in the fondaparinux group compared with five PE 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%) had died (P=0.073).

A meta-analysis of nine RCT (N.=19958) that compared the effects of pharmacological proph-

ylaxis with no prophylaxis in hospitalized medical patients was performed in 2007.<sup>39</sup> There was 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), non-significant 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; CI, 0.73 to 2.37). Anticoagulant prophylaxis had no effect on all-cause mortality.

A recent 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 heparin prophylaxis (LDUH, LMWH and fondaparinux) on PE and total mortality.<sup>40</sup> The authors found 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; 20717 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.

Despite evidence supporting DVT prophylaxis with LDUH, LMWH and fondaparinux, prophylaxis is underutilized in medical patients compared with surgical patients.<sup>1, 6, 41-43</sup> The exact reasons why VTE prophylaxis is so frequently withheld in high-risk patients are not known. Failure to implement VTE prophylaxis is a global problem. In the ENDORSE study, which was a global cross-sectional study, 68183 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%).<sup>44</sup> Among the 9257 US patients from 81 hospitals enrolled in ENDORSE, there was wide variation in VTE prophylaxis practices. More hospitals in the best

performing quartile compared with the lowest quartile had residency training programs (43% vs. 5%), a larger number of beds (277 vs. 140) and had adopted individualized hospital-wide VTE prophylaxis protocols (76% vs. 40%).<sup>45</sup>

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.<sup>46</sup>

All hospitalized medical patients should be assessed for risk of VTE and those at moderate (immobilised patients with active disease) or high risk (stroke, age >70, cardiac failure, shock, history of previous VTE, malignancy or thrombophilia) should receive prophylaxis.<sup>1</sup> There are diverse approaches to improve clinical effectiveness of VTE prophylaxis among hospitalized patients.<sup>47</sup> Computerized decision support with a single screen electronic alert can remind the responsible physician to order VTE prophylaxis.<sup>48</sup> A RCT showed that this approach has been shown to reduce the symptomatic VTE rate by more than 40%.<sup>43</sup> Multiscreen alerts may be more effective than single screen alerts.<sup>49</sup> Such electronic alert systems maintain their effectiveness over time.<sup>50</sup> For those hospitals without the resources to set up and maintain computerized systems, hospital staff can screen for at risk patients not on prophylaxis and alert the responsible physician with a telephone call or page.<sup>51</sup> 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%).<sup>52</sup>

#### 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.

#### ACUTE STROKE

*Acute ischemic stroke.*—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).<sup>53</sup> **A low molecu-**

**lar weight heparinoid** (danaparoid) was also effective (30.4% vs. 2.3%) (RR 0.14; 95% CI 0.03 to 0.64).<sup>54</sup> **LMWH** was effective in reducing asymptomatic DVT when compared with no prophylaxis in two small randomized studies<sup>55, 56</sup> but not in a third one,<sup>57</sup> 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).<sup>58</sup>

Two trials have compared **danaparoid**<sup>59, 60</sup> and one **LMWH** (enoxaparin)<sup>61</sup> with LDUH. A meta-analysis calculated 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).<sup>62</sup>

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 subcutaneously every 12 h for 10 days. The primary efficacy endpoint was a composite of symptomatic or asymptomatic deep vein thrombosis, symptomatic pulmonary embolism, or fatal pulmonary embolism. Enoxaparin reduced the risk of venous thromboembolism by 43% compared with unfractionated heparin (10% vs. 18%) (RR 0.57; 95% CI 0.44 to 0.76). The occurrence of any bleeding was 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.<sup>63</sup>

Two RCT investigated the effect of GEC on the incidence of DVT in immobile medical patients with stroke. In the first study (CLOTS trial 1),<sup>64</sup> 2518 patients who were admitted to 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% 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),<sup>65</sup> 1552 patients were randomized to thigh-length stockings and 1562 patients to below-knee stockings to wear while in the hospital. Ultrasonographers performed a duplex scan in 1406 patients (96% of survivors) in each treatment group between seven and 10 days after enrolment. 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 GEC in preventing DVT in moderate risk general surgical patients. 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.<sup>66</sup> This endothelial damage, combined with venous stasis and the hypercoagulable state as a result 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.

*Acute hemorrhagic stroke.*—In patients with acute hemorrhagic stroke, the value of LDUH or LMWH in the prevention of VTE has not been tested by RCT. A 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).<sup>67</sup>

#### DURATION OF THROMBOPROPHYLAXIS

Although VTE prophylaxis is mandated for moderate and high risk patients at the time of

hospital admission, the decision to continue VTE prophylaxis after hospital discharge remains difficult. During hospitalization, nurses and therapists “push” patients to ambulate and minimize immobilization. Patients often receive less physical therapy after discharge leading to a paradoxical worsening immobility and a presumed higher risk of VTE. A review of 1897 VTE episodes occurring in the Worcester, MA, USA healthcare system showed that 74% of patients suffered DVT or PE in the outpatient setting and not during hospitalization. A large proportion of patients with VTE (37%) had been hospitalized during the three months prior to developing acute VTE.<sup>68</sup> The median length of hospitalization had been four days.

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.<sup>69</sup> 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.<sup>70</sup> Overall in EXCLAIM, extended-duration enoxaparin significantly reduced VTE at 28 days from 4% 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%, 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. Because of the change in eligibility criteria during the trial, estimates of efficacy and safety for the overall trial population were difficult to interpret.

In the MAGELLAN trial involving 8101 acutely ill medical patients,<sup>71</sup> extended duration of prophylaxis with rivaroxaban for 35 days was tested against enoxaparin for 10 days followed by

placebo. 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; 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 ADOPT trial involving 4495 evaluable acutely ill medical patients, apixaban 2.5 mg b.d. administered orally for 30 days was compared with enoxaparin 40 mg daily administered for six to 14 days.<sup>72</sup> 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).

### *Recommendations*

All acutely ill medical patients should be routinely assessed for risk of VTE and considered for thromboprophylaxis. In particular, patients over the age of 40 with acute medical illness and/or reduced mobility with one of the following morbidities: acute 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, thrombophilia, rheumatic disease, ischemic stroke or acute myocardial infarction should be considered for prophylaxis. Patients with acute medical illness with lower limb paralysis or reduced mobil-

ity and one of the following risk factors: history of VTE, malignant disease or age over 75 should also be considered for prophylaxis.

For acutely ill medical patients prophylaxis with **LDUH 5000 IU b.d. or t.d.s. (Level of evidence: high) or LMWH (enoxaparin 40 mg o.d. or dalteparin 5000 U o.d.) (Level of evidence: high) for 6-14 days** are recommended. **Single daily doses of 2.5 mg of fondaparinux is an alternative (level of evidence: high).** 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. Extended duration of thromboprophylaxis may be considered in female patients, patients older than 75 years or severe immobility, but should be determined on an individual basis.

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**). This recommendation is based on extrapolation of data from trials in neurosurgical patients<sup>73-76</sup> and surgical patients<sup>77</sup> and one randomized controlled study in patients with ischemic hemorrhagic stroke.<sup>67</sup> For patients who are not candidates for prophylactic anticoagulation, intermittent pneumatic compression appears cost-effective.<sup>78</sup>

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# CRITICAL CARE MEDICAL PATIENTS

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## The risk

The incidence of DVT in patients in the intensive care unit (ICU) ranges from 25% to 32%.<sup>1-3</sup> Most of these patients have several risk factors for VTE<sup>4,5</sup> and approximately 5% develop DVT prior to admission to the ICU.<sup>6-9</sup>

The patients pose a special challenge for VTE prophylaxis<sup>8,10,11</sup> because they often have multi-system disease which renders routine methods of prevention problematic. For example, thrombocytopenia, renal insufficiency or active bleeding (often gastrointestinal) may preclude the use of pharmacologic prophylaxis. Thus, it is paradoxical that this group of patients may not be able to safely or effectively use some of the standard prophylaxis measures.

## Prophylactic methods and recommendations

### General considerations

A randomized double-blind placebo controlled study in critically ill high risk patients demonstrated that **LDUH** is effective in reducing asymptomatic DVT from 29% in the control group to 13% in the heparin group (RR 0.37; 95% CI 0.28 to 0.5).<sup>2</sup>

In another study involving 223 patients mechanically ventilated for acute decompensated chronic obstructive pulmonary disease, LMWH reduced the incidence of DVT from 28% in the control group to 15.5% in the LMWH group (RR

0.55; 95% CI 0.3 to 0.99) without any difference in adverse effects.<sup>3</sup>

A meta-analysis of two RCT<sup>12,13</sup> in a total of 562 trauma patients comparing IPC with LMWH has not shown any significant difference in VTE between the two methods for prophylaxis.<sup>14</sup>

A recent large multicenter RCT compared **dalteparin** (5000 IU plus a second placebo injection daily) with LDUH (5000 IU b.d.) in 3746 critically ill medical and surgical patients for the duration of their stay in ICU.<sup>15</sup> There was no significant difference in the rate of proximal DVT detected by ultrasound (5.1% vs. 5.8%), but there was a lower incidence of PE in the dalteparin group (1.3% vs. 2.3%) (RR 0.28; 95% CI 0.17 to 0.47). There was no significant difference in the rate of bleeding between the groups. Prophylactic doses of dalteparin did not appear to accumulate in patients with renal dysfunction.

### Recommendations

**LMWH** (dalteparin as per label) is recommended (**level of evidence: high**). For patients with contraindications to pharmacologic prophylaxis, the use of **GEC stockings with IPC** is an alternative (**level of evidence: low**). In the absence of contraindications, we suggest **combined mechanical plus pharmacologic prophylaxis (level of evidence: low)**. For patients with contraindications to prophylaxis, **surveillance with duplex scanning** is indicated (**level of evidence: low**).

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# CANCER PATIENTS

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## The risk

Venous thromboembolism (VTE) is an important and potentially fatal complication in patients with cancer, who have a sevenfold increased risk of VTE compared with patients without malignancy.<sup>1</sup> The results of a record-linkage study of 66329 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.<sup>2</sup> The risk of VTE varies with the type of malignancy. At six months after diagnosis of cancer, the highest rates reported were in patients with tumors of the bone (37.7 per 1000), ovary (32.6 per 1000), brain (32.1 per 1000), and pancreas (22.7 per 1000).<sup>2</sup> The risk for developing VTE in cancer patients undergoing surgery is approximately twice that for patients without cancer,<sup>3-5</sup> and PE has been cited as the most common cause of death among patients undergoing general, urologic or gynecologic surgery for cancer.<sup>6</sup> For patients with solid tumors, the risk of VTE is greater in the presence of metastatic disease compared with patients with only local disease.<sup>1, 2, 7</sup>

Studies consistently show a higher risk of VTE during the first six months of cancer diagnosis decreasing rapidly thereafter.<sup>1, 7, 8</sup> This early risk is likely to be related to the use of cancer treatments, especially chemothera-

py and hormonal therapy.<sup>1, 2, 9, 10</sup> In a breast cancer prevention trial where women at high risk for the development of cancer were randomized to placebo or the hormone therapy 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).<sup>11</sup> Corresponding rates for PE were 0.23 per 1000 and 0.69 per 1000 (RR 3.01; 95% CI 1.15 to 9.27). Increase in 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.<sup>12-17</sup> Rates for other tumor stages or types are summarized in Tables 11.I and 11.II.

The Stockholm surgical studies evaluated potential benefits from preoperative radiotherapy to reduce local recurrence in patients with rectal cancer undergoing operative intervention. Patients who received radiotherapy had a higher frequency of VTE within three months of therapy and surgery compared with those who did not (7.5% vs. 3.5%).<sup>18</sup> In a more recent cohort study of 66329 patients, individuals who underwent chemotherapy as initial treatment were at increased risk of VTE *versus* those who did not receive this therapy, whereas there was no such 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).<sup>2</sup>

Despite the use of venous thromboprophyl-

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

Study	Treatment	Number of patients	Patients with thrombosis (%)
<i>Node-Negative</i>			
Fisher 1990 <sup>14</sup>	T	1318	0.9
	Placebo	1326	0.15
	CMFT	768	4.2
	T	771	0.8
<i>Node-Positive</i>			
Levine 1988 <sup>13</sup>	CMFVP	102	8.8
	CMFVP + AT	103	4.9
Pritchard 1996 <sup>17</sup>	CMF + T	353	9.6
	T	352	1.4
Clahsen 1994 <sup>16</sup>	Perioperative FAC	1292	2.1
Rivkin 1994 <sup>55</sup>	No Rx	1332	0.8
	CMFVP + T	303	3.6
Fisher 1990 <sup>14</sup>	CMFVP	300	1.3
	T	295	0
Weiss 1981 <sup>12</sup>	ACT	383	3.1
	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.

laxis, patients with a malignancy remain at risk of a thrombotic event. In a *post-hoc* analysis of a randomized study in 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 postprophylaxis.<sup>19</sup>

There is a well-validated VTE risk assessment model for ambulatory cancer patients requiring chemotherapy that has been validated in multiple outpatient cancer groups.<sup>20</sup> Five predictive variables were identified in a multivariate model namely site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet count of  $350 \times 10^9/L$  or more, hemoglobin less than 100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents, leukocyte count more than  $11 \times 10^9/L$ , and body mass index of 35 kg/m<sup>2</sup> 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  $\geq 3$ ) category over a median of 2.5 months (C-statistic=0.7 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.

## Prophylactic methods and recommendations

### General considerations

#### SURGICAL PATIENTS

In surgical patients with malignancy, **LDUH** reduces the risk of DVT and fatal PE<sup>15, 21-24</sup> and **LMWH** is at least as effective as **LDUH**.<sup>25-29</sup> The intensity of perioperative 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,<sup>30</sup> whereas **administration three times a day was effective (RR 0.47; 95% CI 0.22 to 0.98)**.<sup>24</sup> In a study of 2070 patients, 65% of whom underwent laparotomy for malignant disease, two different doses of the LMWH (dalteparin sodium) were assessed.<sup>31</sup> The frequency of VTE was reduced from 14.9% in patients receiving 2500 anti-Xa U 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 perioperative bleeding complications.

**Continuation of LMWH** for four weeks after discharge home reduces the risk of asymptomatic DVT as demonstrated by venography from 13.8% to 5.5% (RR 0.36; 95% CI 0.16 to 0.79).<sup>32</sup> A systematic review comparing the relative efficacy and safety of four weeks' therapy *versus* limited duration LMWH thromboprophylaxis confirmed

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

Study	Tumor type	Patients (N.)	Cumulative incidence of VTE (%)	Follow-up
Alcalay <i>et al.</i> 2006 <sup>8</sup>	Colorectal	68142	3.1	2 years
Mandala <i>et al.</i> 2009 <sup>36</sup>	Advanced colorectal + chemotherapy	266	10.2	3.3 years
Caruso <i>et al.</i> , 2010 <sup>10</sup>	Lymphoma	18018	5.3	1-3 years
	Non-Hodgkin	997	6.5	1-3 years
	Hodgkin	2505	4.7	1-3 years
Tateo <i>et al.</i> , 2005 <sup>56</sup>	Ovarian	253	16.6 (6.4% during chemotherapy)	12 years
Brandes <i>et al.</i> , 1997 <sup>57</sup>	Malignant glioma	77	26	
Weijl <i>et al.</i> , 2000 <sup>58</sup>	Germ cell	179	8.4	
Chew <i>et al.</i> 2006 <sup>7</sup>	Prostate (localized)	33383	1.0	2 years
	Prostate (regional)	7041	1.3	2 years
	Prostate (remote)	3515	1.2	2 years
	Breast (localized)	27014	0.8	2 years
	Breast (regional)	13629	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)	22486	2.4	2 years
	Jacobson <i>et al.</i> 2009 <sup>59</sup>	Cervical cancer	436	11.7
Jacobson <i>et al.</i> 2005 <sup>60</sup>	Invasive cervical cancer + chemoradiation	48	16.7	≥8 months

this finding 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).<sup>33</sup>

In a randomized, double-blind study (CANBESURE), 625 patients admitted for abdominal or pelvic surgery for cancer received bempiparin once daily for eight days followed by either bempiparin or placebo for 20 days.<sup>34</sup> While extended thromboprophylaxis with bempiparin did not result in an improvement in the primary efficacy endpoint of venographically detected DVT, non-fatal PE and all-cause mortality (10.1% in bempiparin group *vs.* 13.3% in the placebo group) (RR reduction: 24.4%; 95% CI 23.7 to 53.8%; *P*=0.26), the incidence of major VTE (proximal DVT, non-fatal PE and VTE-related deaths) was decreased (0.8% *vs.* 4.6%; RRR 82.4%; 95% CI 21.5 to 96.1%; *P*=0.010) without any increase in major bleeding complications.

### Medical cancer patients

**LMWH** is effective for preventing thromboembolic disease associated with acute medical illness (see Section 9: Medical patients).

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.<sup>35</sup> The frequency of symptomatic VTE was reduced from 4.5% with placebo to 0.8% with warfarin (Fisher's exact test 0.038) (RR 0.14; 95% CI 0.02 to 1.18).

In a randomized, double-blind study in ambulatory patients with metastatic or locally advanced cancer, 1,150 patients received either the **LMWH nadroparin** (3800 IU anti-Xa once daily, SC) or placebo.<sup>36</sup> 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 recent large study compared subcutaneous semuloparin 20 mg once daily with placebo for ambulatory patients receiving chemotherapy for cancer.<sup>37</sup> The median treatment duration was 3.5 months. Venous thromboembolism occurred in 20 (1.2%) of 1608 patients receiving semuloparin, as 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% 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 a meta-analysis of three randomized trials of patients with lung cancer, concomitant treatment with **warfarin** was associated with an increased risk of bleeding (odds ratio 1.7; 95% CI 1.2 to 2.6) whereas no such association was apparent for **LMWH**.<sup>38</sup>

For bedridden hospitalized cancer patients, no specific studies have evaluated the potential benefits of thromboprophylaxis. Therefore, data derived from contemporary trials assessing the value of LMWH in the prevention of thromboembolic disease in acutely ill medical patients need to be extrapolated to the cancer population.

Prophylactic anticoagulation with **warfarin** reduced significantly the risk of DVT in patients treated with thalidomide for a variety of indications (5.5% vs. 23.7%,  $P=0.010$ ).<sup>9</sup> The role of warfarin among patients with cancer receiving thalidomide requires further investigation. The potential role of **LMWH** in prolonging survival among patients with cancer is currently under investigation.<sup>39</sup>

#### *Prevention of thromboembolic disease in patients with central venous catheters*

Historical data suggest that cancer patients with central venous catheters have a high frequency for development of VTE. More recent research suggests a low incidence of symptomatic catheter-related thrombosis, of 5% or less,<sup>40-43</sup> but reported rates of venographically detected

upper limb DVT in the absence of thromboprophylaxis, while highly variable, remain high (18%).<sup>41, 44</sup>

The use of **LMWH** (dalteparin sodium 2500 U once daily) in cancer patients with central venous catheters has been shown in one study to be effective in reducing venographic thrombosis from 62% to 6% (RR 0.04; 95% CI 0.01 to 0.42).<sup>45</sup> **Warfarin** (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).<sup>46</sup> However, more recent clinical trials evaluating **low dose warfarin, fixed dose warfarin or LMWH**<sup>40-42, 47-51</sup> as well as several meta-analyses<sup>44, 52-54</sup> have shown no benefit from 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. Further adequately powered studies are needed to determine the benefits and harms of new anticoagulant drugs in cancer patients with indwelling central venous catheters and in specific subgroups of patients.

#### *Recommendations*

In surgical patients with cancer, **LDUH** (5000 IU 8 h commenced prior to operation) (**level of evidence: high**) or **LMWH** (initiated and dosed according to manufacturer's recommendations) (**level of evidence: high**) should be used. In the postdischarge period prolonged thromboprophylaxis with LMWH (enoxaparin, dalteparin or bemivarin) for up to four weeks after operation **should be considered (level of evidence: moderate)**.

In ambulant non-surgical patients with advanced breast cancer receiving chemotherapy, the use of VKA to maintain an INR of between 1.3 and 1.9 may be considered (**level of evidence: moderate**). Semuloparin is an alternative (**level of evidence: high**).

For cancer patients hospitalized with acute medical illness, thromboprophylaxis should be based on the risk for VTE determined by the acute medical comorbidity. **LMWH** (initiated and dosed according to manufacturer's recommendations) or **LDUH** should be used (5000 IU 8 h) (**level of evidence: high**).

For cancer patients with central venous cath-

eters, routine use of thromboprophylaxis to prevent central venous catheter associated thrombosis is not recommended (**level of evidence: moderate**).

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# COMBINED MODALITIES IN SURGICAL PATIENTS

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## General considerations

Despite contemporary developments in pharmacology and biomedical engineering, VTE is not fully preventable and thus still 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 19<sup>th</sup> century.<sup>1</sup> 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.<sup>2</sup> While elastic stockings are effective in reducing further VTE rates achieved by perioperative antithrombotic prophylactic pharmacotherapy, as indicated in several places in this document, most modern studies have evaluated the role of the combination of IPC with pharmacological methods, and this will be the focus of this section.

A recent Cochrane review evaluated the efficacy of combined modalities (**IPC and pharmacological prophylaxis**: treatment group) against single modalities alone (control group) to pre-

vent PE and DVT in patients at high risk for VTE.<sup>3</sup> Eleven studies that included 7431 patients were identified, of which six were RCT. The studies evaluated orthopedic patients (N.=6), urology patients (N.=2), and general surgery, cardiothoracic and gynecology patients (N.=3). Compared with compression alone, combined modalities significantly reduced the incidence of both symptomatic PE (from about 3% to 1%) (OR 0.39; 95% CI 0.25 to 0.63) and DVT (from about 4% to 1%) (OR 0.43; 95% CI 0.24 to 0.76). Compared with pharmacological prophylaxis alone, combined modalities significantly reduced the incidence of DVT (from 4.21% to 0.65%) (OR 0.16; 95% CI 0.07 to 0.34). The studies were underpowered with regard to PE.

The comparison of compression plus pharmacological prophylaxis versus compression plus aspirin showed a non-significant reduction in PE and DVT in favor of the former group. Repeat analysis restricted to the RCT confirmed the above findings.

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

The results of the above meta-analyses endorse a recommendation that high risk patients should receive multimodal prophylaxis. Although most patients that used combined modalities in the studies reviewed were considered to be at high

risk for developing VTE, future studies on this topic should use the most recent and validated criteria 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**). Individual recommendations for specific groups of patients appear in the relevant sections of this document.

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# THROMBOPHILIA

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## *General considerations*

Thrombophilia is a congenital or acquired condition that disturbs the balance of hemostasis towards hypercoagulability, characterized by predisposition to a first episode of VTE and increased risk of recurrence. Thrombophilia is associated with blood alterations which are recognized in about 50 % of subjects who had experienced a VTE (Table 13.I).

## HEREDITARY THROMBOPHILIA

Hereditary deficiency in the natural coagulation inhibitors antithrombin (AT), protein C (PC) and protein S (PS) was the first to be recognized as being associated with VTE. Hereditary deficiency of AT was discovered by Egeberg in 1965 and hereditary deficiencies of PC and PS were discovered in the 1980s.<sup>1-3</sup> Factor V Leiden mutation related to activated protein C resistance (APCR) was identified as a cause of hereditary thrombophilia in 1994, and the mutation G20210A on the prothrombin gene was identified in 1996.<sup>4-6</sup> These biological risk factors are all transmitted as an autosomal dominant trait. Since then, significant increase of the levels of several clotting factors (*i.e.*, FVIII, FIX, FXI) and several single nucleotide polymorphisms (SNPs) at the genes coding blood coagulation factors and natural coagulation inhibitors have been identified. but they have a weak relationship with VTE.<sup>7</sup>

VTE in patients with hereditary thrombophilia is most frequently associated with a triggering

factor such as surgery, trauma, post-partum, 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 risk of VTE. Identification of risk factors on an individual basis and classification of patients in risk groups is of major importance to optimize thromboprophylaxis. Unprovoked VTE occurs more frequently in patients with hereditary thrombophilia than patients without thrombophilia (hazard risk ratio = 22).<sup>8</sup>

**The most common and most important** blood disorders related with hereditary thrombophilia are antithrombin deficiency, protein C deficiency, protein S deficiency, resistance to activated protein C which is due to the mutation of Factor V Leiden, G20210A mutation in the prothrombin gene (FII G20210A) and combination of these thrombophilias (the most frequent being mutations FV Leiden and FII G20210A).

Other disorders associated with thrombophilia are increasing concentration of coagulation factors (FVIII, FIX, FXI), deficiency of FXII, hyperhomocysteinemia and some forms of dysfibrinogenemias.

The presence of hereditary thrombophilia increases the risk of VTE on average about sevenfold.<sup>8</sup> A family history of VTE in asymptomatic patients with hereditary thrombophilia increases the risk of VTE.<sup>9</sup> However, all hematological disorders associated with hereditary thrombophilia do not induce the same increase of VTE risk.

TABLE 13.I.—*Classification of hematological disorders related with VTE according to their origin.*

Hereditary thrombophilia	Acquired thrombophilia	Thrombophilia of mixed or unknown origin
Antithrombin deficiency	Acquired deficiency of natural inhibitors of coagulation	High levels of factor VIII
Protein C deficiency		High levels of factor IX
Protein S deficiency	Antiphospholipid syndrome	High levels of factor XI
Factor V Leiden (FVL)		High levels of fibrinogen
Prothrombin 20210A		High levels of TAFI
Dysfibrinogenemia	Myeloproliferative syndromes and the presence of the mutation JAK2V617F	Low levels of TFPI
Factor XIII 34val		APC-resistance in the absence of FVL
Fibrinogen (G) 10034T	Nocturnal paroxysmal hemoglobinuria	Hyperhomocysteinemia
Non-O blood group		High levels of PCI (PAI-3)
JAK 2		
Factor IX Padua		

TAFI: thrombin-activatable fibrinolysis inhibitor; TFPI: tissue factor pathway inhibitor; PCI: protein C inhibitor; PAI-3, plasminogen-activator inhibitor-3.

**The prevalence** of the most frequent hematological disorders related with clinical thrombophilia is summarized in Table 13.II.<sup>8-19</sup>

**Clinical manifestations** of hereditary thrombophilia are heterogeneous. Venous thrombosis is frequently associated with DVT 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 newborn or skin necrosis at the start of vitamin K antagonist treatments. These rare manifestations are mainly related to homozygous deficiencies in PC or PS.<sup>20</sup> In contrast, the heterozygous type II HBS type of AT is not associated with an increased risk of VTE.<sup>21</sup> Thus, since the risk of VTE presents a significant variability among the various hereditary thrombophilic disorders, biological thrombophilias are classified as high or moderate risk for VTE (Table 13.III). 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<sup>22</sup> and risk factors for the first and recurrent episodes are not the same.<sup>10</sup>

#### ACQUIRED RISK FACTORS

The most important acquired hematological alterations related to hypercoagulability and VTE are antiphospholipid syndrome, acquired deficiency of natural inhibitors of coagulation, myeloproliferative syndromes, the presence of the mutation JAK2V617F and nocturnal par-

oxysmal hemoglobinuria. Some hematological disorders are of mixed or unknown origin (Table 13.I).

**The antiphospholipid syndrome (APS)** identifies a condition for increased risk of vascular occlusion and/or pregnancy complications. APS was defined in 2005 based on an international consensus. It is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPL) or anticardiolipin antibodies (aCL) or antibodies against the  $\beta$ 2 glycoprotein I (anti- $\beta$ 2GPI) of IgG or IgM class which are directed against proteins with an affinity for negatively charged phospholipids. 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 or three or more miscarriages before 10 weeks' gestation). Clinical and serological features necessary to diagnose APS are based on the revised Sapporo criteria<sup>23</sup> (Table 13.IV).

**The catastrophic antiphospholipid syndrome (CAS)** is a life-threatening medical condition with 50% mortality. Disseminated intravascular coagulation is present in 25% of cases. The diagnosis of CAS is based on 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. **The therapeutic principles for the CAS** are the following: 1) aggressive

TABLE 13.II.—Prevalence and odds ratio for VTE of the most common hereditary and acquired hematological alterations related to clinical thrombophilia.

	Prevalence in general population	Prevalence in patients with VTE	Relative risk for VTE compared to community controls	Reference
Heterozygous AT deficiency	0.02%	1%	10-30	Mahmoodi <i>et al.</i> 2010 <sup>8</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup> Rossi <i>et al.</i> 2011 <sup>9</sup>
Homozygous AT deficiency	not compatible with the life except the type II HBS			
Heterozygous PC deficiency	0.2-0.5%	1-3%	10	Mahmoodi <i>et al.</i> 2010 <sup>8</sup> Margaglione and Grandone 2011 <sup>19</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup> Rossi <i>et al.</i> 2011 <sup>9</sup>
Homozygous PC deficiency			very high risk	Vossen <i>et al.</i> 2005 <sup>18</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup>
Heterozygous PS deficiency	0.1-0.7%	1-2%	8	Mahmoodi <i>et al.</i> 2010 <sup>8</sup> Margaglione and Grandone 2011 <sup>19</sup> Vossen <i>et al.</i> 2004 <sup>11</sup> Vossen <i>et al.</i> 2005 <sup>18</sup> Rossi <i>et al.</i> 2011 <sup>9</sup>
Homozygous PS deficiency			very high risk	Vossen <i>et al.</i> 2005 <sup>18</sup>
FV Leiden heterozygous	2-7%	3-7%	3-7	Margaglione and Grandone 2011 <sup>19</sup> Vossen <i>et al.</i> 2004 <sup>11</sup> Vossen <i>et al.</i> 2005 <sup>18</sup> Rossi <i>et al.</i> 2011 <sup>9</sup>
FV Leiden homozygous	0.06-0.25%	-	80	Vossen <i>et al.</i> 2004 <sup>11</sup> Vossen <i>et al.</i> 2005 <sup>18</sup>
FII G20210A heterozygous	1-2%	3-5%	3-7	Margaglione & Grandone 2011 <sup>19</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup> Rossi <i>et al.</i> 2011 <sup>9</sup>
FII G20210A homozygous	Rare	Rare	10-20	De Stefano <i>et al.</i> 2004 <sup>17</sup> Vossen <i>et al.</i> 2005 <sup>18</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup>
Combined heterozygosity in FV Leiden and FII G20210A or other genetic risk factor (two or more defects)	Rare	Rare	10-20	Vossen <i>et al.</i> 2004 <sup>11</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup>
FVIII>150%	11%	25%	2	Jenkins <i>et al.</i> 2012 <sup>82</sup> Lijfering <i>et al.</i> 2009 <sup>10</sup>
Hyperhomocysteinemia	5%	10%	1.5	Vossen <i>et al.</i> 2005 <sup>18</sup>  Lijfering <i>et al.</i> 2009 <sup>10</sup>
Antiphospholipid syndrome	2%	4% - 15%	7	Pengo <i>et al.</i> 2012 <sup>16</sup>
JAK2 mutation		32% (mainly with splanchnic vein thrombosis)	53	Dentali <i>et al.</i> 2009 <sup>15</sup>
Dysfibrinogenemia	Very rare	Very rare	High risk	Travlou <i>et al.</i> 2010 <sup>14</sup> Kraiem <i>et al.</i> 2010 <sup>13</sup> De Moerloose <i>et al.</i> 2010 <sup>12</sup>

TABLE 13.III.—*Classification of the most common hematological causes of thrombophilia according to the risk for VTE.*

Strong risk factors for VTE	Mild risk factors for VTE
Antithrombin deficiency	FV Leiden heterozygous
Combined hereditary thrombophilias	FII G20210A heterozygous
Homozygous FV Leiden or FII G20210A	Heterozygous PC deficiency
Antiphospholipid syndrome	Heterozygous PS deficiency
Homozygous deficiency of PC	
Homozygous deficiency of PS	

treatment against possible precipitating factors such as antibiotics for bacterial infection; 2) effective anticoagulation with unfractionated heparin 5000 IU bolus then 18 IU/kg/h followed by vitamin K antagonists aiming an INR 2-3 (Table 13.V); 3) intravenous corticosteroids, such as methylprednisolone 1000 mg per day i.v. for 3-5 days then 1-2 mg/kg per day; 4) intravenous immunoglobulins 0.4 g/kg for 4-5 days and 5) plasma exchange to remove aPL, cytokines such as tumour necrosis factor- $\alpha$ , complement products and procoagulant factors.

Acquired deficiency of natural coagulation inhibitors (AT, PC or PS) is an independent risk factor for VTE. The causes of acquired deficiency of natural coagulation inhibitors are summarized in Table 13.VI.

#### THROMBOPHILIA AND ORAL CONTRACEPTION

Hormonal contraceptive methods include combined contraception with an estrogen and a progestin by the oral or non-oral (patch, vaginal ring) route, or progestin-only contraception by the oral or non-oral route (implant, injections, IUD with levonorgestrel or emergency contraception).

Combined contraception with a synthetic estrogen, ethinyl-estradiol and a progestin is associated with about a four-fold increased risk of VTE, whatever the route of administration.<sup>24-29</sup> The risk depends on the dose of the ethinyl-estradiol (lower risk for doses less than 50  $\mu$ g) and the type of progestin (lower risk for second generation such as levonorgestrel as compared with third generation or others such as desogestrel, gestodene, cyproterone acetate, drospirenone.<sup>24, 30-33</sup> Coagulation changes of decrease in PS and

acquired APC resistance observed during oral and non-oral combined contraception are more pronounced with third than second generation progestins, conferring a biological plausibility to the clinical risk of VTE.<sup>34-38</sup> Sex hormone binding globulin (SHBG), a marker of estrogenicity reflecting the balance between the estrogen and the progestin content, has been shown to be also a good marker of VTE, and the increase in SHBG is more important with third than second generation progestins associated with the same dose of ethinyl estradiol.<sup>39-41</sup> The risk of VTE is higher during the first year, and even more during the first three months of use. Different risk factors modulate the risk of VTE especially age above 40, previous VTE, immobilization, surgery, long travel, antiphospholipid syndrome and hereditary thrombophilia. The risk of VTE is increased in women with hereditary thrombophilia, (OR 4.88 to 15.62), depending on the type of thrombophilia.<sup>42</sup>

Combined contraception with estradiol valerate or 17 $\beta$  estradiol instead of synthetic estrogen is now on the market. The risk of VTE is not yet known and coagulation studies are scarce. While waiting for more information, caution is required since oral estradiol increases the risk of VTE in menopausal women.

Progestin-only contraception with oral levonorgestrel, norethisterone or desogestrel or IUD with levonorgestrel (and no estrogen) is neither associated with an increased risk of VTE nor with changes in coagulation parameters or SHBG levels.<sup>24, 28</sup> In 204 women with a history of VTE and/or hereditary thrombophilia, the risk of chlormadinone acetate contraception in 102 women was compared to the risk in 102 women without contraception and no significant risk was observed (RR 0.8, CI 95% 0.2-3.9).<sup>43</sup> Increased risk of VTE has been reported with injectable depot medroxyprogesterone.<sup>44</sup>

#### THROMBOPHILIA AND HORMONAL TREATMENT OF MENOPAUSE

Hormonal treatments for menopause include an estrogen and a progestin, which are different to those used for oral contraception. Conjugated equine estrogens or estradiol (estradiol valerate or 17  $\beta$  estradiol) administered by the oral route are associated with coagulation changes and

TABLE 13.IV.—*Diagnosis of antiphospholipid syndrome.*

Clinical criteria	laboratory criteria	Diagnosis of APS
Arterial thrombosis Venous thrombosis Vascular occlusion at unusual sites Complications of pregnancy	Lupus anti-coagulant Antiphospholipid antibodies Anticardiolipin antibodies Antibodies against $\beta 2$ 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

TABLE 13.V.—*Management of anticoagulation in patients with antiphospholipid syndrome.*

Venous and arterial thromboembolism	Acute myocardial infarction	High risk* patients with arterial thrombosis	Pregnancy morbidity alone	High risk** pregnancy morbidity. Catastrophic APS
VKA aimed at INR 2-3	VKA aimed at INR 3-4	VKA aimed at INR 3-4 plus aspirin 100 mg per day	Low dose heparin plus aspirin 100 mg per day	High dose heparin plus aspirin 100 mg per day plus plasmapheresis/immunoglobulins

\*Patients with confirmed positive laboratory tests, more than one clinical event, multiple lesions at cerebral imaging, acute myocardial infarction.  
\*\* high risk pregnancies are those in patients with previous thromboembolism or confirmed positive laboratory tests.

with an increased risk of VTE.<sup>45-49</sup> The risk is higher in the first year of use.<sup>47</sup> In a randomized study, treatment for menopause including oral estrogens was compared with a placebo in women with a history of VTE. The study had to be stopped due to the increased number of VTE events in treated women.<sup>50</sup> Factor V Leiden and FII G20210A mutation carriers are at increased risk when oral estrogens are administered.<sup>51, 52</sup> In contrast, estradiol by non-oral route (patch or gel) is not associated with an increased risk of VTE, especially when the progestin is natural progesterone.<sup>48, 53, 54</sup> These treatments with estradiol by non-oral route neither increase the risk in Factor V Leiden carriers nor the risk of recurrence in women with a history of VTE.<sup>55, 56</sup>

#### THROMBOPHILIA, PREGNANCY AND ASSISTED REPRODUCTIVE TECHNIQUES

Pregnancy is an important risk factor for VTE. The overall prevalence of VTE is approximately 0.3 to 1 per 1000 pregnancies with a higher risk in the post- as compared to the ante-partum period.<sup>57-61</sup> It is about 10 times higher than in women not pregnant and not using combined contraception.

Thrombotic events are mostly DVT of the left lower limb or PE.<sup>57, 60</sup> They are observed during the three trimesters of pregnancy with a tendency to an increase at the end of pregnancy.<sup>60, 62</sup> However,

cases have been reported during the first trimester, possibly related to risk factors such as thrombophilia or severe ovarian hyperstimulation.<sup>63</sup> The most important additional risk factors that may be associated with pregnancy are a history of VTE, age above 35 and thrombophilia.<sup>59</sup> Women with a history of VTE have a higher risk when they become pregnant, especially when the first episode was idiopathic or related to pregnancy or estrogen treatments. In contrast, the risk is lower if the first episode was related to a transitory risk factor such as surgery or prolonged immobilization by a plaster cast without any other risk factor,<sup>64-66</sup> A family history of VTE in a first degree relative before the age of 50 is also a risk factor. Thrombophilias are associated with an increased risk of VTE during post-partum but the risk during ante-partum differs. Heterozygous Factor V Leiden or FII G20210A has been reported to be associated with a very low risk for VTE in ante-partum women, and antithrombin deficiency with the highest risk of VTE.<sup>67-69</sup> Heterozygous AT deficiency and homozygous Factor V Leiden and FII G20210A mutations are very rare. In a review of different studies, homozygous Factor V Leiden or FII G20210A and even, heterozygous mutations had a higher risk than AT deficiency.<sup>70</sup> Results of this latter study do not correspond to the impression of professionals who have been in charge of such patients but might be explained by the lack of information on these rare thrombophilias and

TABLE 13.VI.—*Acquired deficiencies in coagulation inhibitors.*

Acquired AT deficiency	Acquired PC deficiency	Acquired PS deficiency
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
Uremic Hemolytic Syndrome	Adult Respiratory Distress Syndrome (ARDS)	Hemodialysis/plasmapheresis
Hemodialysis/plasmapheresis	Purpura fulminants	Estrogen therapy
Leucemia	Hemodialysis/plasmapheresis	Chemotherapy or hormone therapy for breast cancer
Estrogen therapy	vitamin K deficiency	Myeloproliferative syndromes
Treatment with L-asparaginase	Treatment with L-asparaginase or methotrexate or endoxan or 5-fluoracil	Sickle cell disease
		Pregnancy

the subsequent low power of evidence. Other risk factors associated with pregnancy are multiparity, twin or multiple pregnancy, obesity, immobilization or long travel.<sup>61</sup>

Women on long-term oral anticoagulant are at high risk of recurrence. They have either APS, are hereditary thrombophilia carriers and/or have had repeated episodes of VTE.

Antithrombotic treatment may be required for treatment of thrombosis in pregnant women or prevention of VTE in women at increased risk of thrombosis because of personal and/or family history of venous thrombosis and/or thrombophilia.

Assisted reproductive techniques (ART) are widely used in Europe and North America. The stimulation strategies used for ART tend to be adapted to patients' characteristics aiming to improve efficacy, comfort and tolerance. Personalisation of ART is also expected to reduce the risk of treatment-related complications. Cases of VTE have been reported during ART programmes but the incidence is still unknown. In retrospective studies, thrombosis was observed in 0.1% of cycles.<sup>71, 72</sup> There is a four-fold increase ante-partum for singleton pregnancies and a six-fold increase for twin pregnancies.<sup>59</sup> This figure represents a significant increase of VTE risk in women undergoing ART compared with age matched non pregnant women (0.06%) and a slight increase as compared to VTE incidence in pregnant women (0.13 VTE episodes per 100 deliveries). However, the absolute risk is relatively low. Severe ovarian hyperstimulation syndrome is associated with an increased risk of VTE that persists during the first trimester of pregnancy.<sup>63,</sup>

<sup>73</sup> Thrombophilia might further increase the risk of ATR-related VTE but sufficient information is lacking.<sup>73</sup> Thrombophilia has not been found to have an impact on ART outcome.<sup>74</sup>

In women participating in ART programs, administration of estrogens before stimulation induces a hypercoagulable state and may also act as a triggering factor for VTE. The presence of intrinsic risk factors such as comorbidities from autoimmune diseases, obesity or age significantly contribute to an increased VTE risk.

Detection of women at high risk for severe hyperstimulation syndrome and of women with risk factors for VTE prior to ART should reduce the number of thromboses.

#### TREATMENT OF AN ACUTE EPISODE OF VTE IN PREGNANT WOMEN WITH THROMBOPHILIA

Treatment of VTE during pregnancy in women with hereditary thrombophilia is usually no different to that for treatment of pregnant women without thrombophilia. LMWH is preferred to UFH because of their commodity (one or two subcutaneous injections per day as compared with two or three injections) and the lower risk of heparin-induced thrombocytopenia and osteoporosis. Enoxaparin (1 mg/kg body weight) or dalteparin (100 IU/kg) are administered every 12 hours. Tinzaparin (175 IU/kg) every 24 hours has been associated with rare cases of severe osteoporosis after prolonged administration at therapeutic doses, but because of the once-a-day administration, it is an alternative, preferably in women with no risk factors for osteoporosis.<sup>75, 76</sup> In AT deficient women, treatment with AT con-

centrates together with UFH or LMWH at sufficient doses to obtain an AT plasma level above 80% (starting at 30 to 50 u/kg body weight and repeating injections once a day) may be beneficial during the acute phase of VTE and at the time of delivery.<sup>77, 78</sup> However, the efficacy of this association has not been demonstrated.

#### PROPHYLAXIS OF VTE IN PREGNANT WOMEN WITH THROMBOPHILIA

Prophylaxis of VTE in women with thrombophilia depends on the type of thrombophilia and also on other risk factors such as age 35 years or more, personal or family history of VTE, obesity, immobilization during pregnancy, multiparity, twin pregnancy or assisted reproductive techniques.<sup>22, 59</sup> Prophylaxis consists of clinical surveillance, elastic compression stockings and/or LMWH administration. It is often decided on an individual basis because available data stem mainly from observational studies since conducting randomized studies is a very difficult task during pregnancy. The type of prophylaxis is often subject to discussion but some consensus exists for the following:

1. repeated screening with noninvasive tests for DVT, such as compression ultrasonography, is not recommended;
2. the higher risk of AT-deficient women is recognized by professionals although discussed in some studies;
3. women who are on long-term treatment are at high risk of recurrence;
4. elastic compression stockings are recommended during pregnancy and post-partum in all women with a history of DVT;
5. in women at risk of VTE, prevention of thrombosis should be planned before pregnancy and appropriate prophylaxis defined for pregnancy and the post-partum periods.

Women with inherited thrombophilia have an increased risk of thrombosis post-partum but the magnitude of the risk ante-partum is not similar for the different forms of thrombophilia. The risk is considered to be **very high** in the presence of heterozygous AT deficiency (except type II HBS) with personal history of VTE, women with long-term anticoagulant treatment, homozygous PC or PS deficiency; The risk is **high** in the presence of AT deficiency without personal history of

VTE, compound heterozygosity for Factor V Leiden and prothrombin 20210A or homozygosity for these mutations, combined thrombophilias with or without prior VTE. The risk is **moderate** in the presence of heterozygous PC or PS deficiency, heterozygous FV Leiden or prothrombin 20210A mutations.

Prevention of VTE during pregnancy is required in thrombophilic women in the following different situations: 1) inherited thrombophilia and family history of VTE but no personal history; 2) inherited thrombophilia and personal history; and 3) women with long-term anticoagulant treatment

#### THROMBOPHILIA SCREENING

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 treatment after VTE. Screening is greatly influenced by the age at first episode of VTE, its provoked or unprovoked characteristics and by the presence or absence of family history.

It is generally accepted that thrombophilia screening should not be performed in unselected patients.<sup>79, 80</sup>

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 idiopathic or provoked by pregnancy or estrogen treatment, in contrast to VTE provoked by a transient risk factor. However, all thrombophilias are not the same as they each have a different prevalence and severity. Confirmed hereditary AT deficiency is considered as a high-risk thrombophilia (except heterozygous AT type II HBS) but information is lacking since it is a rare finding, studies are small-sized and level of evidence is low. In contrast, heterozygous muta-

tions of Factor V Leiden or Factor II are associated with a lower risk but they are frequent. In addition, detection of a 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 independent of the presence of a thrombophilia, raising the question of the utility of its detection. However, VTE in the relative has to be proven and documented and, that is sometimes difficult to confirm.

When thrombophilia screening is indicated, only main hereditary thrombophilias associated with a two-fold or greater increased risk are searched for together with antiphospholipid syndrome (APS) which is the most important acquired risk factor for VTE.

### *Recommendations*

#### WHO SHOULD BE TESTED FOR THROMBOPHILIA?

All patients with a first episode of spontaneous VTE **are not** candidates for thrombophilia screening.

According to the literature and the accumulated experience of centers specialized on thrombophilia, screening for thrombophilia should be performed in the following patients (**level of evidence: moderate**):

1. patients with first episode of VTE under the age of 40;
2. patients with estrogen therapy or pregnancy as the only risk factor;
3. patients younger than 60 years with first unprovoked episode of VTE. It is suggested not to screen for thrombophilia if a significant triggering factor has been identified;
4. patients with recurrent VTE irrespective of the presence of risk factors;
5. patients with recurrent superficial vein thrombosis in the absence of varicose veins;
6. patients with VTE at unusual sites such as cerebral venous sinus, mesenteric or hepatic veins or under the age of 50 years;

7. patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related to sepsis;

8. asymptomatic first-degree relatives of individuals with proven symptomatic thrombophilia. This is particularly important for females in the childbearing age.

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

#### HOW TO TEST FOR THROMBOPHILIA?

The main tests to be performed are: blood cell count, prothrombin (PT) and activated thromboplastin time (APTT), coagulation inhibitors (AT, PC, PS), APC-resistance (if positive, Factor V Leiden mutation, or genetic study as at first), FII G20210A mutation, lupus anticoagulant detection, antiphospholipid and anti- $\beta_2$  GP1 antibodies

Non-clot based assays as PCR for detection of Factor V Leiden and Factor II mutation

can be performed at any time. Clotting-based assays may be influenced by the acute phase of thrombosis, pregnancy, oral contraception or by treatment with vitamin K antagonists (PC and PS assays). A precise diagnosis of AT deficiency is mandatory since heterozygous AT type II HBS is not associated with an increased risk of VTE.

AT assay performed at the time of diagnosis of the thrombotic episode may have an impact on the treatment (association of AT concentrates may be beneficial with heparin or LMWH).

Prolonged treatment with UFH slightly decreases the levels of AT. PC and PS deficiency should be controlled at least two months after cessation of vitamin K antagonist treatment.

Diagnosis of hereditary deficiency of AT, PC or PS should be only established after ruling-out acquired deficiency of these proteins.

#### 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 the anticoagulant treatment regarding the

choice of the anticoagulant drug and duration of treatment.

Observational studies indicate that anticoagulants are equally effective in patients with and without thrombophilia so that the presence of thrombophilia should not influence the choice of anticoagulant or the intensity of therapy (**level of evidence: low**).

The risk of recurrent VTE after stopping anticoagulant therapy may be higher in patients with thrombophilia, but not enough to influence whether anticoagulants should be stopped at three months or continued indefinitely.<sup>81</sup> However the risk of recurrent VTE after stopping the anticoagulant therapy is not uniform for all the 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 syndromes as compared to those with thrombophilia of moderate severity Table 13.II).

For the decision on the duration of anticoagulant treatment in patients with thrombophilia the general recommendations of the Chapter 14 (duration of anticoagulant treatment in VTE) are applied (**level of evidence: low**).

In patients with hereditary thrombophilia, prolongation of anticoagulant treatment should be considered after careful evaluation of the following factors (**level of evidence: low**):

- the number of the previous VTE episodes and their relation with triggering risk factors;
- the form of thrombophilia;
- bleeding risk factors;
- patients' preferences.

#### ORAL CONTRACEPTION IN WOMEN WITH THROMBOPHILIA

In women with hereditary thrombophilia with or without personal history of VTE, oral and non-oral combined contraception containing ethinyl-estradiol and a progestin of any generation is contra-indicated (**level of evidence: high**).

Oral combined contraception containing estradiol have the same contraindications until more information is provided (**level of evidence: moderate due the lack of information**).

Progestin-only contraception by oral route, IUD, implant or emergency contraception can be used rather than combined contraception (**level of evidence: moderate to high**).

Injectable depot contraception is to be avoided, if possible (**level of evidence: moderate** due to small number of studies)

Any other contraception (barriers, sterilization) is possible (**level of evidence: high**).

In women with family history of VTE before the age of 50 in first degree relatives,

thrombophilia screening is recommended before contraception (**level of evidence: high**).

In women with family history of severe VTE before the age of 50 in first degree

Relatives and without known hereditary thrombophilia, progestin-only contraception is suggested rather than combined contraception (**level of evidence: moderate to low**).

#### PREGNANCY IN WOMEN WITH THROMBOPHILIA

*Treatment.*—Treatment of VTE in pregnant women with thrombophilia is usually not different from VTE in pregnant women without thrombophilia (**level of evidence: high**). AT concentrates are suggested at the acute phase of thrombosis in women with hereditary deficiency in AT (**level of evidence: low**)

*Prevention.*—**Prophylaxis is recommended during six weeks post-partum in all thrombophilic women (level of evidence: high). In high-risk thrombophilic women without history of thrombosis before pregnancy, but with a positive family history, prophylaxis is recommended throughout pregnancy (level of evidence: high).** The dose is not well-defined but prophylactic (enoxaparin 40 mg or dalteparin 5,000 units once-daily) or intermediate (same doses every 12 hours) therapy can be used (**level of evidence: moderate**).

Laboratory surveillance is as follows: perform the usual control of platelet count during the first three weeks of treatment. It is not necessary to measure coagulation activation markers. Anti-Xa activity is not recommended (**level of evidence: moderate to low**). If anti-Xa is measured this should be checked once a month three to four hours after injection and the dose should be adjusted so that a level close to 0.3 u/mL is achieved (**level of evidence: low**).

**In moderate-risk thrombophilic women without history of thrombosis before pregnancy but positive family history, prophylaxis is not systematically recommended during ante-partum (level of evidence: moderate).** However, when associated risk factors are present (age  $\geq 35$ , immobilization, multiparity, gemellarity), the dose of LMWH is 40 mg or 5000 IU per day should be used, but monitoring of anti-Xa is not required (level of evidence: low).

**In high risk thrombophilic women with history of thrombosis before pregnancy, not on long-term VKA, LMWH (enoxaparin 40 mg or dalteparin 5000 U) is administered throughout pregnancy every 12 hours.** If the dose is adjusted, a peak anti-Xa level of 0.2 to 0.6 u/ml is the target. For improved comfort, the twice-daily regimen may be replaced by a once-daily regimen with tinzaparin after checking that the woman has no risk factors of osteoporosis (level of evidence: moderate). In AT-deficient women, it is important to start prophylaxis very rapidly as soon as the pregnancy is diagnosed (level of evidence moderate). AT concentrates at doses of 30 to 50 u/kg body weight may be recommended in AT deficient women the morning of delivery and two days after (level of evidence: low).

**In moderate risk thrombophilic women with history of thrombosis before pregnancy and not on long-term VKA, LMWH (enoxaparin 40 mg or dalteparin 5000 U) is administered once daily throughout or part of pregnancy without anti-Xa monitoring.**

**All thrombophilic women at very high risk of VTE and on long-term VKA should receive prophylaxis throughout pregnancy,** but the dose may differ according to the type of prior thrombosis, the delay between thrombosis and pregnancy and associated risk factors (weight-adjusted therapeutic dose or 75% of this dose).

Due to the lack of blind randomized clinical trials the recommendations for 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 and prolonged during the first trimester of pregnancy (level of evidence: moderate).

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# DIAGNOSIS AND ANTICOAGULANT TREATMENT\*

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## 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 have 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.<sup>1-4</sup> The sensitivity and specificity are in excess of 98% for DVT above the knee and in excess of 95% for DVT in the calf.<sup>5-10</sup> 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,<sup>11-13</sup> Khan<sup>14</sup> Constans<sup>15</sup> and Büller<sup>16</sup> 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.<sup>17</sup> 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 multiple 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 pretest probability can rule out DVT<sup>11, 12</sup> 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.<sup>3, 18-20</sup>

## Diagnosis of PE

The best diagnostic imaging test for PE is the chest CT scan.<sup>21</sup> 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 in order to avoid radiation in young people or the breast. A 16-slice multi-detector-row CT, for example, can image the entire chest with a single breath-hold of less than 10 seconds and can identify the entire range of PE from massive saddle embolism to submillimetre subsegmental PE in sixth-order pulmonary arterial branches.

\*For other more aggressive therapeutic options (thrombolysis, thrombectomy, treatment in cancer patients, IVC filters) please see subsequent chapters.

For suspected PE, the Wells Scoring System for PE relies upon a weighted point score for eight items obtained from the history and physical examination, and may assist in categorizing clinical likelihood into low, moderate, or high probability with a prevalence of PE of 1.3%, 16.2% and 37.5%, respectively.<sup>22</sup> Other scores are the simplified Wells score,<sup>23</sup> the Geneva score and its simplified version.<sup>24</sup> A multicenter study involving 807 patients demonstrated that any of the four scores in combination with a normal D-dimer test showed a similar performance for exclusion of PE.<sup>25</sup> Specificity of the D-dimer test is low (30-40%) and decreases with age, whereas the risk of PE increases with age, so that it has been suggested that an age adjusted cut-off point for D-dimer (patient's age x 10 µg/L) in combination with a low pre-test score would increase the number of patients over 50 years in whom PE could be excluded. This approach has been demonstrated in a series of 5132 consecutive patients with suspected PE<sup>26</sup> and has been validated in a series of 414 patients demonstrating that PE could be safely excluded in 19-22% of patients with any of the four scoring systems compared with 13-14% when the D-dimer cut-off point was not age adjusted.<sup>27</sup>

Avoidance of an unnecessary spiral CT scan prevents patients from exposure to substantial ionizing radiation which has significant risks.<sup>28, 29</sup> 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. Nuclear ventilation lung scanning is not performed in pregnancy.<sup>30</sup>

A meta-analysis involving 2982 patients has indicated that in patients in whom PE has been ruled out by CT-pulmonary angiography, the occurrence rate of PE was 1% (95% CI 0.7% to 1.4%) at three months.<sup>31</sup>

### General considerations

The objectives for treating acute DVT are to prevent death and disability from PE, pulmo-

nary hypertension and peripheral venous disease. Further aims are to prevent recurrence of VTE and development of PTS as a result of persistent venous outflow obstruction and/or dysfunction of the venous valves.<sup>32</sup> Extension of recurrent DVT into the collateral circulation produces further outflow obstruction and progressive swelling of the leg. Massive extension can result in increased compartmental pressure possibly leading to phlegmasia cerulea dolens, which although rare and often associated with metastatic cancer can lead to venous gangrene and limb loss.

It has been demonstrated that asymptomatic below knee DVT can lead to subsequent development of the PTS<sup>33, 34</sup> and that 18% of symptomatic calf DVT are associated with proximal extension or recurrence<sup>35</sup> indicating that below knee DVT merits treatment.

### Anticoagulants

In patients with DVT, initial therapy with VKA alone is associated with an unacceptable high rate of recurrent symptomatic VTE.<sup>36</sup> 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 ( $P < 0.001$ ).<sup>6</sup> Thus, **initial parenteral heparin and subsequent long-term oral anticoagulation are both necessary**.<sup>32, 36</sup>

Findings from randomized clinical trials in the 1990s resulted in **LMWH** replacing UFH in the initial treatment of DVT. These studies concluded that LMWH is at least as effective and safe as initial treatment for acute VTE compared with intravenous unfractionated heparin (UFH).<sup>37-47</sup> **LMWH** was also found to be as effective and safe as intravenous UFH in patients with acute PE.<sup>48-50</sup> Thus, anticoagulation should usually be started with **LMWH** for patients with PE. Treatment with intravenous UFH, which generally requires hospitalization, is now less frequently used but remains 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

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 reduces the rate of recurrent DVT.<sup>51-53</sup> However, other studies did not confirm this finding.<sup>54, 55</sup>

In contrast to UFH, LMWHs have a consistent dose-response with predictable bioavailability when given subcutaneously. They do not require hematologic monitoring apart from the platelet count. The need for anti-Xa monitoring has been reduced by specific labelling of individual regimens in the context of renal insufficiency or obesity (see pharmacopoeia). They may be administered once a day.<sup>40, 56-59</sup> These properties have made LMWH the preferred treatment for patients with uncomplicated DVT as outpatients.<sup>32, 60-68</sup> LMWH should be administered for at least five days<sup>69, 70</sup> and should be discontinued when the patient's INR is stable within the therapeutic range of 2.0 to 3.0.

RCT have demonstrated that **fondaparinux** is as effective as intravenous UFH for the initial treatment of DVT and PE.<sup>71, 72</sup> Fondaparinux is administered once daily. HIT is rare. Attention to labelling is essential in patients with impaired renal function in whom the risk of bleeding is increased.

**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 14.I.<sup>73-75</sup> An INR greater than 4.0 is associated with an increased frequency of hemorrhagic complications.<sup>76-78</sup> VKA may be started on the first day of heparin therapy except when patients require thrombolysis or surgery, or where there are comorbidities that predispose to major bleeding.<sup>69, 70, 79</sup> Whether low-dose warfarin, that produces a targeted INR between 1.5 and 1.9, may offer a suitable option for patients requiring extended periods of anticoagulation has long been debated. One study showed a definite advantage for low-dose warfarin over placebo in patients who had completed an initial 6.5-month period of conventional anticoagulation when compared with placebo. In this study, 508 patients who had been on full VKA therapy for 6.5 months were randomized to low intensity warfarin or placebo. There were 37 recurrences in the placebo group of 253 patients (7.2 per 100 person years) and 14 in the low intensity warfarin group of 255 patients (RR 0.36; 95% CI 0.19 to 0.67; P=0.001).<sup>80</sup> However,

TABLE 14.I.—Major bleeding complication rate according to INR intensity.

Trial	INR Range	Event rate per 100 person-years
Kearon <i>et al.</i> , 1999 <sup>73</sup>	2.0-3.0	3.8
Schulman <i>et al.</i> , 1997 <sup>74</sup>	2.0-2.85	2.4
Kearon <i>et al.</i> , 2003 <sup>75</sup>	2.0-3.0	0.9
Kearon <i>et al.</i> , 2003 <sup>75</sup>	1.5-1.9	1.1

in a direct comparison between conventional anticoagulation and low-dose warfarin, the former proved to be more effective and equally safe.<sup>75</sup> Indeed, in this study involving 738 patients with unprovoked proximal DVT or PE, the incidence of recurrence over a two to four years of follow-up increased from 2% in the conventional intensity treatment group to 4% in the low intensity treatment group (RR 2.67; 95% CI 1.05 to 6.74). The incidence of major hemorrhage was 2% in each group. Thus, the risk of recurrent VTE increases even with INR of <2. We believe that conventional warfarin regimen should be regarded as the first choice. However, a low-intensity regimen can be considered in particular situations depending on individual judgment, for example in patients reputed to be at a higher hemorrhagic risk and in those who have a strong preference for less frequent INR monitoring.

**Rivaroxaban** is a new oral direct inhibitor of Xa. In a phase III non-inferiority study, 3,449 patients with acute, symptomatic DVT were randomized to rivaroxaban (15 mg bd for three weeks, followed by 20 mg once daily without initial parenteral therapy) or subcutaneous 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.<sup>81</sup>

The efficacy of rivaroxaban in the prevention of recurrent VTE was tested in the EINSTEIN-extension study performed in parallel and reported in the same publication. In this study, 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 ( $P = 0.11$ ).<sup>81</sup>

In a RCT involving 4,832 patients who had symptomatic PE with or without DVT, **rivaroxaban** (15 mg b.d. 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;  $P = 0.003$ ).<sup>82</sup>

**Apixaban**, an oral reversible inhibitor of factor Xa was tested in a dose ranging study involving 520 consecutive patients with symptomatic DVT against standard therapy (LMWH for a minimum of five days followed by VKA) for three months.<sup>83</sup> Symptomatic recurrence of VTE and extension of thrombus as detected by ultrasound occurred in 4.7% of the patients in the apixaban groups (it was comparable in all three groups) and 4.2% in the standard therapy group. The rate of major and clinically relevant non-major bleeding was 7.3% in the apixaban groups and 7.9% in the standard therapy group. Phase III studies are in progress.

**Dabigatran** is a new oral direct inhibitor of thrombin. In a phase III non-inferiority study, 2539 patients with acute symptomatic DVT who were initially given parenteral anticoagulation therapy for 8-11 days, were randomized to dabigatran or subcutaneous heparin (UFH or LMWH) followed by VKA for six months. 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). Adverse events leading to discontinuation of the study drug occurred in 9.0% of patients in the dabigatran group and in 6.8% of patients in the warfarin group ( $P = 0.05$ ).<sup>84</sup>

The efficacy of **dabigatran** in the prevention of recurrent VTE was tested in two subsequent studies. In the first (RE-SONATE study) 1343 pa-

tients who had completed their anticoagulation (6-18 months) were randomized to continue with dabigatran or placebo for a further six month period.<sup>85</sup> 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 (RE-MEDY study) 2856 patients who had completed their anticoagulation (3-12 months) were randomized to receive dabigatran or conventional warfarin for up to 36 months.<sup>86</sup> 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%;  $P = 0.02$ ).

The efficacy of **aspirin** (100 mg daily for two years) in the prevention of recurrent VTE was recently investigated in a RCT involving 402 patients who had completed 6-18 months standard therapy for first-ever unprovoked VTE. The incidence of recurrent VTE was 6.6% in the aspirin group and 11.2% in the placebo group (RR 0.58; 95% CI 0.36 to 0.93). One patient in each group had major bleeding.<sup>87</sup> Thus, extended treatment with aspirin may be an appropriate choice in patients who are at high risk of bleeding with VKA. However, confirmatory studies are needed. It should be noted that the 42% reduction of recurrent VTE reported in the above study is approximately half of that produced by rivaroxaban and dabigatran. Compared with placebo, these oral anticoagulants reduced the risk of recurrent VTE by more than 80% (see above).

#### *Long-term treatment with LMWH*

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,<sup>88-92</sup> mainly in non-cancer patients although three studies included some patients with cancer.<sup>88, 91, 92</sup> One reported the results in the patients with cancer separately.<sup>91</sup> The incidence of

recurrent VTE was 4% 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 compared 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.<sup>93-96</sup> The number of patients involved was 1201 including the cancer patients from the study above that reported the results in the patients with cancer separately. 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 reported 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).<sup>97</sup>

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.

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. A number of studies that compared **long-term treatment with LMWH versus** standard therapy demonstrated **better recanalization in the long-term LMWH groups**.<sup>90, 91, 98-101</sup> A meta-analysis on five studies that reported on total recanalization demonstrated a risk ratio of 0.66 (95% CI 0.57 to 0.77;  $P < 0.0001$ ) in favour of long term LMWH.<sup>102</sup> In a large multicenter study involving 480 patients there was a reduction in PTS (RR 0.77;  $P = 0.001$ ).<sup>89</sup> Pooled analysis on two studies reporting on the subsequent development of leg ulcers<sup>89, 103</sup> yielded an 87% risk reduction for venous ulcers with LMWH ( $P = 0.019$ ).<sup>102</sup>

**Idraparinux** is a synthetic pentasaccharide which inhibits factor Xa mediated through antithrombin. In a RCT involving 2904 patients with DVT, treatment with idraparinux (2.5 mg mg s.c. once weekly) was associated with DVT recurrence in 2.9% compared with 3% in the standard therapy group (initial heparin followed by VKA) at three months. These results satisfied the prespecified non-inferiority requirement. Clinically relevant bleeding was 4.5% in the id-

raparinux group and 7% in the standard therapy group ( $P = 0.004$ ). Bleeding rates were similar at six months.<sup>104</sup>

A second RCT involving 1,215 patients who had completed six months of treatment with an anticoagulant (idraparinux or VKA), compared 2.5 mg of subcutaneous idraparinux weekly with a placebo for a further six months. The incidence of recurrent VTE was 1% in the idraparinux group and 3.7% in the placebo group ( $P < 0.001$ ). Patients on idraparinux had a higher incidence of major bleeding (3.1% vs. 0.9%).<sup>104</sup>

Two studies investigated the efficacy and safety of idraparinux in the treatment of PE. In the first study which involved 2215 patients, the incidence of recurrence in the idraparinux (2.5 mg s.c. weekly) at three months was 3.4% compared with 1.6% in the standard therapy group (OR 2.14; 95% CI 1.21 to 3.78). These results did not meet the non-inferiority requirement.<sup>104</sup> In the second study, 3202 patients with PE were randomized to 5-10 days of enoxaparin followed by idrabiotaparinux 3 mg weekly or warfarin (INR 2.0-3.0) for three or six months. Idrabiotaparinux has the same pharmacodynamic effects as idraparinux, but has the advantage of rapid neutralization by intravenous avidin. The incidence of recurrent PE was 2% in the idrabiotaparinux group and 3% in the warfarin group ( $P$  for non-inferiority = 0.0001). Clinically relevant bleeding occurred in 5% of patients in the idrabiotaparinux group and 7% in the warfarin group (OR 0.67; 95% CI 0.49 to 0.91) ( $P$  for superiority = 0.0098). It is of interest that the efficacy of idrabiotaparinux given for three to six months persisted beyond the end of treatment until at least one year, whereas there was an almost immediate consistent increase over time for recurrent VTE in the control population after ceasing warfarin.<sup>105</sup>

#### *Duration of anticoagulation therapy*

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<sup>106-117</sup> or occurs in the presence of active cancer.<sup>106, 112, 113, 118</sup> Patients with symptomatic PE have a higher risk of PE recurrence than those with DVT alone.<sup>119</sup>

The lowest risk is found when surgery is the reversible risk factor.<sup>109, 120</sup> 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.<sup>97</sup> The RR is 2.0 for proximal DVT or PE compared with calf DVT,<sup>111, 114, 116, 117, 119</sup> 1.5 if DVT is a second episode,<sup>93, 118, 121</sup> 2.0 if antiphospholipid antibody is present,<sup>73, 122-124</sup> 1.5 in the presence of a hereditary thrombophilia,<sup>73, 80, 109, 110, 124-132</sup> 1.5 in the presence of residual thrombosis in the proximal veins<sup>73, 124, 133-138</sup> and 1.6 for male gender.<sup>139, 140</sup> The risk is higher in the presence of multiple risk factors, homozygous inherited thrombophilia or a combination of heterozygous thrombophilias (see section on thrombophilia).

In patients with unprovoked VTE almost every contemporary trial has found that prolonged anticoagulation with VKA reduces long-term recurrence by about two thirds,<sup>117</sup> but increases the risk of major bleeding.<sup>141</sup> In addition, while the case-fatality rate of major bleeding complications is consistently around 11%, that for recurrent VTE decreases after completing an initial treatment period of three to six months from 11% to 3.6%.<sup>142</sup> Accordingly, the benefit-to-risk for indefinitely prolonging anticoagulation in patients with unprovoked VTE should be carefully assessed and individually tailored.

Unfortunately, there is no validated prediction tool to stratify the risk of major bleeding during extended anticoagulant therapy for patients with VTE, but this risk appears to increase with the prevalence of the following factors: age >65 years, additional increase of risk if age >75 years, previous gastrointestinal bleeding if not associated with a reversible cause, previous non-cardioembolic stroke, chronic renal impairment, chronic hepatic impairment, anemia, thrombocytopenia, diabetes, concomitant antiplatelet therapy, other chronic illness that impairs platelet function, poor control of anticoagulation (*i.e.*, variable INR results) including suboptimal access to monitoring or active cancer with additional increased risk if there is metastatic cancer.<sup>143</sup>

VKA generally should be continued for a minimum of three months.<sup>107, 116, 117, 135</sup> Three months is sufficient for patients with a reversible risk factor. For patients with a known irreversible major risk, protein C, protein S, lupus anticoagulant)

or without a known risk factor, prolonged anticoagulant therapy with periodic reassessment should be considered.<sup>32, 116</sup> The review process involves balance of benefit and harm. Patients presenting with recurrent DVT should be treated with a more prolonged anticoagulation regimen compared with those having a first episode.<sup>74</sup> The optimal duration of oral anticoagulant therapy depends on the risk of VTE recurrence.

**Isolated calf DVT.**—A randomised study of 51 patients with isolated calf DVT, of whom 23 received warfarin for three months and 28 did not, investigated the rate of recurrence.<sup>144</sup> Recurrences and their extent were confirmed with venography. Both groups received an initial course of heparin and all 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 recurrence with proximal extension and one had a pulmonary embolus. At one year, one out of 23 patients in the warfarin group had a recurrence, compared with 19 out of 28 in the non-warfarin group (RR 0.13; 95% CI 0.02 to 0.99). The findings indicate that oral anticoagulants should be given to all patients with symptomatic isolated calf DVT and that three months seems to be sufficient.

**4-6 weeks vs. 3-6 months.**—Four studies involving 1988 patients with a first unprovoked DVT (mainly proximal) or PE compared 4-6 weeks anticoagulation with VKA with three or six months. Follow-up was 1-2 years.<sup>107, 108, 116, 135</sup> 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% in the 3-6 months group (RR 1.65; 95% CI 0.60 to 4.53).

**Three months vs. 6-12 months.**—Four studies involving 1,736 patients with first unprovoked DVT (mainly proximal) or PE compared three months of anticoagulation with VKA with six or 12 months.<sup>114, 134, 145, 146</sup> 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 3-6 months of anticoagulation with VKA (INR 2-3) with indefinite duration of anticoagulation.<sup>73, 74, 147, 148</sup> Follow-up was 1.4 to four years. The incidence of recurrence was reduced from 18.8% in the 3-6 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).

#### *D-Dimer as a guide to continue anticoagulation*

Elevation of D-dimer has been reported to increase the risk of recurrent VTE. A meta-analysis of four studies which included 1539 patients indicated a 16.6% recurrence of DVT in patients with elevated D-dimer one month after discontinuation of VKA therapy compared with a 7.2% rate in those with normal levels of D-dimer (RR 2.30; 95% CI 1.71 to 3.10).<sup>149</sup> A meta-analysis of seven prospective studies involving 1,818 patients investigated the association between elevated D-dimer and VTE recurrence in patients with a first unprovoked VTE episode (DVT, PE or both). In a Cox proportional hazards model, a positive D-dimer one month after cessation of anticoagulation had a hazard ratio of 2.59 (95% CI 1.90 to 3.52). Of all the other factors studied which included inherited thrombophilia, only male sex had a significant effect on risk.<sup>126</sup> Thus, an elevated D-dimer is an indication to continue anticoagulation therapy. However, cessation of anticoagulation does not imply absence of recurrence.

#### *Residual thrombosis as a risk factor for recurrence*

A systematic review (11 studies; 3203 patients) showed a positive relationship between residual thrombosis and recurrent VTE during follow-up.<sup>150</sup> A subsequent systematic review and meta-analysis of nine prospective cohort studies and

five RCT demonstrated that the presence of residual venous obstruction was not associated with increased risk of recurrent VTE (OR 1.24; 95% CI 0.90 to 1.7) in patients with unprovoked DVT who stopped oral anticoagulation therapy. However, residual venous obstruction was associated with recurrent VTE in patients with any (unprovoked or provoked) DVT (OR 1.5; 95% CI 1.1 to 2.0).<sup>137</sup> In a recent randomized trial, recurrent VTE developed in 17.2% of patients allocated to conventional fixed anticoagulant duration (three months for provoked DVT and six months for unprovoked DVT) and in 11.9% of those randomized to flexible duration according to persistence of residual vein thrombosis, leading to an adjusted RR of 0.64 (95% CI, 0.39 to 0.99).<sup>151</sup> More studies on this flexible approach are needed.

#### *Compression therapy and the post-thrombotic syndrome*

Effective compression reduces edema and minimises damage to the microcirculation.<sup>152, 153</sup> Four RCT involving 745 patients demonstrated that elastic compression for two years in patients with proximal DVT reduced the incidence of PTS from 39% to 19% (RR 0.49; 95% CI 0.38 to 0.62).<sup>154-157</sup> It appears that treatment with **LMWH combined with early ambulation and elastic compression** will further prevent the PTS.<sup>158, 159</sup>

### **Recommendations for treating VTE**

#### *Methods of treatment*

Initial treatment is with intravenous **UFH, LMWH or fondaparinux** for at least five days (**level of evidence: high**). LMWH is preferred in most patients. **VKA** therapy should be commenced on day one and continued according to the INR. Initial therapy with LMWH, IV UFH or Fondaparinux should be discontinued when the stable INR is in the therapeutic range (2.0-3.0) (**level of evidence: high**).

**Rivaroxaban** or **dabigatran** are an alternative therapy in countries where they have been approved (**level of evidence: high**). **While the former can be used as a single therapy,**

**the latter should be preceded by one week of parenteral anticoagulation with either LMWH or fondaparinux.**

In patients with a history of cancer **LMWH for 3-6 months** is the initial treatment (**level of evidence: high**) (see section on cancer for evidence)

**During pregnancy LMWH** is the treatment of choice throughout pregnancy and for the first six weeks after delivery (**level of evidence: low**) (see section on pregnancy for evidence).

**LMWH for 3-6 months** is an alternative to VKA therapy (**level of evidence: high**).

**Isolated calf DVT should be treated for three months (level of evidence: moderate)** or followed by serial ultrasonography on two occasions if anticoagulation is contraindicated (**level of evidence: low**).

#### *Duration of anticoagulation therapy*

All patients should receive long-term antithrombotic therapy for at least three months (**level of evidence: high**).

In patients with a major provoking risk factor that has been removed three months is sufficient (**level of evidence: high**).

In patients with an unknown risk factor, the duration of anticoagulant therapy may be indefinite (**level of evidence: high**). 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 (level of evidence: low)**. The review process involves balance of benefit and harm. In patients at lower risk of bleeding and continuing with VKA treatment, patient preferences are considered.

In patients with a minor provoking risk factor, the duration of anticoagulant therapy is uncertain and should be based once again upon the same principles (**level of evidence: low**).

Role of D-dimer: the evidence to date suggests a role for the use of the D-dimer test for establishing the duration of therapy but current data is insufficient.

The concept of residual DVT by imaging suggests a role for the use of follow-up imaging to establish the duration of long-term antithrombotic therapy but current data is insufficient.

In patients with more than one episode of VTE, the duration of anticoagulant therapy is indefinite (**level of evidence: high**). For long-term prevention of recurrent VTE in patients requiring indefinite anticoagulation rivaroxaban or dabigatran can be considered after completing 3-12 months of conventional anticoagulation (**level of evidence: moderate**) when approved.

**Immediate mobilization with GEC stockings to be worn for at least two years (level of evidence: high)** at an ankle pressure of 30-40 mmHg (class II) leads to a more rapid reduction of pain and swelling and reduces the occurrence of PTS.<sup>154, 155, 158-160</sup>

#### *LMWH and renal insufficiency*

##### PROPHYLACTIC DOSES

An increased risk of bleeding has not been reported in patients with renal insufficiency receiving prophylactic dosages of LMWH. However, it is advised that for prophylaxis in patients with severe renal insufficiency, prophylactic doses of LMWH should be adjusted down according to creatinine clearance and manufacturer's instructions.

##### THERAPEUTIC DOSES

Enoxaparin (see label), fondaparinux (see label). Dalteparin and tinzaparin may have problems in severe renal failure because they are eliminated mainly through the kidneys.

In patients with renal insufficiency, LMWH in therapeutic doses poses a high risk of major bleeding due to its prolonged half-life. The actual risk of major bleeding has not been assessed in prospective studies. Such studies would have to be done with each LMWH because of different pharmacological properties. Major bleeding in patients with a creatinine greater than 2 mg/dL and a similar number of patients receiving enoxaparin at equal or greater doses for the same indications has been assessed in one retrospective study. Major bleeding occurred in one (2%) of 50 patients with normal renal function and 16 (30%) of 53 patients with serum creatinine greater than 2 mg/dL ( $P < 0.001$ ).<sup>161</sup>

Although protamine sulphate is efficacious in stopping LMWH induced bleeding in some animal models, there are only limited data for humans.

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# THROMBOLYTIC THERAPY

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## **PART I: THROMBOLYSIS FOR DEEP VEIN THROMBOSIS (DVT)**

### **General considerations**

Iliofemoral DVT frequently leads to serious morbidity from the post-thrombotic syndrome (PTS). Occlusion of the common femoral, external iliac and common iliac veins obliterate the single venous outflow channel from the lower extremity. Spontaneous recanalization is rarely adequate to restore unobstructed venous drainage.

Observational studies have demonstrated unacceptably high post-thrombotic morbidity, venous ulceration and impaired quality of life (QOL) in patients treated with anticoagulation alone.<sup>1-3</sup> A strategy for successful thrombus removal that avoids re-thrombosis should reduce or eliminate PTS and potentially avoid recurrence.

### *Systemic thrombolysis*

A selected analysis from early randomized trials of systemic streptokinase administration demonstrated that venous valve function may be preserved in patients treated with lytic therapy compared with those treated with standard anticoagulation.<sup>4, 5</sup> An overview of results from six trials reported that systemic thrombolysis was 3.7 times more effective in producing some degree of lysis compared to heparin alone.<sup>6</sup> In a pooled analysis of 13 prospective studies, only 4% of patients treated with heparin had success-

ful or complete lysis compared with 45% of patients receiving systemic thrombolysis.<sup>7</sup> However, prolonged streptokinase infusions were often associated with allergic reactions and a hemorrhagic rate three-fold higher than patients managed with heparin anticoagulation alone.<sup>6</sup>

A randomized trial comparing recombinant tissue plasminogen activator (rt-PA) versus anticoagulation alone demonstrated that 58% of patients receiving rt-PA achieved greater than 50% clot lysis compared to 0% in those receiving anticoagulation alone ( $P=0.002$ ) and that rt-PA-treated patients had a trend toward reduced PTS if lysis was successful (56% vs. 25%,  $P=0.07$ ).<sup>8</sup> However, major bleeding was significantly higher with systemic thrombolysis compared with anticoagulation alone ( $P<0.04$ ).<sup>6, 8, 9</sup>

All trials of systemic thrombolytic therapy for acute DVT admitted patients with proximal DVT, not necessarily specifically those with iliofemoral DVT. Therefore, it is unknown whether patients with the most extensive venous thrombosis will improve, or whether they face lower efficacy due to more extensive obliteration and greater thrombus burden as well as an increased risk of bleeding.

### *Catheter-directed thrombolysis*

Catheter-directed thrombolysis (CDT) refers to infusion of a plasminogen activator directly into the thrombus using ultrasound-guided access to the deep venous system and fluoroscopic positioning of the catheter into the thrombus.

Direct infusion of plasminogen activator into the thrombus takes advantage of accelerated thrombolysis by virtue of the plasminogen activator binding with fibrin-bound LYS-plasminogen. Avoiding systemic infusion has resulted in fewer major bleeding complications, and direct infusion of the lytic agent has been associated with improved efficacy.<sup>10-18</sup>

Successful CDT can be anticipated in 80-90% of patients if treated within 14 days of symptom onset.<sup>10-19</sup> Retrospective observations show that CDT results in improved QoL and that QoL is related to the magnitude of lytic success.<sup>19, 20</sup> The frequency and severity of PTS is directly related to the amount of residual thrombus at the completion of CDT.<sup>21</sup> A randomized trial involving 209 patients compared CDT followed by anticoagulation with anticoagulation alone (control group) for iliofemoral DVT. After 24 months' follow-up, the incidence of PTS was reduced from 55.6% in the control group to 41.1% in the CDT group (P=0.047). The difference in PTS corresponded to an absolute risk reduction of 14.4% (95% CI 0.2-27.9), and the number needed to treat was seven (95% CI 4-502). At six months, iliofemoral patency was found in 65.9% of patients in the CDT group and 47.4% in the control group (P=0.012). Twenty bleeding complications related to CDT included three major and five clinically relevant bleeds. Randomized trials have demonstrated improved patency of the iliofemoral venous system<sup>10, 11</sup> and preserved venous valve function.<sup>10</sup>

Bleeding complications in excess of 10% were observed in early studies,<sup>15</sup> but these have been reduced in more contemporary reports. The CaVenT investigators<sup>22</sup> reported that patients randomized to CDT plus anticoagulation had a major bleeding event rate of 3% versus 0% of patients randomized to anticoagulation alone. They used an rt-PA dose of 0.01 mg/kg/h which was substantially lower than that used in earlier trials. This dose is consistent with most contemporary experiences, which often use a fixed dose of 1-2 mg of rt-PA per hour infused in 50-100 cc solution. Reduction in bleeding complications is likely multifactorial, including lower concentrations and overall dose of plasminogen activators, routine incorporation of ultrasound-guided vein puncture and lower doses of heparin used during lytic infusion.

### *Pharmacomechanical thrombolysis*

Pharmacomechanical thrombolysis refers to percutaneous catheter-based techniques which integrate mechanical clot disruption in conjunction with intra-thrombus infusion of a plasminogen activator.

Evidence does not exist to show that catheter-based mechanical thrombectomy alone, which includes aspiration, maceration and/or fragmentation, has been effective for management of acute DVT.<sup>23-25</sup> Clot manipulation in the absence of concomitant thrombolytic therapy has been associated with increased risk of symptomatic PE.<sup>23-25</sup>

Retrospective studies of pharmacomechanical techniques suggest that similar or improved efficacy can be achieved in shorter treatment times using reduced doses of plasminogen activator and reduced use of hospital and/or ICU length-of-stay without adversely affecting valve function.<sup>18, 26-34</sup> Several observational studies indicate that thrombus can be removed in some patients in a single procedure session,<sup>18, 29-31</sup> which reduces the need for hospitalization and eliminates the need to utilize ICU. Studies comparing post-thrombotic morbidity in patients treated with CDT versus those treated with pharmacomechanical lysis are not available.

### **Recommendations**

Systemic thrombolysis for proximal DVT patients is not recommended due to low efficacy and increased risk of bleeding complications (**level of evidence: high**).

Catheter-directed thrombolysis is recommended for patients with acute iliofemoral DVT (**level of evidence: moderate**). Patients with acute iliofemoral DVT at a center lacking expertise in CDT should be transferred to a center where expertise exists if indications for CDT are present.

Physicians puncturing deep veins should use ultrasound guidance for access (**level of evidence: low**).

In centers where expertise is available, pharmacomechanical thrombolysis is recommended as initial therapy for patients with iliofemoral DVT (**level of evidence: low**).

Pharmacomechanical thrombolysis is recommended in preference to CDT for iliofemoral

DVT in centers where appropriate expertise is available (**level of evidence: low**).

Percutaneous mechanical thrombectomy alone (in the absence of thrombolytic therapy) is not recommended for the management of patients with acute DVT (**level of evidence: low**).

Patients treated with CDT or pharmacomechanical thrombolysis should receive the same intensity and duration of anticoagulation (**level of evidence: low**).

## **PART II: THROMBOLYSIS FOR PULMONARY EMBOLISM (PE)**

### **General considerations**

PE is a significant cause of mortality and can be associated with chronic thromboembolic pulmonary hypertension resulting in ongoing patient morbidity.<sup>35-37</sup> Strategies to eliminate the acute pulmonary embolus are designed to improve survival and reduce long-standing morbidity of chronic thromboembolic pulmonary hypertension.<sup>38</sup>

Outcomes are related to the severity of the PE. Short of sudden death, a number of factors have been used to identify patients at risk of poor outcomes, but although clinical features including age and co-morbidities, influence the prognosis in acute PE<sup>39, 40 34</sup> and have been incorporated into clinical scores,<sup>41-44</sup> they do not sufficiently predict outcome in the absence of imaging or biomarkers.<sup>45</sup>

### *Computed tomographic angiography*

The burden of thrombus alone measured by quantitative assessment of a computed tomographic (CT) angiogram does not predict adverse outcomes.<sup>46</sup> However, CT scan measurement of right ventricular (RV) dilatation is associated with in-hospital mortality,<sup>47</sup> 30-day mortality,<sup>48</sup> and 3-month mortality.<sup>49</sup> A RV/left ventricular (LV) index of more than 0.9 is shown to be associated with adverse clinical outcomes.<sup>48, 50</sup> Ventricular septal deviation has also predicts short-term mortality.<sup>51</sup> A meta-analysis of two studies involving 191 patients showed a pooled sensitivity of 65% (95% CI 35-85%) and specificity of 56% (95% CI 39-71%) for short term mortality.<sup>52</sup>

### *Echocardiography*

Echocardiography can identify large pulmonary emboli obstructing the RV outflow to produce RV dysfunction. Parameters assessed include RV enlargement, septal deviation, tricuspid insufficiency, and increased pulmonary artery pressures. A systematic review of RV dysfunction defined by echocardiography involving five studies of 475 patients with stable PE revealed an odds ratio of 2.53 (95% CI, 1.17-5.50) for short-term mortality.<sup>52</sup> These studies showed a pooled sensitivity of 70% (95% CI 46-86%) and specificity of 57% (95% CI 47-66%) for short term mortality.<sup>52</sup>

### *Troponins*

Troponin-I and troponin-T released from microinfarction of right ventricular muscle are markers of myocardial injury. When elevated, they are associated with an adverse prognosis in patients with acute PE.<sup>53-58</sup> A meta-analysis demonstrated that elevated troponin levels in patients with submassive PE were associated with a 19.7% mortality compared with 3.7% in patients with normal troponins (RR 4.72; 95% CI 3.45 to 6.47).<sup>59</sup>

### *Natriuretic peptides*

Natriuretic peptides which include brain natriuretic peptides (BNP) and N-terminal pro-BNP are released when the myocardium is placed on stretch and have been shown to predict adverse short-term outcomes in patients with acute PE. Literature reviews have demonstrated that mortality is increased 5 to 9.5 fold depending upon whether BNP or N-terminal pro-BNP was studied.<sup>60-62</sup> A meta-analysis of two studies involving 170 patients showed a pooled sensitivity of 93% (95% CI 14-100%) and specificity of 59% (95% CI 14-92%) for short term mortality.<sup>52</sup>

### *Electrocardiography*

There is a worse short-term prognosis if a PE is large enough to cause abnormalities in the conducting system that reveal right heart strain.<sup>63-73</sup> These include sinus tachycardia, atrial arrhythmias, right bundle branch block, S1Q3T3 pattern and ST-segment changes in V1-V4.

### *Risk stratification for acute PE*

The outcome for patients with acute PE depends on the hemodynamic compromise, the impact on the myocardium identified by RV dysfunction, myocardial damage, myocardial stretch and cardiac electrical activity. Stratifying patients according to risk of morbidity and mortality is clinically helpful and is recommended in order to appropriately evaluate patients for treatment.

**Massive PE** is defined as acute PE causing sustained hypotension (systolic blood pressure less than 90 mmHg for more than 15 minutes or requiring inotropic support), severe bradycardia (heart rate less than 40 bpm) or signs or symptoms of cardiogenic shock. In the MAPPET registry, in-hospital mortality was 25% for patients presenting in cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation compared with 8.1% in those who were hemodynamically stable.<sup>74</sup> Reports based on clinical predictors alone identify a systolic blood pressure less than 100 mmHg as a predictor for an adverse outcome.<sup>43, 44</sup> In the ICOPER registry, the 90-day mortality rate for patients with acute PE and systolic blood pressure less than 90 mmHg at presentation was 52.4% versus 14.7% in the remaining patients.<sup>75</sup>

**Submassive PE** refers to the broad subset of patients who are defined as hemodynamically stable but with acute pulmonary emboli large enough to cause tachycardia, electrical disturbances on EKG, RV dysfunction, or an increase in cardiac biomarkers.

Low-risk PE refers to patients who are normotensive with no RV dysfunction and normal biomarkers. Prognosis in these patients is good, with a short-term mortality rate of approximately 1%.<sup>45, 58, 76</sup>

### *Effect of thrombolysis in patients with PE*

Most well-controlled randomized trials of thrombolysis for acute PE included a spectrum of patients with PE, many of whom would be well managed with anticoagulation alone. Many patients with low-risk or submassive PE would not be expected to die so that judging success from mortality rates alone may underestimate the value of thrombolysis. Likewise, treating patients who

may not benefit from lytic therapy will needlessly expose patients to an increased bleeding risk.

Randomized controlled NIH-sponsored trials<sup>77, 78</sup> that compared lytic therapy versus heparin demonstrated more rapid and complete clearing of pulmonary emboli with lysis but with no reduction of mortality and an increased risk of bleeding. At one year follow-up, lytic patients had better oxygen diffusing capacity and pulmonary capillary blood volume.<sup>79</sup> At seven year follow-up, right heart catheterization demonstrated significantly reduced pulmonary artery pressures and pulmonary vascular resistance at rest and exercise.<sup>80</sup> This translated into significantly fewer lytic patients suffering from heart failure. The lytic group also had fewer recurrent DVTs and PEs as well as a reduced need for inferior vena cava (IVC) filters.

A European randomized trial of thrombolytic therapy plus heparin versus heparin alone for submassive PE demonstrated improved results with primary lysis with significantly fewer patients requiring salvage lysis or aggressive clinical support.<sup>81</sup>

A randomized study of patients with massive PE appeared to show a meaningful reduction in either recurrent PE or death, to 9.4% with thrombolytic therapy compared to 19.0% with anticoagulation alone (OR 0.45, 95% CI 0.22-0.90).<sup>82</sup> A small randomized study of massive PE was terminated by the Data and Safety Monitoring Committee because all four patients randomized to anticoagulation died whereas all four patients randomized to thrombolytic therapy survived.<sup>83</sup>

### *Catheter-based interventions for PE*

Direct mechanical intervention may be life-saving for patients with massive or submassive PE who are deteriorating. Percutaneous catheter-based techniques can be performed as an alternative to systemic thrombolysis if there is a contraindication to systemic lysis or if surgical embolectomy is unavailable. Either catheter-based interventions or surgical embolectomy can be life-saving if systemic thrombolysis has failed.<sup>84</sup>

The early technique of aspiration thrombectomy with the Greenfield suction and embolectomy catheter (Boston Scientific, Natick, MA, USA) is currently the only FDA-approved device,<sup>85</sup> but it

has not been widely adopted because it is cumbersome and associated with many technical and physiologic difficulties. Advances in catheter-based technology has demonstrated that thrombus fragmentation can be performed with balloon catheters, pigtail catheters, impeller-based homogenization, rheolytic intervention, and ultrasound-accelerated thrombolysis.<sup>86-92</sup>

A systematic review of percutaneous therapy alone for patients with massive PE found an 81% success rate with mechanical therapy and 95% success rate when combined with infusion of a thrombolytic agent.<sup>91</sup> Since limited doses of plasminogen activators can be used safely without systemic effect and may substantially increase interventional success, it seems reasonable to incorporate both the pharmacologic and mechanical advantage from catheter techniques for massive PE. The risk of pulmonary artery perforation increases when arteries smaller than 6 mm in diameter are treated.<sup>93</sup>

### *Surgical embolectomy*

Operative embolectomy for acute massive PE remains a viable treatment option. It has been shown to be effective to rescue patients with failed systemic thrombolysis for massive PE.<sup>84</sup> Previous reports of operative mortality in the range of 25-30% have reduced enthusiasm for operative approaches, favoring alternative therapies.<sup>91</sup> However, recent contemporary series are associated with substantially improved outcomes.<sup>94, 95</sup> The contemporary procedure can often be performed without placing the patient on cardiopulmonary bypass and without aortic cross-clamping.

In light of the variety of techniques now available for patients with massive PE, it is advisable to develop a multidisciplinary team of surgeons, interventionalists and physicians expert in thrombolytic therapy to design treatment algorithms for patients with potentially fatal PE.

### **Recommendations**

All patients with PE should undergo risk stratification (**level of evidence: high**).

Patients with massive PE should undergo thrombolytic therapy in the absence of risk fac-

tors for bleeding complications (**level of evidence: high**).

Thrombolytic therapy should be considered in patients with submassive acute PE if they are not at high risk for bleeding complications (**level of evidence: moderate**).

Thrombolytic therapy is not recommended for patients with low risk PE (**level of evidence: moderate**).

The same intensity and duration of anticoagulation should be offered to patients treated with thrombolytic therapy for PE (**level of evidence: low**).

In patients with massive PE, catheter-based intervention or surgical embolectomy are reasonable alternatives (**level of evidence: low**).

Catheter-based embolectomy or surgical embolectomy is recommended following unsuccessful thrombolysis for PE (**level of evidence: low**).

Catheter-based intervention or operative surgical embolectomy can be considered for patients with submassive PE who are at increased risk for bleeding from systemic thrombolytic therapy (**level of evidence: low**).

Patients with acute PE who are at low risk are best treated with anticoagulation alone (**level of evidence: moderate**).

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# INFERIOR VENA CAVA FILTERS

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Indications for IVC filter insertion can be categorized as absolute, relative and prophylactic. In reality, all vena caval 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) venous thromboembolic complications associated with a contraindication to anticoagulation; 2) documented failure of anticoagulation; and 3) complications of anticoagulation. Evidence suggests that most patients treated with vena cava filters have none of the three accepted absolute indications.<sup>1</sup>

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 to be 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.

The only randomized trial of IVC filters versus no filtration evaluated the adjunctive benefit of filters in patients with acute DVT undergoing routine anticoagulation.<sup>2</sup> The primary endpoint was PE at 12 days and patients randomized to IVC filters had significantly fewer PE versus

those without a filter (1.1% vs. 4.8%). Eight-year follow-up data showed that the cumulative recurrent PE rate was 6.2% in patients with filters versus 15.1% in those without. However, patients receiving filters had an increased incidence of recurrent DVT at two years (20.8% vs. 11.6%) and at eight years (35.7% vs. 27.5%). Unfortunately, multiple filter types were used and not all filters achieve the same results.

It has been observed that thrombotic risk and retrievability (of optional filters) varies between filters.<sup>3</sup> 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.<sup>4, 5</sup> These hemodynamic observations have translated into clinically relevant findings as observed in a randomized trial.<sup>6</sup>

A recent Cochrane review of IVC filters to prevent PE confirmed lack of information as to efficacy of filters.<sup>7</sup> Therefore, strong recommendations cannot be given for IVC filters on the basis of established evidence.

Increasing numbers of optional (retrievable) filters are being used. A recent systematic review of retrievable IVC filters comprising 37 studies and 6834 patients found a mean retrieval rate of 34%.<sup>8</sup> 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.<sup>9</sup> Early complications included incomplete or asymmetric deployment, malpo-

sitioning 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 type of filters. Filter migration and tilting were more common with Bard filters compared with other types. IVC thrombosis was commonly seen with TrapEase (Cordis) filters in patients with underlying malignancy or other hypercoagulable states. The incidence of other complications appeared to be similar among various IVC filters.<sup>9</sup>

### Recommendations

Patients who have PE or proximal DVT with contraindications to anticoagulation should receive an IVC filter (**level of evidence: moderate**).

Patients who have recurrent acute PE despite therapeutic anticoagulation should receive an IVC filter (**level of evidence: low**).

Patients with acute PE and poor cardiopulmonary reserve should be considered for an IVC filter (**level of evidence: low**).

Patients who receive a retrievable IVC filter should be evaluated for filter removal within the specific filter's retrieval window (**level of evidence: low**).

An IVC filter should not be used routinely as an adjunct to anticoagulation (**level of evidence: low**).

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).

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# SURGICAL THROMBECTOMY

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## General considerations

Restoring patency to a thrombosed vein and preserving valve function is important to reduce the risk and severity of the PTS. Long-term studies demonstrate improved patency of iliac veins following thrombectomy with anticoagulation alone.<sup>1-5</sup> A randomized trial of iliofemoral venous thrombectomy with a temporary arteriovenous fistula versus anticoagulation demonstrated improved venous patency and improved clinical and hemodynamic outcome with preserved valve function in the thrombectomy group.<sup>3-5</sup> Further studies comparing thrombectomy with conventional treatment are needed to determine recurrence and late outcome rates.

## Recommendation

**Surgical venous thrombectomy should be considered for patients with symptomatic**

**iliofemoral DVT who are not candidates for catheter-directed thrombolysis (level of evidence: low).**

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# TREATMENT IN CANCER PATIENTS

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## General considerations

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.<sup>1</sup> 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<sup>2</sup> and more frequent bleeding in the cancer patients (12.4% vs. 4.9%; HR 2.2).

### *Initial treatment of VTE in cancer*

Studies have not addressed the initial treatment of VTE in cancer patients. However, many trials that compared **UFH** with **LMWH** for initial treatment of DVT included patients with malignant disease. Meta-analyses of these studies indicate 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.<sup>3-6</sup>

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 *versus* 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)).<sup>7</sup> 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.<sup>8-12</sup> 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.<sup>11, 13</sup> A single study of 108 patients with PE, 22% of whom had cancer, evaluated the potential for outpatient use of the LMWH (dalteparin sodium).<sup>14</sup> 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.

A recent systematic review identified 13 stud-

ies that compared LMWH to UFH and two that compared fondaparinux to UFH. 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 were 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 to 1.63) 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.<sup>22</sup>

Outpatient therapy with LMWH is preferred in cancer patients with a potentially shortened duration of life where quality of life is an essential issue.

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.<sup>15</sup>

#### *Long-term anticoagulation for secondary prevention of VTE*

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.<sup>16</sup> A study involving 676 patients with cancer-associated VTE was sufficiently powered to define long-term treatment outcomes.<sup>17</sup> All patients received 5-7 days' treatment with the LMWH dalteparin sodium 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 sodium (8.0%

with dalteparin *vs.* 15.8% with VKA), with no significant increase in the risk of bleeding complications. These findings are supported by data from two randomized open-label trials.<sup>18, 19</sup> In the prospective multicenter LITE trial,<sup>18</sup> 200 patients with cancer and acute symptomatic proximal vein thrombosis were randomized to usual care (intravenous heparin followed by long-term warfarin sodium) or the LMWH tinzaparin. At 12 months, the rate of recurrent VTE was 15% in the usual-care group *versus* 7% in the tinzaparin group (P=0.044).<sup>18</sup> 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.<sup>16, 20, 21</sup> One such analysis, that involved six RCTs comparing LMWH with VKA, 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).<sup>20</sup>

#### *Potential survival benefit of LMWH*

As indicated above, data from several prospective randomized clinical trials suggest that cancer patients receiving LMWH over a prolonged period have improved survival.<sup>17, 23-29</sup> These data are of considerable interest because LMWH therapy when compared with placebo was not associated with adverse safety (no increase in bleeding), and thus may present a potential novel adjuvant anticancer therapy.

The potential role of LMWH to prolong survival appears dependent upon the tumor stage. Two randomized trials in patients with advanced malignancy did not demonstrate any survival benefit with LMWH therapy *versus* placebo<sup>30, 31</sup>. In one of these studies, Kaplan-Meier survival estimates in patients alive 17 months after randomization<sup>30</sup> showed improved survival with LMWH *versus* placebo (78% *vs.* 55% at two years and 60% *vs.* 36% at three years, respectively, P=0.03), but these patients were not defined *a priori*.<sup>30</sup> In a further randomized study in 302 patients with advanced solid malignancy without VTE,<sup>32</sup> a six-week course of nadroparin *vs.* placebo was associated with a lower risk of death at 12 months (median survival 8.0 *vs.* 6.6 months; HR

0.75, 95% CI 0.59 to 0.96), which remained significant after adjustment for confounders. An a-priori analysis in patients with a life expectancy of six months or more at enrollment demonstrated a greater benefit from LMWH treatment (15.4 vs. 9.4 month survival; HR 0.64, 95% CI 0.45 to 0.90), which was reduced in patients with a shorter life expectancy (HR 0.88, 95% CI 0.62 to 1.25). A recent systematic review of five randomized clinical trials involving heparin treatment (UFH or LMWH) demonstrated a survival benefit with heparin treatment (HR 0.77; 95% CI 0.65 to 0.91) without any increased risk of bleeding (RR 1.78; 95% CI 0.73 to 4.38). The benefit was most notable in the subgroup with limited small cell lung cancer (HR 0.56; 95% CI 0.38 to 0.83) and was not significant for patients with extensive small cell lung cancer (HR 0.80; 95% CI 0.60 to 1.06) or advanced cancer (HR 0.84; 95% CI 0.68 to 1.03). These data suggest that LMWH may offer a survival benefit, which is greater in patients with less advanced disease and better prognosis. These preliminary data need to be confirmed in further prospective clinical trials with appropriate designs and power to assess cancer outcome before any recommendations can be made.

### Recommendations

The initial and long term treatment of DVT and PE in patients with cancer is **LMWH administered for 3-6 months (level of evidence: high)**. If the health care economics of a system do not allow for use of long term LMWH, it is acceptable to treat initially with UFH or LMWH followed by long-term VKA therapy (**level of evidence: high**).

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# HEPARIN-INDUCED THROMBOCYTOPENIA

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## General considerations

Heparin-induced thrombocytopenia (HIT) is an important adverse effect of heparin. HIT is a life-threatening prothrombotic, immune-mediated coagulopathy caused by antibodies that bind to the complex of platelet factor 4 (PF4) and heparin.<sup>1</sup> HIT occurs most frequently after cardiac or orthopedic surgery or in and medical patients,<sup>2-10</sup> but can be found in other patient populations and clinical settings.<sup>11-15</sup> Progression to overt thrombosis, which can occur anywhere throughout the venous and arterial circulation, is the most serious complication from HIT as it often leads to amputation or death.<sup>16-19</sup> Spontaneous bleeding and petechiae are rare.

HIT (also known as HIT Type II) needs to be distinguished from other more common and benign causes of thrombocytopenia, such as HIT Type I and pseudothrombocytopenia. HIT Type I is a transient but self-limited fall in platelet count that occurs in up to 30% of treated patients. It results from a non-immunological mechanism in the first 24 hours of receiving heparin and resolves within 24-48 hours.<sup>20</sup>

The frequency of HIT is influenced by several factors. The risk of developing HIT is higher from exposure to UFH (bovine more than porcine<sup>21</sup>) than LMWH,<sup>7, 22-27</sup> and is more duration-dependent than dose-dependent.<sup>8, 28, 29</sup> However, HIT can occur with a higher frequency in LMWH treated patients who were previously exposed to UFH.<sup>29</sup> HIT due to LMWH is as severe as UFH induced HIT.<sup>22</sup> HIT can also occur with

prophylactic doses of heparin<sup>28</sup> and heparin from exogenous sources (*e.g.*, heparin flushes, heparin coated catheters).<sup>30</sup> Preventive measures include the use of LMWH, fondaparinux, and non-heparin anticoagulants rather than UFH for post-surgical prophylaxis, use of porcine rather than bovine UFH and avoiding unnecessary and prolonged exposure to UFH.

The diagnosis of HIT is based on clinical findings and platelet count. In patients being treated or having been recently treated with heparin, HIT should be suspected on the basis of a 30% decrease in platelet count from baseline in the absence of other reasons for thrombocytopenia.<sup>1, 31, 32</sup> The diagnosis can be made if the platelet count reduction is 50% of baseline, assuming no other reasons for thrombocytopenia.<sup>1, 31, 32</sup> 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 x 10<sup>9</sup>/L), and unexplained thrombosis are also characteristics of HIT.<sup>1, 31, 32</sup> Symptoms typically appear four to 14 days after exposure to UFH,<sup>33, 34</sup> or eight to 14 days after exposure to LMWH.<sup>22</sup> Patients who received heparin within the prior 100 days can have an immediate rapid-onset HIT when restarting UFH or LMWH.<sup>33, 34</sup> Delayed-onset HIT has been observed with symptoms appearing several days after discontinuation of UFH.<sup>1, 35</sup>

The diagnosis of HIT is difficult in patients after surgery as post-operative thrombocytopenia is frequently present after a surgical procedure. It is particularly difficult after cardiac surgery, as

the platelet count always falls following cardiac surgery using cardiopulmonary bypass. 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 5-10 days post-operation (a biphasic platelet count pattern).<sup>36-38</sup> However, HIT cannot be definitely excluded in these patients if there is a monophasic pattern of persistent post-operative thrombocytopenia.<sup>36-38</sup>

Another clinical presentation of HIT that can be challenging is where a patient has only mild thrombocytopenia receiving heparin or LMWH treatment. Such patients need to be individually assessed for their risk of having HIT considering past exposure to heparin, competing causes for thrombocytopenia, new thrombosis. The level of risk will determine whether or not to continue heparin or LMWH treatment while laboratory testing is sent to confirm the diagnosis.<sup>39</sup>

Clinical scoring systems are available and continue to be developed to assist in the diagnosis of HIT.<sup>38-41</sup>

A clinical diagnosis of HIT should be confirmed by a laboratory assay that detects heparin-dependent antibodies. Pathologic HIT immune complexes are composed of the PF4-heparin complex bound to an immunoglobulin G (IgG).<sup>42-46</sup> These complexes bind to platelet FcγIIa receptors (CD 32), inducing platelet activation, aggregation and generation of platelet microparticles.<sup>47, 48</sup> IgA and IgM have also been identified in HIT patients.<sup>49</sup> HIT antibodies provoke leukocyte and endothelial cell activation that augment both the hypercoagulable and inflammatory states.<sup>44, 50-54</sup> This combined cellular activation leads to a burst of thrombin generation.<sup>55</sup> Of all patients at risk of thrombosis, those with HIT are at highest risk (>30%).<sup>31</sup> Non-drug factors such as type of surgery, severity of trauma, severity of thrombocytopenia (particularly at baseline), renal impairment, low cardiac output and timing of first anticoagulant dose, also influence the risk of developing HIT and related clinical outcomes.<sup>56-59</sup> The association of HIT antibodies, in the absence of thrombocytopenia and thrombosis with future cardiovascular and other thrombotic events has been reported and remains under investigation.<sup>60</sup>

There are two types of laboratory assays that detect heparin-dependent antibodies. These are

platelet function tests (serotonin release and platelet aggregation assays) and immunoassays that detect antibodies to the PF4-heparin complex.<sup>61-64</sup> Each test has particular performance characteristics and provides unique information, so that appropriate use and knowledgeable interpretation of the test results are important.<sup>64-67</sup> Platelet function assays that use washed platelets have a better sensitivity than plasma-based assays but false negative results can still be obtained. Immunoassays have a high rate of positive results that are not always associated with clinical HIT in the patient.<sup>65, 68-70</sup> For immunoassays, the option to report the titre results rather than a simple positive or negative result, and the option to utilize the high heparin concentration confirmatory step, are gaining favor as these provide a closer correlation to the risk of thrombosis and mortality in patients with HIT.<sup>26, 71-75</sup> Exclusive reliance on laboratory tests for the diagnosis of HIT can lead to erroneous diagnostic conclusions.

Clinical trials and clinical experience have shown the direct thrombin inhibitors (DTIs) argatroban<sup>76-82</sup> and lepirudin<sup>83, 84</sup> to be safe and effective for reducing the risk of thrombosis and associated morbidity or mortality in patients with HIT. These drugs do not cross-react with HIT antibodies. Development of antibodies to lepirudin has been observed in approximately 50% of patients after ten days of treatment, including severe anaphylactic reactions with fatal outcomes in cases of re-exposure to lepirudin.<sup>85, 86</sup> Dose adjustments for argatroban in specific populations<sup>79, 87, 88</sup> and for lepirudin in general<sup>89-91</sup> have been recently recommended. The DTI desirudin, which has the advantage of subcutaneous dosing, has been successfully used in a limited number of patients with HIT.<sup>92, 93</sup> The DTI bivalirudin, which has a short half-life and enzymatic degradation, has been used for anticoagulation of HIT patients during cardiac surgery.<sup>94-96</sup> DTIs have also been used successfully in HIT patients requiring invasive cardiac procedures.<sup>97, 98</sup> DTIs should be treated as individual drugs as each has its own pharmacologic characteristics.

The heparinoid danaparoid, has been used to treat HIT patients with success<sup>99-101</sup> but there are reports that danaparoid cross-reacts with some HIT antibodies leading to treatment fail-

ures.<sup>101-105</sup> The synthetic heparin pentasaccharide, fondaparinux, has been shown to be useful for the management of patients with HIT through several small published case series and is gaining favor.<sup>106-109</sup>

LMWH can cross-react with most HIT antibodies and is contraindicated for use in patients with HIT.<sup>27, 110, 111</sup>

Vitamin K antagonists (VKAs) are recommended for long-term treatment of HIT associated thrombosis.<sup>31</sup> VKAs are not recommended for use in the acute phase of HIT due to their potential to intensify the prothrombotic state from a transient protein C deficiency.<sup>112, 113</sup> VKAs should be initiated when platelet counts have normalized to a steady state then brought on under bridging with a DTI.<sup>114-116</sup>

There is emerging evidence that the newly developed small molecule anticoagulants including apixaban, dabigatran, edoxaban, otamixaban, and rivaroxaban may become new immediate and long-term treatment options for thrombosis in patients with HIT.<sup>109</sup>

### *Recommendations*

Early diagnosis and treatment are important to improve clinical outcomes. 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 2-3 days in patients treated with LMWH and daily if treated with UFH, if the patient's risk of developing HIT is high (Level of evidence: moderate).** For medical and obstetric patients treated with LMWH exclusively and no prior exposure to UFH it is no longer considered necessary to monitor the platelet count. Patients with co-morbidities are at higher risk of poorer clinical outcomes. All clinical settings including the Emergency Department need to be aware of a patient's history of HIT and prior UFH or LMWH exposure.

Several clinical scoring systems are available which can help diagnose HIT. **Laboratory testing should be performed when there is a strong suspicion of HIT (Level of evidence: moderate).** Laboratory tests are used to confirm a diagnosis of HIT, but negative results do not exclude the diagnosis. It is useful to perform a combination of tests and to repeat testing over

a period of several days. Initial therapeutic decisions should not be dependent upon a positive laboratory test, but should be based upon clinical findings particularly thrombocytopenia and/or new thromboembolic events.

**UFH and LMWH should be stopped when the diagnosis of HIT is strongly suspected or confirmed (level of evidence: high).** It is not sufficient to merely remove the heparin. Due to the strong hypercoagulable state and high risk of thrombosis associated with HIT, it is recommended that all HIT patients be treated with a non-heparin anticoagulant such as **argatroban, lepirudin, or danaparoid (level of evidence: moderate)**. Differences between these drugs need to be considered when making a clinical treatment decision (*e.g.*, patient renal or liver clearance, drug pharmacokinetics, patient risk of bleeding, prior exposure of patient to lepirudin, physician's experience with the drug, drug availability, acute anticoagulant need, long-term treatment, cross-reactivity of drug to HIT antibodies, etc.). With danaparoid treatment, if daily platelet counts do not show signs of recovery within three days, it is mandatory to check for immune cross-reactivity of patient antibodies to danaparoid using a functional platelet assay and discontinue treatment if positive. **Fondaparinux may be considered as a second-line agent in the management of patients with suspected HIT (level of evidence: low).** LMWH is contraindicated in patients with HIT (level of evidence: moderate).

For long-term anticoagulation, a VKA can be used. To avoid warfarin-induced limb gangrene or skin necrosis in patients with HIT, **the VKA should only be administered after rise of platelet counts with substantial recovery to  $>100 \times 10^9/L$  or to pre-HIT values (level of evidence: low)**. Starting doses need to be low (5 mg warfarin, 6 mg phenprocoumon), and given with overlapping administration of argatroban, lepirudin, or danaparoid for at least five days.

**For HIT patients undergoing coronary artery interventional procedures, bivalirudin or argatroban anticoagulation is recommended (Level of evidence: moderate).** For special populations of patients with HIT requiring anticoagulation such as pregnant or pediatric patients or patients undergoing cardiac surgery or hemodialysis, specific drug and dose issues need

to be considered. For postoperative cardiac surgery patients, LMWH not UFH should be used to decrease the risk of developing HIT, and if HIT is suspected, a non-heparin anticoagulant should be used.

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# SUPERFICIAL VEIN THROMBOSIS

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## General considerations

The incidence of superficial vein (SVT) in the general population ranges from 3% to 11%.<sup>1-4</sup> The prevalence 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.<sup>3</sup> The mean age of presentation is 60 years<sup>1, 5-10</sup> and the older the patient, the fewer risk factors are present.<sup>10, 11</sup> SVT is more common (50-70%) in women.<sup>1, 5, 7, 8, 12-18</sup> The great saphenous system is involved in 60-80% of patients, and the small saphenous system in 10-20%.<sup>1, 7, 19, 20</sup> Bilateral SVT is reported in 5-10% of patients.<sup>1, 5, 7, 20, 21</sup>

Development of SVT in patients with varicose veins ranges from 4-59%,<sup>1, 7, 12, 16, 20</sup> and it is confined more frequently to varicose tributaries rather than to the saphenous trunks.<sup>1, 16</sup> Obesity, age and Protein-S deficiency have been found as factors associated with SVT episodes in patients with varicose veins.<sup>22</sup>

SVT in patients without varicose veins is found in 5-10% of all patients<sup>7, 8, 23</sup> and the etiology includes: autoimmune disease (Behçet's, Buerger's and Mondor's disease),<sup>4, 5</sup> malignancy,<sup>4, 5, 21, 24</sup> thrombophilia,<sup>2, 4-6, 13, 25-34</sup> mechanical or chemical trauma or injury (venous infusion, catheter introduction),<sup>35</sup> radiation injury<sup>35</sup> and bacterial or fungal infections.<sup>35</sup>

Risk factors are the same as those for deep vein thrombosis<sup>13, 36</sup> including: previous thromboembolic events, long-haul flights,<sup>37, 38</sup> pregnancy,<sup>39, 40</sup> oral contraceptives, hormone replacement thera-

py, immobilization,<sup>14, 41</sup> obesity, recent surgery,<sup>14</sup> trauma<sup>14, 41</sup> and sclerotherapy.<sup>42</sup>

Obesity as assessed by increased BMI is associated with an increase in prothrombotic factors (fibrinogen, von Willebrand Factor, factor VII and viscosity)<sup>43</sup> and is an independent risk factor not only for VTE,<sup>44-46</sup> but also for SVT.<sup>1, 25, 36</sup>

SVT may coexist with DVT in 6-53% of patients presenting with SVT.<sup>4, 7, 12, 15, 16, 20, 47-58</sup> The most common is extension from the great saphenous vein into the femoral vein.<sup>20</sup> SVT of the great saphenous vein above knee is associated with 17-19% incidence of DVT whereas SVT confined to the below knee segment has an incidence of associated only in 4-5% of patients.<sup>10, 36, 48</sup> DVT may complicate "isolated" SVT in a short term.<sup>4, 7, 8, 59</sup> SVT is a risk factor for the development and recurrence of DVT.<sup>1, 4, 7, 19, 60</sup>

PE has been observed in 1.5-33% of SVT patients.<sup>4, 7, 8, 15, 20, 52, 54, 61, 62</sup> PE was reported in 18% of patients when the thrombotic process was in the GSV above the knee and 4% when in the SSV.<sup>20</sup> PE may complicate "isolated" SVT in the short term (3-4 months after the episode of SVT).<sup>7, 8, 36</sup> SVT is a risk factor for development and recurrent PE.<sup>1, 4, 7, 19, 60</sup> It is unclear whether PE associated with SVT arises from extension to deep veins or from thrombus that is only in the superficial venous system.<sup>1</sup>

The link between SVT and pregnancy remains unclear<sup>1, 13, 39, 40, 63-65</sup> and the prevalence is very low (0.05-0.1%) but it may be underestimated as only symptomatic patients are included.<sup>39, 40</sup>

SVT presents with local pain, warmth, ery-

thema, swelling and the superficial vein becomes solid like a cord.<sup>1, 5, 29, 66</sup> Diagnosis should include Duplex ultrasound for confirmation, estimation of thrombus extent, exclusion of deep venous thrombosis and for follow-up.<sup>4, 5, 9, 10, 17, 20, 21, 49-53, 56, 57, 67</sup>

The term superficial thrombophlebitis should be discouraged because inflammation and infection is not the primary pathology.<sup>35</sup> It should be called superficial vein thrombosis in order to avoid the unnecessary administration of antibiotics and the misconception that SVT is benign.

### *Treatment*

The rationale and evidence for treatment as summarized in this chapter has been provided by a recent guideline document.<sup>35</sup>

There is great variation in treatment. In a national cross-sectional and prospective epidemiologic cohort study (POST) in France,<sup>7</sup> 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 one or more anticoagulant drugs either at therapeutic doses 374 (62.9%) or at prophylactic doses 216 (36.7%) while 99 (16.8%) received vitamin K antagonists. Elastic stockings compression stockings received 584 (97.7%), topical NSAIDs received 278 (47.2%) and oral NSAID 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%).

A randomized open trial 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 with regard to SVT extension at three months.<sup>68</sup>

A randomized double blind trial involving 427 patients compared **LMWH** (enoxaparin 40 mg and 1.5 mg/kg) with a non-steroidal anti-inflammatory agent (tenoxicam) and placebo for 8-12 days.<sup>69</sup> Rates of DVT and SVT as detected by ultrasonography at 12 days was 30.6% in the placebo, 14.9% in the tenoxicam, 6.9% in the enoxa-

parin 1.5mg/kg and 8.3% in the enoxaparin 40 mg (P<0.01).

In another open randomized trial involving 117 patients, **LMWH** (nadroparin) was superior to a non-steroidal anti-inflammatory agent in reducing symptoms at six days (P<0.001) and eight weeks (P=0.007).<sup>70</sup>

**High doses of UFH** b.d. (12500 IU for one week followed by 10000 IU for three weeks) were superior to prophylactic doses (5000) b.d. in 60 randomized patients. During the six 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).<sup>71</sup> 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.<sup>72</sup>

In a systematic review that included five randomized controlled trials,<sup>73</sup> pooling of the data was not possible due to their heterogeneity. Three of these studies had serious methodological drawbacks limiting the clinical applicability of their results. In the remaining two studies, a non-significant trend in favour of high- compared to low-dose UFH for the prevention of VTE was observed in one and a non-significant trend in favor of short-term treatment with LMWH or NSAID as compared to placebo in respect to VTE was observed in the other. The authors recommended treatment with at least intermediate doses of LMWH.

Another systematic review on the treatment of SVT included 24 studies that were of poor methodological quality. The analysis included in total 2469 patients,<sup>74</sup> and treatment ranged from LMWH to NSAIDs, topical treatment, surgery or wearing compression stockings. The LMWH studies were more rigorous. The conclusion was that both LMWH and non-steroidal anti-inflammatory agents significantly reduced the incidence of extension or recurrence of SVT by approximately 70% compared with placebo and both had similar safety and efficacy. Topical treatments improved local symptoms but there was not any report on the progression to DVT. Surgical treatment combined with elastic stockings was associated with lower rate of VTE and progression of SVT compared with elastic stockings alone. The authors recommended an intermediate dose of LMWH for at least one month

and pointed out that further research was needed to assess the role of NSAIDs and LMWH, the optimal doses, and duration of treatment, and whether combination therapy may be more effective than single treatment.

A small RCT involving 72 patients compared **LMWH (dalteparin)** with a **non-steroidal anti-inflammatory drug (ibuprofen)** for 14 days.<sup>75</sup> There was extension of the thrombosis in four (11%) patients in the dalteparin group and in none in the ibuprofen group ( $P=0.05$ ). There was a significant reduction in pain in both groups when compared with baseline, but there was no difference in the reduction of pain between the groups during the treatment period or at 14 days. There was no statistical difference in the extension of thrombosis at three months after treatment was stopped.

A recent international randomized double blind trial involving 3002 patients<sup>8</sup> 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 five cm long as confirmed by compression ultrasonography. Exclusion criteria were the interval between the onset of symptoms and planned randomization more than three weeks; treatment for cancer within the previous six months; presence of symptomatic or asymptomatic DVT, symptomatic documented PE, SVT associated with sclerotherapy or placement of an intravenous catheter, SVP located within three cm of the saphenofemoral junction, DVT or PE within the previous six months, if the patients with SVT had received an antithrombotic agent (other than aspirin at a dose of  $\leq 325$  mg per day) for more than 48 hours or a NSAID for more than 72 hours for the current episode, if in the investigator's opinion a saphenofemoral junction ligation was required, major surgery within the previous three months, if there were conditions that could confer predisposition to bleeding including creatinine clearance  $< 30$  mL/min or platelet count  $< 100,000/\text{mm}^3$  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 at day 77. No difference was observed in major bleeding between the two groups.

A review of six studies comparing **surgery** to anticoagulation showed similar rates of SVT progression, but the incidence of VTE and complications was higher with surgery.<sup>76</sup> Surgical treatment with elastic stockings was associated with lower VT rate and SVT progression compared to elastic stockings alone.<sup>79</sup> In another study no difference was seen between surgery and enoxaparin for four weeks.<sup>77</sup>

**Antibiotics** have no role in the management of SVT<sup>35, 78</sup> except in cases secondary to indwelling intravenous catheters. **Hirudoids** have some effect in alleviating pain and local inflammatory signs and some topical agents (hirudoid cream, piroxicam cream, piroxicam patch) are available in some countries.<sup>79</sup> Local application of heparinoid cream was better than placebo.<sup>80, 81</sup> Local application of heparin was reported to have effects on symptoms comparable to LMWH.<sup>82</sup> **Elastic stockings** are traditionally used if tolerated as an adjunctive treatment together with anticoagulation.<sup>5, 31</sup>

### *Recommendations*

All patients with SVT should have bilateral duplex scanning to exclude DVT (**level of evidence: high**).

**LMWH in intermediate doses** for at least one month is recommended (level of evidence: moderate).

**Fondaparinux 2.5 mg daily** for at least four weeks is an effective treatment (**level of evidence: high**).

**Surgery is not better than LMWHs (level of evidence: low)**.

When thrombus is close to saphenofemoral or saphenopopliteal junctions **LMWHs in therapeutic doses** or **surgery** (ligation) are both acceptable options depending on the patient's characteristics and the treating physician's preference (**level of evidence: low**).

For isolated SVT at the below knee segment confined to varicosities, local application of **heparinoids, NSAIDs and elastic stockings** is an acceptable treatment option (**level of evidence: low**).

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# PREVENTION OF POST-THROMBOTIC SYNDROME

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## General considerations

Despite conventional anticoagulation therapy (LMWH for five days followed by warfarin), 30-50 % of patients with DVT will develop the post-thrombotic syndrome (PTS) <sup>1</sup> which consists of a constellation of symptoms and signs of variable severity. These include limb swelling, pain, heaviness, itching, skin changes and ulceration.<sup>2</sup> The most predictive single clinical finding is the presence of a venous ulcer which may occur as early as three months.<sup>3</sup> The established post-thrombotic syndrome (PTS) is a significant cause of chronic incapacity and inability to work with considerable consequences for both the patient and society.<sup>4-7</sup>

PTS is the result of venous hypertension produced by reflux in veins with damaged valves and/or persisting outflow obstruction.<sup>8</sup> Venous hypertension is associated with chronic inflammation affecting not only the venous wall but also the microcirculation producing excessive capillary leakage and impairment of skin nutrition with skin changes and eventual skin ulceration.<sup>9</sup>

Factors associated with the development of PTS consist of iliofemoral DVT,<sup>4, 5</sup> chronic iliofemoral vein obstruction,<sup>10, 11</sup> increased BMI,<sup>5, 12</sup> recurrent DVT,<sup>12</sup> which often obstructs part of the collateral circulation and sub-therapeutic anticoagulant therapy which allows recurrence.<sup>13</sup> More recently, it has been demonstrated that elevated inflammatory biomarkers such as Il-6, ICAM-1 and CRP <sup>14, 15</sup> are also associated with increased rates of PTS following DVT.

## Prevention of PTS

### PREVENTION OF PRIMARY AND SECONDARY DVT

Prevention of DVT should reduce the prevalence of PTS in the general population. There is an interplay between PTS and recurrent DVT. Patients with PTS suffer a high frequency of recurrent DVT. Recurrent DVT in the same leg results in a higher frequency and severity of PTS. Until recently, PTS was viewed as a late complication. However, recent data show that PTS occurs early and that review of signs and symptoms at one month after the onset of DVT is highly predictive of the presence of PTS.<sup>5</sup> Prevention of recurrence in patients with DVT will lessen the severity and frequency of PTS. The evidence and guidelines for primary prevention have been summarised in sections 3-12 and for secondary prevention in sections 14, 15, 17 and 18. Guidelines aiming to reduce PTS and leg ulcers by 50% in the next ten years have been published.<sup>16</sup>

### GRADUATED ELASTIC COMPRESSION

Effective elastic compression has been shown to reduce venous hypertension and edema, and to minimise damage to the microcirculation.<sup>17, 18</sup> Four RCT involving 745 patients demonstrated that in patients with proximal DVT, elastic compression for two years reduces the incidence of PTS from 39% to 19% (RR 0.49; 95% CI 0.38 to 0.62).<sup>19-22</sup> It appears that **treatment with LMWH combined with early ambulation and elastic compression further prevents PTS.**<sup>23, 24</sup>

TABLE I.—American College of Chest Physicians: suggested risk stratification for perioperative thromboembolism.<sup>5</sup>

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10%/year risk of ATE or >10%/month risk of VTE)	Any mechanical mitral valve	CHADS <sub>2</sub> score of 5 or 6	Recent (<3 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 Antiphospholipid antibodies Multiple thrombophilias
Moderate (4–10%/year risk of ATE or 4–10%/month risk of VTE)	Recent (<6 month) stroke or TIA	Rheumatic valvular heart disease	
	Bileaflet AVR with major risk factors for stroke	CHADS <sub>2</sub> score of 3 or 4	VTE within past 3–12 months Recurrent VTE Non-severe thrombophilia Active cancer
Low (<4%/year risk of ATE or <2%/month risk of VTE)	Bileaflet AVR without major risk factors for stroke	CHADS <sub>2</sub> score of 0–2 (and no prior stroke or TIA)	VTE more than 12 months ago

ACCP: American College of Chest Physicians; ATE arterial thromboembolism; VTE:venous thromboembolism; AVR: aortic valve; TIA: transient ischemic attack.

#### EARLY THROMBUS REMOVAL

Thrombectomy was popularised 30 years ago. Early surgical thrombectomy in a small series of patients with iliofemoral DVT was associated with increased iliac vein patency compared with standard anticoagulation therapy alone (67% vs. 34%) (RR for patency 1.92; 95% CI 1.06 to 3.51) 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).<sup>25, 26</sup>

Limited data with catheter directed thrombolysis (CDT) from observational cohort studies and comparative non-randomized studies appear to demonstrate increased vein patency and reduction in the incidence of PTS compared with conventional anticoagulation.<sup>27-30</sup>

Two RCT compared pharmacologic catheter-directed thrombolysis with standard anticoagulation involving a total of 138 patients with iliofemoral DVT.<sup>31, 32</sup> At six months, the patency rate was 70% in the catheter-directed thrombolysis group and 33% in the standard anticoagulation group (RR 0.48; 95% CI 0.33 to 0.70). The second study continued to recruit 209 patients and has recently reported on iliofemoral patency and PTS.<sup>33</sup> Ilio-femoral patency at six months was 64% in the catheter-directed thrombolysis group and 47% in the conventional treatment group (RR for patency 1.42; 95% CI 1.09 to 1.85).

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). Clinically relevant bleeding events occurred in 9% of patients. More RCT are needed with PTS as the primary endpoint to assess efficacy and harm.

#### RELIEF OF CHRONIC POST-THROMBOTIC OBSTRUCTION OF ILIOFEMORAL SEGMENT

Prospective observational studies have raised the hope that percutaneous endovascular venoplasty and stenting to relieve chronic venous obstruction may alleviate the symptoms of PTS.<sup>10, 34</sup> RCT are needed to demonstrate the efficacy of endovascular venoplasty and stenting for preventing symptoms and ulcer recurrence.

In the largest series published,<sup>10</sup> primary, assisted-primary and secondary cumulative patency rates at 72 months were 79%, 100%, and 100% respectively for nonthrombotic disease and 57%, 80% and 86%, respectively for thrombotic disease. Severe leg pain (visual analogue scale >5) and leg swelling (grade 3) decreased from 54% and 44% respectively prior to stenting to 11% and 18% after stenting. At five years, cumulative rates for complete relief of pain and swelling were 62% and 32%, respectively, and ulcer healing occurred in 58%. The mean CIVIQ scores

of QOL improved significantly in all categories. RCT are needed to determine efficacy.

#### LONG-TERM LMWH

Standard treatment of DVT (initial LMWH for five days followed by VKA) prevents thrombus extension and embolization but does not directly lyse the thrombus which often results in only partial recanalization. Several studies have compared **long-term treatment with LMWH versus standard therapy**<sup>35-40</sup> and have demonstrated **better recanalization in the long-term LMWH groups**. A meta-analysis on five studies that reported on total recanalisation demonstrated a risk ratio of 0.66 (95% CI 0.57 to 0.77;  $P < 0.0001$ ) in favor of long-term LMWH.<sup>41</sup> In a large multicenter study involving 480 patients there was a reduction in PTS (RR 0.77;  $P = 0.001$ ).<sup>42</sup> Pooled analysis from two studies reporting on subsequent development of leg ulcers<sup>42, 43</sup> yielded an 87% risk reduction with LMWH for the incidence of venous ulcers ( $P = 0.019$ ).<sup>41</sup>

#### Recommendations

Adherence to the guidelines for the **prevention of primary DVT** in hospitalised patients is essential. In patients who present with DVT, every effort should be made to **reduce recurrence rates. This can be achieved by using adequate intensity and duration of anticoagulation according to the guidelines.**

**Early thrombus removal using CDT (level of evidence: low) or pharmacomechanical thrombolysis (level of evidence: low)** may be used in expert centers in selected patients with iliofemoral DVT. If thrombolysis is contraindicated, surgical thrombectomy could be used in expert centers (**level of evidence: low**). Angioplasty and stenting of a proximal stenosis along with early thrombus removal may be required (**level of evidence: low**). However, a method to select appropriate patients for this procedure is not available.

Although **conventional anticoagulation** (LMWH for five days followed by VKA) is based on a **high level of evidence in terms of VTE recurrence, prolonged therapy with LMWH in patients with proximal DVT is preferable in terms of PTS prevention (level of evidence: moderate).**

In patients with proximal DVT, **graduated elastic compression stockings for at least two years** in addition to appropriate anticoagulation are recommended (**level of evidence: high**).

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# PERIPROCEDURAL MANAGEMENT OF ANTITHROMBOTIC THERAPY AND USE OF BRIDGING ANTICOAGULATION

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## General considerations

The periprocedural management of patients requiring temporary interruption of vitamin K antagonists (VKA) such as warfarin due to an elective invasive procedure or elective surgery is a common clinical problem.<sup>1</sup> In North America alone an annual estimate of 250,000 patients who are receiving antithrombotic therapy will be assessed for an elective surgical or invasive procedure.<sup>2</sup> Management of these patients is difficult due to the risk of bleeding when antithrombotic therapy is administered in close proximity to an invasive procedure or surgery *versus* the risk of thromboembolism if antithrombotic therapy is 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 antithrombotic therapy is needed in the periprocedural period; and 2) if bridging anticoagulation is needed among those patients requiring temporary interruption of antithrombotic therapy. Bridging anticoagulation can be defined as the use of short-acting parenteral anticoagulants such as UFH or subcutaneous LMWH - usually in therapeutic doses - in the pre- and post-procedural period to maintain an anticoagulant effect during temporary interruption of VKA when the INR is subtherapeutic.

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%.<sup>3</sup> Moreo-

ver, postoperative bleeding delays resumption of antithrombotic therapy, thereby placing patients at risk for thromboembolism.<sup>4</sup> Bleeding risk assessment involves considerations of 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 characterize procedures into a two-tiered risk scheme of high and low bleed risk in developing a periprocedural management strategy. High bleeding risk procedures include most major operations lasting >45 minutes, vascular procedures, major orthopedic procedures, cardiothoracic procedures, extensive cancer surgery, and prostate or bladder surgery.<sup>5</sup> In addition, invasive procedures such as resection of colonic polyps, prostate, liver, or kidney biopsy, or pacemaker or defibrillator implantation may place the patient at increased risk of bleeding or significant pocket hematomas.<sup>6, 7</sup> Most operations lasting <45 minutes or minor invasive procedures including diagnostic gastrointestinal procedures, dermatological and dental procedures or ophthalmologic procedures carry a low bleeding risk.<sup>8</sup>

Thrombotic risk assessment should account for the estimated risk of arterial thromboembolism or VTE and include procedural-related risks. A thrombotic risk assessment is based on the three most common indications for VKA therapy (mechanical heart valve, atrial fibrilla-

tion or VTE, and patients may be classified into a high, moderate, and low VTE risk groups (Table 22.I). Although an increased risk of VTE in the post-operative 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 modeling) in the perioperative setting, especially among patients undergoing major surgery.<sup>9</sup>

An overall risk assessment of bleeding and thrombotic risk factors for arterial thromboembolism or VTE should be made taking into account both patient-related and procedure-related factors in order to develop a periprocedural antithrombotic strategy. The case-fatality of a major bleed is approximately 8-9%, an embolic stroke is associated with a case-fatality or permanent major neurologic defect approaching 70%, and thrombosis of a heart valve can lead to fatality 15% of the time.<sup>3, 10, 11</sup> For VTE, the case-fatality is approximately 5-9%.<sup>3</sup> Lastly, it seems that an INR >3 at the time of surgery may confer a higher risk for bleeding complications (OR 1.6; 95% CI: 0.4-4.0).<sup>12</sup>

### **Periprocedural management of patients undergoing minor procedures**

Minor dental, dermatological or ophthalmological procedures comprise approximately 20% of procedures in patients receiving VKA.<sup>5</sup> Randomized trials and prospective cohort studies indicate that patients who continue VKA during dental extraction, especially with co-administration of anti-fibrinolytic 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.<sup>13-15</sup> Partial interruption of VKA 2-3 days prior to a dental procedure has also been associated with low bleed risk.<sup>16</sup> In addition, prospective cohort studies in patients undergoing 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.<sup>17-19</sup>

### *Interruption of VKA and bridging anticoagulation*

Basic principles for patients receiving VKA who require temporary interruption and bridging anticoagulation with parenteral UFH or LMWH are as follows.

1. For patients undergoing a high-bleeding risk procedure or surgery where there is intent to minimize the antithrombotic effect of VKA in the pre-procedural period, approximately five days of interruption of warfarin is needed, based on a half-life of approximately 36-42 hours.<sup>16</sup> 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.<sup>20</sup>

2. There appears to be a detectable residual anticoagulant effect, as measured by anti-FXA  $\geq 0.10$  IU/mL, if therapeutic-dose LMWH is given within 12 hours of the start of the procedure.<sup>21</sup>

3. Preoperative administration of low-dose vitamin K orally (1-2.5 mg) in patients with an elevated INR (<sup>3</sup>1.5) does not appear to be associated with resistance to re-anticoagulation when VKA is resumed after surgery.<sup>22</sup>

4. Current global coagulation tests such as the activated partial thromboplastin time (aPTT), prothrombin time (PT), and heparin anti-FXA level are likely to be inadequate to measure the dual anticoagulant effects of both VKA and heparin in the periprocedural period, while other emerging tests such as the thrombin generation (TG) assay may have improved sensitivity in detecting the global anticoagulant effects of both LMWH and VKA.<sup>23</sup>

5. In the post-procedural period, administration of antithrombotic therapy at close proximity to the procedure or at therapeutic *versus* prophylactic doses may increase the bleeding risk. Therefore in high bleeding risk procedures, delaying resumption of bridging therapy (for 48-72 hours after the procedure), decreasing the dose of bridging therapy (*i.e.*, prophylactic-dose), or avoiding post-procedure bridging anticoagulation may decrease the risk of bleeding.<sup>24</sup>

6. There is no evidence that non-therapeutic-dose bridging anticoagulation with UFH or LMWH is effective for preventing arterial thromboembolism.<sup>25</sup>

7. 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.<sup>26</sup>

8. 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.<sup>27</sup>

#### *Bridging anticoagulation in patients with a mechanical heart valve (MHV), AF or VTE receiving VKA*

There are multiple prospective cohort studies in which bridging anticoagulation has been assessed in patients with a MHV that included patients with aortic, mitral, or dual position MHVs, as well as a minority of patients with older, caged-ball MHVs. The majority of these studies included therapeutic-dose LMWH regimens (*i.e.*, enoxaparin 1mg/kg sc b.d. or 1.5mg/kg once-daily, dalteparin 100 IU/kg b.d. 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%.<sup>4, 28-31</sup> One recent study of 172 patients with prosthetic heart valves on chronic VKA needing temporary interruption for an elective procedure or surgery found one arterial thromboembolic event and an overall adverse event rate of 5.5% using mostly outpatient-based treatment-dose LMWH as bridging therapy.<sup>28</sup>

Some recent cohort studies have assessed intermediate-dose LMWH as bridging therapy (*i.e.*, 70 anti-Xa IU/kg b.d.) with low thromboembolic and bleed rates.<sup>32</sup> The incidence of thromboembolic events with older studies using intravenous UFH as bridging therapy found more variable arterial thromboembolic event rates.<sup>33</sup> Mathematical modeling of a patient with a MHV not treated with a VKA in the periprocedural period is estimated at 0.046% per day (17% annual risk divided by 365 days) or ~0.4% for eight days. The finding of a higher arterial thromboembolic event rates in bridging studies suggest a higher than expected risk.

There are also prospective cohort studies in which mostly therapeutic-dose LMWH bridging

anticoagulation was assessed in patients with AF.<sup>4, 24, 29, 30, 34</sup> The pooled risk of perioperative arterial thromboembolism was also ~1%. Most patients described in such studies had at least one additional stroke risk factor as per CHADS<sub>2</sub> criteria. There are reports that collectively describe an arterial thromboembolic event rate of ~1% in patients with permanent AF that did not receive bridging anticoagulation, which is higher than mathematical modeling predicts (*i.e.*, ~0.1% for eight days, 5% annual risk divided by 365 days).<sup>35</sup> More recent larger studies have included intermediate-dose LMWH bridging regimens with good outcomes in patient populations that have included patients with atrial fibrillation.<sup>32, 36, 37</sup>

There is a need for placebo-controlled studies in VKA-treated patients with MHV or AF indications for warfarin to obtain strong evidence for efficacy and safety of bridging anticoagulation in the periprocedural period. Towards this end the PERIOP-2 (clinicaltrials.gov/NCT00432796) and BRIDGE (clinicaltrials.gov/NCT00786474) studies have been initiated and are actively enrolling VKA-treated patients who require elective surgery and will be randomly allocated to bridging or no bridging regimens.

Multiple prospective cohort studies have evaluated bridging anticoagulation with therapeutic-, intermediate- or low-dose regimens of various LMWHs in patients with VTE.<sup>24, 29, 34, 36, 38</sup> The pooled risk for recurrent symptomatic VTE was low (<1%). These studies did not include control groups.

There are no clinical data available to optimize periprocedural administration of the novel small molecule antithrombotic agents such as the direct thrombin inhibitor dabigatran and direct anti-FXa inhibitor rivaroxaban. However, the pharmacological properties of these agents with their relatively short half-lives have the potential to eliminate the need for bridging therapy. Perioperative guidelines for the use of these agents based on their pharmacokinetic and pharmacodynamic properties have been suggested.<sup>39-41</sup> Dabigatran (with its mostly renal elimination) can be discontinued 24 hours before a low bleed risk procedure and approximately 2-4 days before a high-bleed risk procedure in patients with a creatinine clearance (CrCl) >50 mL/min.<sup>40</sup> In patients with moderate renal insufficiency (CrCl

30-50 mL/min), dabigatran should be discontinued at least two days before a low bleed risk procedure and four days before a high bleed risk procedure, respectively. As rivaroxaban is not predominately cleared by renal elimination, it can be stopped approximately 24-48 hours before a procedure in most circumstances.<sup>39</sup> Resumption of therapy for both agents can occur within 24 hours after low bleed risk procedures and approximately 48-72 hours after high bleed risk procedures.<sup>39</sup> Prospective cohort studies with dabigatran in the periprocedural period have recently been initiated.

### Recommendations

In patients undergoing minor dermatological and ophthalmological procedures (specifically cataract extraction) and are receiving VKA, **continuing VKA** around the time of procedure should be considered (level of evidence: low). For dental procedures, consider co-administration of an oral prohemostatic agent (tranexamic acid) while **continuing VKAs (level of evidence: moderate)**. Another option in patients undergoing dental procedures includes stopping VKA 2-3 days before the procedure (level of evidence: low).

In patients undergoing a high-bleeding risk procedure or surgery, discontinuation of VKA (warfarin) approximately five days prior to allow adequate time for the INR to normalize is indicated (**level of evidence: moderate**). In patients who are receiving **therapeutic-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**). **For intravenous UFH**, we suggest stopping approximately four hours prior to the procedure or surgery (**level of evidence: low**). In patients whose INR is still elevated 1-2 days before the procedure (INR  $\geq 1.5$ ), consider administering low-dose (1-2.5 mg) oral vitamin K to normalize the INR (**level of evidence: low**). In patients undergoing a minor invasive or surgical procedure, bridging anticoagulation with LMWH should be resumed **within 24 hours** after the procedure if there is adequate hemostasis (**level of evidence: low**). In patients undergoing major surgery or high-bleeding risk procedures,

consider one of three options: 1) **delay LMWH approximately 48-72 hours** after surgery until hemostasis is achieved; 2) administer low-dose LMWH (usually within 24 h after a procedure); or 3) avoid post-procedural bridging therapy altogether (**level of evidence: low**). **LMWH** should be used in the outpatient setting as bridging therapy over in-hospital **UFH** to avoid hospitalization (**level of evidence: low**).

In patients with MHV and 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**). LMWH should be preferred over UFH. In patients at moderate arterial thromboembolic or VTE risk, assessment of individual patient- and surgery related factors should be considered over a standardized approach on whether to use bridging therapy (**level of evidence: low**). In patients at **low arterial thromboembolic or VTE risk, no bridging therapy** should be considered (**level of evidence: low**). In all patients undergoing major procedures or operations for which there are international guideline recommendations for VTE prevention in the post-operative period, an appropriate prophylactic agent should be used during re-initiation of VKA if postoperative heparin bridging is not used (**level of evidence: moderate**).

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# COST-EFFECTIVENESS OF PREVENTION AND TREATMENT OF VTE

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## Cost-effectiveness of primary prevention

There is now an extensive literature concerning cost-effectiveness of approaches commonly used for primary prevention of VTE.<sup>1-40</sup>

In selecting and evaluating studies for this section, we include only those in which data for comparative effectiveness of approaches is based on randomized trials and/or systematic reviews of such trials, and which follow established guidelines for valid cost-effectiveness analysis.<sup>41-43</sup> 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 considered to be 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.<sup>44, 45</sup>

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".<sup>1-6, 18, 27</sup> Primary prevention is also cost-effective compared with case-finding (screening) for DVT.<sup>2</sup> Case-finding does not prevent development of DVT and therefore does not reduce morbidity from PTS and its associated costs. 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.

There have been several studies evaluating cost-effectiveness of primary prophylaxis using different anticoagulant drugs in patients having hip or knee replacement surgery or surgery for fractured hip.<sup>12, 13, 19, 32, 33</sup> Two studies based on the US healthcare system,<sup>12, 19</sup> and one study based on the Norwegian system,<sup>13</sup> 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. A study based on the UK National Health Service found dabigatran etexilate was cost-saving compared with enoxaparin.<sup>40</sup> (40 mg once daily) in patients having total hip or knee replacement.<sup>33</sup> A study based on the Irish healthcare system evaluated cost-effectiveness of prophylaxis using either dabigatran etexilate or rivaroxaban compared to enoxaparin.<sup>32</sup> Finally, a study from the perspective of the Canadian health system found rivaroxaban to be a cost-effective alternative to enoxaparin.<sup>38</sup> Thus, the available evidence from studies in three different health systems indicates that both dabigatran and rivaroxaban are cost-effective alternatives to enoxaparin.<sup>32, 33, 38</sup> The available evidence is inconclusive regarding the relative cost-effectiveness of rivaroxaban and dabigatran.<sup>32</sup>

The cost-effectiveness of an extended duration of prophylaxis (28 to 35 days) after hip replacement or surgery for fractured hip has been

evaluated in multiple studies.<sup>20, 24, 30, 35, 37</sup> Two Canadian studies evaluated extended prophylaxis with LMWH compared with warfarin or no extended prophylaxis<sup>24,30</sup>. Dranitsaris *et al.*<sup>30</sup> reported the incremental cost of 35 days of prophylaxis with dalteparin was Cdn \$ 31200-40100 per QALY, whereas Skedgel *et al.*<sup>24</sup> 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<sup>30</sup> and Skedgel *et al.* found extended prophylaxis with LMWH met the cost-effective threshold of Cdn \$ 50000 per QALY when less than 10% of patients require home nursing services.<sup>24</sup> Two studies, one from Sweden,<sup>20</sup> and the other from Italy,<sup>35</sup> 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 replacement patients included a duration of prophylaxis of 35 days.<sup>38</sup>

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.

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.<sup>46</sup> 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.<sup>21</sup> 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.<sup>29</sup>

Using the perspective of US Medicare reimbursement, Heerey and Suri<sup>14</sup> evaluated the cost-effectiveness of two regimens of LMWH (dalteparin 5000 U or 2500 U daily) compared with unfractionated heparin 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 \$ 50000 per QALY gained.<sup>14</sup> 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.<sup>14</sup> 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.

The cost-effectiveness of primary prevention in hospitalized medical patients using LMWH or unfractionated heparin has been evaluated in four studies;<sup>10, 18, 22, 27</sup> the health system was in the US in three studies<sup>10, 22, 27</sup> and in Germany in one study.<sup>18</sup> The results of all four studies are consistent indicating that prophylaxis with LMWH is more effective and less costly than with unfractionated heparin.

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.<sup>15</sup> 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 venous thromboembolism)**

The criteria for selecting studies to evaluate cost-effectiveness of alternative approaches for secondary prevention included randomized trials and/or systematic reviews of such trials to determine comparative effectiveness, and established guidelines for cost-effectiveness.<sup>41-43</sup> However, most studies to date have not used the QALY as the measure of effectiveness, and conclusions from these studies are based on cost-per-event of recurrent VTE.

The current standard care for most patients with established DVT or PE is anticoagulation consisting of initial treatment with either LMWH or intravenous unfractionated heparin followed by long-term treatment with a vitamin-K antagonist (*e.g.*, warfarin). The cost-effectiveness of anticoagulant therapy has been formally evaluated.<sup>47-50</sup> The cost-effectiveness of other approaches such as intravenous thrombolytic therapy, catheter-directed thrombolytic therapy and/or thrombus removal, or insertion of a vena cava filter has not been evaluated; these approaches have usually been reserved for specific indications in selected patients.

Two studies have compared the cost-effectiveness of intravenous unfractionated heparin with subcutaneous LMWH for the initial treatment of patients with DVT.<sup>47, 48</sup> The findings are consistent and indicate that LMWH is cost-effective. Hospitalization is the major driver for cost.<sup>47, 48</sup> LMWH is an effective approach to treat DVT out of hospital.<sup>51, 52</sup> LMWH for initial therapy is a cost saving approach if 8% or more of patients are treated entirely as outpatients, or 13% or more have a reduced hospital stay.<sup>47</sup>

Long-term anticoagulation is required in patients with VTE to prevent recurrent thromboembolism. The standard approach has been treatment with a vitamin-K antagonist with the dose adjusted according to laboratory monitoring of the anticoagulant effect. Long-term therapy with a vitamin-K antagonist is highly effective, and is cost-effective compared with inadequate long-term therapy.<sup>50</sup> However, the need for laboratory monitoring is associated with significant costs<sup>49, 50</sup> and is a burden which influences quality of life in many patients. Approaches to improve the

effectiveness, safety and efficiency of oral VKA therapy include specialized anticoagulation clinics and patient self monitoring. The data on cost-effectiveness of these approaches in patients with VTE is limited, since the studies have 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 is unlikely to be more cost-effective than specialized anticoagulation clinics, using a threshold of £ 30000 per QALY,<sup>49</sup> although patient self-monitoring may improve quality of life for some patients who travel frequently or have difficulty travelling to the clinic.<sup>49</sup>

LMWH therapy given in fixed doses without anticoagulant monitoring is an effective and safe approach to treat VTE for three to six months<sup>53-55</sup> but the cost-effectiveness of three to six months therapy with LMWH has not been formally evaluated. LMWH is preferred in cancer patients with VTE because it is markedly more effective than VKA treatment (NNT to prevent one recurrent VTE of approximately 13).<sup>53, 54</sup> LMWH is also effective in the broad spectrum of VTE patients without cancer, and in such patients, is associated with improvement in the patient's perceived quality of life.<sup>55</sup>

The new oral anticoagulants dabigatran and rivaroxaban have been evaluated for treatment of VTE including long-term therapy for three to 12 months.<sup>56, 57</sup> These drugs do not require laboratory monitoring of the anticoagulant effect and therefore, greatly simplify long-term anticoagulant treatment, but their cost-effectiveness remains to be evaluated.

The role of laboratory screening for thrombophilia in guiding clinical decisions about an extended or indefinite duration of anticoagulant therapy has garnered 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.<sup>58</sup> The relative cost-effectiveness of routine screening for thrombophilia versus targeted screening based on patient and family history requires further studies.<sup>58</sup>

A recent meta-analysis indicates that patients with unprovoked (idiopathic) proximal DVT or PE have a high annual risk of recurrence whenever treatment is stopped, whether the duration of treatment is three, six, 12 or 27 months.<sup>59</sup> This finding has important implications for future cost-effectiveness analysis.

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# KEY QUESTIONS TO BE ANSWERED

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Statements and recommendations made in this document are based on a literature review using clearly defined levels of evidence. This process has revealed a number of key questions that require to be addressed by future studies. They are summarised 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 and use of clinical nurse specialists have been shown to result in a marked increase in appropriate application of guidelines.

The risk of DVT after various minimally invasive abdominal surgical procedures and advanced laparoscopic surgery, as well as upper limb surgery, needs to be established.

Recurrence rates of DVT in relation to the residual thrombus, increased D-dimer or risk factors following treatment of the first episode needs to be determined.

A database needs to be created to establish the risk of pulmonary hypertension in patients with PE

The value of spiral CT evidence of right heart failure as predictor of a high-risk group in patients with PE requiring thrombolysis needs to be determined.

## Prophylaxis

Further studies are needed to assess additive effects on the efficacy, cost-effectiveness and safety of chemical agents (oral and injectable) and mechanical methods in high and medium-risk patients for various medical and surgical specialities.

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.

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 anaesthesia. 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 RCT.

In a cost-constrained system, the relative efficacy, cost and safety of aspirin and the new oral agents requires proper and definitive study with a randomised trial in various groups, particularly knee replacement and hip fracture.

Now that the fatal PE rates after arthroplasty are so low, the equivalence of symptomatic VTE events and symptomatic bleeding events with different prophylactic modalities should be eval-

uated with regards to morbidity, cost and medicolegal liability.

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.

Prophylaxis for those at high risk of VTE having day case surgery need further study. The day surgery environment may preclude administration of in-hospital chemical prophylaxis due to the bleeding risk with proximity to surgery. This will require administration for an adequate period of time, as yet unknown, in an out-of-hospital environment. Oral agents have a pragmatic advantage in this group but their safety and efficacy require study.

RCT in high risk patients having plastic surgery are needed to determine the efficacy and safety of pharmacological and mechanical prophylaxis.

RCT in patients having prostatectomy are needed to determine the efficacy and safety of pharmacological and mechanical prophylaxis.

RCT in patients having elective spine surgery are needed to determine the efficacy and safety of pharmacological and mechanical prophylaxis.

RCT in patients having spinal cord injury are needed to determine the efficacy and safety of combined pharmacological and mechanical prophylaxis.

RCT in patients with burns are needed to determine the efficacy and safety of pharmacological and mechanical prophylaxis.

RCT are needed to determine the optimal duration of extended prophylaxis and whether or not mortality is influenced in general surgical patients.

Further studies are needed before recommendations can be made for prophylaxis beyond 35 days in patients having hip surgery.

The value of new oral anticoagulants in the prophylaxis for different groups of patients having non-orthopedic surgery needs to be determined.

RCT in patients with acute stroke are needed to determine the efficacy and safety of combined pharmacological and mechanical prophylaxis.

A multicenter trial assessing efficacy, cost-effectiveness and safety of thromboprophylaxis in high-risk pregnant patients is required.

The optimum prophylactic therapy in patients having laparoscopic surgery needs to be determined.

There is a need for further studies to assess the efficacy of mechanical methods in medical patients.

Well-designed RCT are needed to determine optimal duration of thromboprophylaxis in high risk medical patients.

There is a need to adequately validate VTE and bleeding risk assessment models in hospitalized medical patients.

Phase four studies (post-marketing surveillance) to address long term potential harm from prophylactic methods should be encouraged.

The value of routine thromboprophylaxis in those receiving radiotherapy needs to be evaluated.

Adequately powered studies are needed to determine the benefits and harms of new anticoagulant drugs in cancer patients with indwelling central venous catheters and in specific subgroups of patients.

## Treatment regimens

The value of extended treatment with aspirin in patients who are at high risk of bleeding when taking VKA needs to be confirmed by further studies.

The efficacy and safety of thrombolytic therapy in patients with PE and right ventricular dysfunction requires confirmation by randomized trials.

A randomized study comparing catheter directed thrombolysis of proximal DVT with conventional anticoagulation therapy in preventing the post-thrombotic syndrome is required.

Studies comparing post-thrombotic morbidity in patients treated with CDT versus those treated with pharmaco-mechanical lysis are needed.

The best approach for LMWH use (*e.g.*, dose adjustment or anti Xa monitoring) in pregnancy, obesity and patients with renal impairment needs to be determined (Note: there are increasingly clear guidelines for dose adjustment without anti Xa monitoring).

How do we manage bleeding in patients treated with low molecular weight heparins, fondaparinux and the new oral anticoagulants? Stud-

ies should explore the efficacy of protamine sulphate in patients bleeding from LMWH.

The role of long-term LMWH *vs.* VKA in the treatment of DVT and prevention of post-thrombotic syndrome should be determined by further randomised trials.

The value of prognostic markers such as D-dimer, C reactive protein and extent of residual clot burden in guiding the duration of long-term oral anticoagulant therapy needs to be studied further.

New drugs in terms of production of HIT antibodies and their use as an alternative to UFH or LMWH in patients with HIT need clinical evaluation.

More RCT are needed to determine the complications or harm produced by prophylactic methods.

Further trials are needed to clarify whether LMWH is possibly superior to UFH in the initial treatment of VTE in patients with cancer.

The improved survival in patients with cancer treated with LMWH needs to be confirmed by further prospective clinical trials with appropriate design and power to assess cancer outcome before recommendations can be made.

The safety and efficacy of inferior vena cava filters for management of cancer-associated thrombosis need to be evaluated.

The relative benefit/harm from the new oral anticoagulants needs to be further determined.

RCT are needed to determine the efficacy of percutaneous endovascular venoplasty and stenting to relieve chronic venous obstruction and whether this may alleviate symptoms of PTS.

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ERRATA CORRIGE.—In volume 31, issue no. 3 – June, pages 227-33, in the article entitled “Epidemiologic aspects of abnormal ankle brachial index in the HIV infected population”, the correct authors’ names are:

Qaqa A. Y., Debari V. A., El-Kersh K., Sison R., Isbitan A., Mohammad N., Slim J., Perez G., Shamoan F. E.

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## INTERNATIONAL ANGIOLOGY

A. OLIARO, *Managing Editor*

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Published by Edizioni Minerva Medica, Corso Bramante 83-85, Turin, Italy (Casella postale 491 - 10100 Torino) - Tel. (011) 67.82.82 - Fax (011) 67.45.02

Printed by Edizioni Minerva Medica, Tipografia di Saluzzo, Corso IV Novembre 29-31, Saluzzo, Italy - Tel. (0175) 24.94.05 - Fax (0175) 24.94.07

[Autorizzazione Tribunale di Torino N. 2983 del 15-X-1980]

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# EUROPEAN VENOUS FORUM

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## Impact of the 3<sup>rd</sup> EVF HOW 95% of Delegates to Change Their Practice

P. NEGLÉN, B. EKLÖF, A. NICOLAIDES

The 3<sup>rd</sup> EVF HOW (European Venous Forum Hands-on Workshop on Venous Disease) was organized at the Golden Bay Hotel outside Larnaca, Cyprus during four days early last November. The Workshop provided a unique comprehensive program focused on hands-on learning and was greatly appreciated by delegates. The primary reason given for attendance by the delegates was to update overall knowledge about venous disease and its treatment (62%), to learn particular techniques (22%) or to be introduced to venous disease (13%). In an assessment after the course, the overwhelming majority of the delegates indicated that EVF HOW met their expectations (99%) and that the course will make them change their venous practice in the future (95%). These results were especially gratifying for the organizing committee and the European Venous Forum since the purpose of the creation of the EVF HOW was to fulfill a need for a structured comprehensive hands-on workshop for physicians interested in venous disease. The goal was not only to provide understanding of modern practical management, but also for the delegates to learn hands-on individual procedures to treat venous disease. It appears that EVF has achieved this.

Half of the delegates were vascular surgeons followed by other specialties such as interventional radiology, phlebology, angiology, cardiology and dermatology. Although the EVF HOW was created mainly for Europe, it has attracted international attention with representation from all over the world (54% - Western Europe, 20% - Eastern Europe, 12% - Middle East, 4% - Asia and 10% - Africa, South America, USA and Australia). Thus, the concept of the EVF HOW (Hands-on Workshop on Venous Disease) has

been well received internationally. The 4<sup>th</sup> EVF HOW is scheduled for 31 Oct–2 Nov, 2013 in Stockholm, Sweden.

### The Format of the EVF HOW

The EVF HOW has from the start been built on a few principles important for its success. The number of delegates are limited (max. 100 delegates) to facilitate interaction between instructors and delegates. The hands-on sessions are truly hands-on for the delegates, not small lectures or only a demonstration of procedures. All learning sessions are informal and in a relaxed setting to allow uninhibited communication between delegates, faculty members and industry representatives. There are plenty of time is set aside for discussion. There is no exhibition or parallel activity.

The format of the EVF HOW in 2013 will be similar to previous years including approximately 30 formal lectures, 15 case discussions and 2 live demonstrations on duplex scanning covering acute and chronic venous diseases. The focus will be on hands-on training on procedures and devices during 12 hours. Faculty members in collaboration with the industry experts will instruct at 24 workshop stations. The delegates will attend each workshop station during 30 min in small groups (4-5 delegates), giving each participant time to try out the devices.

The program is always modified based on the feed-back from the participants and faculty. Just like 2012, the delegates may bring their own cases for discussion. This year, however, case presentations will be imbedded in the formal lectures. The organizing committee hope to build a web-based portfolio for each

delegate in the future, where extra text material, videos of procedures, the formal lectures, case presentations and other study material can be placed. Participation in the EVF HOW will give access to this portfolio long-term. As only 100 participants are accepted on a “first come – first served” basis, it is recommended to register early to ensure a place. Please contact Anne Taft, Administrative Director, European Venous Forum; tel/fax +44 (0)20 8575 7044; email [admin@europeanvenousforum.org](mailto:admin@europeanvenousforum.org). More information is available at [www.europeanvenousforum.org](http://www.europeanvenousforum.org).

### **The Program of EVF HOW 2012**

The program of the 3<sup>rd</sup> Hands-on Workshop on Venous Disease, 2012, was given by an international faculty with 30 experts from Europe and the USA. They did not only present the formal lectures, but also actively discussed case presentations and were an integral part of the workshop giving practical tips and tricks from their own experience. The clinical input by the faculty members balanced well the specific device information presented by the industry representatives.

#### *Lectures*

The lectures spanned the following subjects:

- *Basic principles* of venous pathophysiology; accuracy of tests; and classification and assessment of treatment outcome

- *Treatment of varicose veins* conservatively with drugs and compression; with invasive procedures such as open surgery or saphenous ablation with laser, radiofrequency, foam sclerotherapy and steam; and with techniques preserving the saphenous vein. After intense discussion, Professor Andrew Bradbury tried to make sense of it all. The controversies of the perforators were elucidated and interventions for recurrent or residual varicose veins (PRE-VAIT – Presences of varices after intervention) were outlined.

- *Guidelines* for prevention and treatment of venous thrombo-embolism (VTE) and superficial thrombophlebitis (SVT).

- *Treatment of acute VTE* with traditional

conservative measures, new oral anticoagulants, catheter-directed thrombolysis, pharmacomechanical thrombectomy was described and outcome presented; and the role of IVC filters presented.

- *The association between MS and venous obstruction* was critically appraised.

- *Pelvic congestive syndrome*

- *Diagnosis and treatment of chronic venous insufficiency* using a sequential treatment plan was presented including compression treatment; the role of fasciotomy in legs with increased compartment pressure; treatment of deep venous obstruction; and the role of valve reconstruction in limbs with primary deep venous reflux or postthrombotic disease including the use of the Vedensky spiral.

#### *Case reports*

Dr. Jan Christenson organized the presentation of 18 interesting clinical cases. This year five cases were brought by the delegates for discussion. Each case was presented in stages and the moderator encouraged the delegates to join in at all stages, which lead to lively discussions. There was a wide range of cases illustrating the previously given lectures: From varicose veins to acute iliofemoral DVT; from chronic outflow obstruction to ovarian venous reflux.

#### *Hands-on workshops*

As previously emphasized, this component of the EVF HOW is most important. The function of the device or the method presented at each workshop station was explained in detail by the industry expert. Its role in the treatment of venous disease and personal clinical tips and tricks were highlighted by the faculty member. Each delegate trained hands-on under expert supervision after a short demonstration.

#### **WORKSHOP 1**

The delegates performed live imaging in patients with different types of vein pathologies. Dr Stylianos Papas from Limassol, Cyprus had collected numerous patients from his practice, well representing a variety of disease. The aim was that the delegate should be able to position

the patient properly, use appropriate transducers, know imaging principles and how to optimize the image after this workshop but also to be able to identify acute and chronic disease, reflux, obstruction, and pathology surrounding the vessels.

— Station 1: Lower limb with normal findings (Sonosite; faculty: Evi Kalodiki).

— Station 4: Abdominal and pelvic vein investigation (ZONARE; faculty: Nikki Giorgiou).

— Station 2: Lower limb with superficial reflux (Esaote; faculty: Stylianos Papas).

— Station 3: Lower limb with deep incompetence (Esaote; faculty: Theo Tyllis/Andrew Nicolaides).

## WORKSHOP 2

— Station 1: Tips and tricks. Examination of a patient clinically and ultrasound mapping of the source of reflux was practiced on patients. The anatomy of the veins to be ablated was described in detail, and the influence of vein size, tortuosity and the relation to the skin, nerves and deep veins were discussed (Covidien; faculty Lars Rasmussen).

— Station 2: Endovenous thrombectomy using the AngioJet device was practiced on a patient simulator (Bayer Healthcare; faculty: Haraldur Bjarnasson).

— Station 3: IVC filter placement and retrieval was practiced in a tube model (Cook Medical; faculty: Cees Wittens/Evgeny Shaydakov) (Figure 1).

— Station 4: The delegates practiced to choose a correct medical compression stocking (MCS) by measurement and applying long- and short-stretched MCS with and without fitting aid and measuring the working pressure with these stockings on using a Picopress device. (Bauerfeind; faculty: Niels Baekgaard/Michel Perrin)

## WORKSHOP 3

— Station 1: Intravascular Ultrasound (IVUS). The delegates familiarized themselves with the IVUS tower and the corresponding catheters. Case studies of procedures using IVUS video-loop recordings were reviewed to demonstrate differences in venogram and IVUS images dur-



Figura 1.—Delegates practicing on a tubular model.



Figura 2.—Delegates practising on each other.

ing treatment of patients with obstruction (Volcano; faculty: Jan Christenson).

— Station 2: Ovarian vein embolization was practiced in a specially designed tubular venous model (Cook Medical; faculty: Tilo Kölbel).

— Station 3: Strong short-stretch compression bandage was applied by each delegate, sub-bandage pressure measurements were monitored, and the delegates were made aware of what a correctly applied bandage on their own leg feels like (Lohmann & Rauscher; faculty: Hugo Partsch/Giovanni Mosti) (Figure 2).

— Station 4: Placement of the Veniti Vici venous stent was practiced in a specially designed venous tubular model replicating the ilio-caval vein segment (Veniti; faculty: Marzia Lugli/Oscar Maleti).



Figure 3.—Practicing on a phantom leg

#### WORKSHOP 4

Each delegate practiced on phantom legs longitudinal and transverse access to the vein under ultrasound guidance, insertion and placement of ablation devices, and the correct use of each device. Tips and tricks were pointed out.

— Station 1: Saphenous laser ablation using a radial fiber with a 1470 nm laser generator and how to decide the dosage of energy were practiced. (Biolitec; faculty: Athanasios Giannoukas).

— Station 2: Saphenous laser ablation including planning of adequate dosage and selection of the correct treatment setting were practiced. (KLS Martin Group; faculty: Zbigniew Rybak (Figure 3)).

— Station 3: Saphenous radiofrequency ablation using the ClosureFAST catheter was practiced including how to accurately place the catheter tip at the sapheno-femoral confluence and to sequentially position the catheter (Covidien; faculty: Marianne De Maeseneer/Ravi Singh-Ranger).

— Station 4: Saphenous and vein tributary steam ablation with the Veni RF Plus steam catheter was practiced in a venous model. The delegate should also understand the effect of steam on veins. (Veniti; faculty: René Milleret).

#### WORKSHOP 5

— Station 1: Insertion of an IVC filter was performed by each delegate using a computerized



Figure 4.—Practicing on a computerized simulator.

Mentice simulator mimicking an angio-room set up (Mentice; faculty: Lars Lönn) (Figure 4).

— Station 2: Compression therapy/ulcer care. The delegate learned how to choose and apply the appropriate wound dressing for a venous ulcer and how to measure a leg and apply the appropriate stocking (BSN/Jobst; faculty: Sylvain Chastenet).

— Station 3: The concept of Circaid in-elastic compression device was explained and the device applied by each delegate (Circaid; faculty: Sandra Shaw/Else Brouwer).

— Station 4: Foam sclerotherapy. The delegates made foam using STD and discussed different treatment plans according to ultrasound scanning results. This was followed by ultrasound-guided cannulation and injection of foam in a phantom leg. The appropriate compression bandage following foam sclerotherapy was placed on each other (STD Pharma; faculty: Andrew Bradbury and Gareth Bate).

#### Evaluation and future meeting

The EVF HOW 2012 was appreciated by the delegates, faculty members and industry representatives. They all greatly enjoyed the learning sessions because of the informal close interaction. Here are some of the written comments by the delegates:

*.....Very good interaction with faculty during workshops – very well arranged..... This workshop opened new horizons for me. I learned new things and I learned a lot about what I am not do-*

*ing right. Thank you very much.....Many tips in ultrasound examinations and laser treatment..... Very good update in current research. First ideas of new techniques. Best meeting since years: visiting so many of them, I dare to say.....Very good interaction with faculty during workshops – very well arranged.....Overall good workshop but need more time..... Important to keep the workshops (practical part) included in the price..... All the information given is badly needed in my practice. No similar workshop can compete with this workshop. It is superb in every aspect..... All aspects of*

*venous disease will be revised in my practice..... Very good meeting – highly recommended.....*

The next workshop will be limited to 3 days by removing a free afternoon. Despite this there will be an additional 4 workshop stations added at the 4<sup>th</sup> EVF HOW in Stockholm. Additional case reports brought by the delegates will be encouraged. Hopefully it will be possible to create personal portfolios with additional study material accessed on the web. Otherwise, on the whole the next workshop will have a similar program as outlined above.



# INTERNATIONAL UNION OF ANGIOLOGY

*a Society for Vascular Medicine, Vascular Surgery and Endovascular Interventions*

## UNION INTERNATIONALE D'ANGIOLOGIE

une société pour la Médecine et la Chirurgie Vasculaire ainsi que les  
Interventions Endovasculaires

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### ACCREDITATION OF VASCULAR CENTRES

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#### THE PROGRAMME IS NOW ACTIVE APPLICATIONS CAN BE SUBMITTED

**Main Criteria, Rules of Procedure and Application Form** can be obtained from the Administrative Secretariat of the IUA ([secretariat@angiology.org](mailto:secretariat@angiology.org)) or downloaded on the IUA website [www.I.U.Angiology.org](http://www.I.U.Angiology.org)

\* \* \* \* \*

Multidisciplinary vascular cares are the best way to manage the vascular patients and to achieve the most favourable results. Coordination and collaboration of Angiologist, Endovascular Therapist and Vascular Surgeon are key to precise indications and effective treatment. Such a goal can only be reached in well organised multidisciplinary Vascular Centres.

Therefore the IUA decided in 2010 to operate a Program for the recognition of multidisciplinary institutions devoted to diagnosis and treatment of vascular diseases and formed an *ad hoc* **European Commission for the Accreditation of Vascular Centres** focused particularly, but not only, on certifying such centres in the European countries. Angiologists and Vascular Surgeons are present in such Commission in equal numbers.

The mandate was to take as a base the "*Guidelines for the Organisation of Vascular Centres in Europe*", already published in *Int. Angiology 2009, 28:347-352*, and to start operating by 2012. The Commission worked up the **Main Criteria** for assessment, the practical **Rules of Procedure** to assure smooth operations and provided also a standard **Application Form** for the best convenience of whoever likes to apply.

**Accreditation by the IUA will testify that a certified Vascular Centre is really a multidisciplinary professional body, offers an excellent organisation and operates at the highest European standard.**

Fabrizio Benedetti-Valentini (Italy), Vascular Surgeon, is the Chairman of the Commission and Karel Roztocil (Czech Republic), Angiologist and President of the IUA, is the CoChairman. Patrick Carpentier, also an Angiologist, is the Secretary; other Commissioners are three Angiologists Jill Belch (UK) Denis Clement (Belgium) and Pier Luigi Antignani (Italy), and three Vascular Surgeons David Bergqvist (Sweden) Nicos Angelides (Cyprus) and José Fernandes e Fernandes (Portugal).

For additional information please contact [fbvroma@gmail.com](mailto:fbvroma@gmail.com) or [secretariat@angiology.org](mailto:secretariat@angiology.org)



**14<sup>th</sup>**

# ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM

Thursday 27 June – Sunday 30 June 2013

**Belgrade  
Serbia**



European Venous Forum



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# 4<sup>th</sup> EVF HOW 2013

## THE MOST COMPREHENSIVE WORKSHOP ON VENOUS DISEASE IN EUROPE

4<sup>th</sup> EVF Hands-on Workshop on Venous Disease  
Elite Hotel Marina Tower, Stockholm, Sweden  
31 October – 2 November 2013

The 4<sup>th</sup> EVF HOW in Sweden in 2013 gives you a unique comprehensive program focused on hands-on learning, a review of the latest updates and “state-of-the art” management of venous disease, an opportunity to share in discussions and actively engage with the faculty and industrial partners in a relaxed surrounding. The 4<sup>th</sup> EVF HOW will train you in methods to diagnose and treat acute and chronic venous disease such as duplex investigation; saphenous ablation techniques such as RF, laser, steam and foam sclerotherapy; endovenous thrombectomy; IVC filter placement; IVUS; stenting; and compression therapy. The workshop is open to all specialty physicians, including physicians in training, wanting to learn the latest in venous disease management. Delegates are limited to 100: “first come, first served”

- Over 30 presentations by the Faculty
  - Lots of time for discussions
  - Live demonstrations
- Clinical Case Presentations – bring your own!
- Interactive engaging Hands-on Workshops
  - On-line access to the presentations

### For further details please contact

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