PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

Cardiovascular Disease Educational and Research Trust (UK)
European Venous Forum
North American Thrombosis Forum
International Union of Angiology and
Union Internationale du Phlebologie

Introduction to the Prevention and Treatment of Venous Thromboembolism Consensus Statement

Chapter 1

Prevention and Treatment of Venous Thromboembolism Consensus Statement

- **Aim**
  - Provide a concise account of the evidence of efficacy or harm for various methods available to prevent and treat venous thromboembolism (VTE)
  - Provide recommendations based on critical evaluation of the evidence

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Methodology-Literature Search

- **The 2013 publication is the fifth revision of this document which was last published in 2006**
- **Literature Search**
  - January 2005 through August 2012, by independent agency (Pharmaceutical Strategic Initiatives, NC, USA)
  - Medline and Pub-Med using standard key terms
- **Randomized controlled trials (RCT) and meta-analyses were used**
- **Observational studies and registries used only when RCT were not available**
- **Excluded studies**
  - Clinical diagnosis of VTE without confirmation by objective test
  - Abstracts without full publication

Levels of Evidence

- **High level of evidence was considered to be provided by**
  - RCTs with consistent results, or
  - systematic reviews that were directly applicable to the target population
  - also, by single randomized trials which have been rigorously performed, methodologically reliable, and sufficiently large to give clear results that are applicable to most patients in most circumstances

Levels 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
  - Also, by RCT extrapolated to the target population from a different group of patients.

Levels of Evidence

- **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.

- **Lack of evidence**
  - Lack of evidence or low level evidence resulted in a number of key questions that require to be addressed by future studies
  - These key questions are stated throughout the document and are summarised in the final section (Chapter 24).

Costs and Cost-Effectiveness

- **Deliberately refrained from incorporating consideration of costs in the recommendations**
  - 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

- **Decisions about costs and resource allocations are more appropriately made by local healthcare systems**
  - Thus, we have summarised available cost-effectiveness evidence for primary prevention and treatment of VTE in Chapter 23

Outcomes

- **Evidence is presented for the following outcomes**
  - 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**

Arguments

- The relationship between asymptomatic and symptomatic VTE including PE has been known for some time.[1-3]
- Reduction in the incidence of asymptomatic DVT has been shown to be associated with a reduction of symptomatic DVT and PE[4-6]
- Large studies 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.[7]

1. Kakkar VV.*Ann R Coll Surg Engl.* Nov 1969;45:257-276.
2. Philbrick JT et al A*rch Intern Med.* Oct 1988;148(10):2131-2138.
3. Hull RD et al *Ann Intern Med.* Jun 1983;98(6):891-899.
4. Giannoukas AD et al *Eur J Vasc Endovasc Surg.* Nov 1995;10(4):398-404.
5. Hull RD et al *Ann Intern Med.* Nov 20 2001;135(10):858-869.
6. Eikelboom JW et al *Lancet* 2001;358:9-15.
7. Kakkar VV et al *Lancet.* July 12 1975;306(7924):45-51.

Arguments

- Regulatory authorities have recognized asymptomatic proximal DVT as a valid endpoint of clinical trials and drug evaluation
- 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.

Arguments

- **Adoption of such endpoints for efficacy evaluation is also validated by**
  - Demonstration that asymptomatic below knee DVT is associated with subsequent development of the PTS,[1, 2] that
  - 20% of asymptomatic calf DVT extend proximal to the knee if untreated[3] and
  - that 18% of symptomatic calf DVT are associated with proximal extension or recurrence[4]

1. Wille-Jorgensen P et al *Thromb Haemost.* 2005;93:236-241.
2. Schindler OS et al *J Orthop Surg (Hong Kong).*2005;13:113-119.
3. Kakkar VV et al *Am J Surg.* 1970;120:527-530.
4. Gillet JL et al *J Vasc Surg.* 2007;46:513-519.

Arguments

- **and**
  - PTS, which results in a marked reduction of quality of life (QOL) can be prevented by DVT prophylaxis, adequate treatment of lower limb DVT and prevention of DVT recurrence[1-5]

1. Prandoni P et al Ann Intern Med 2004; 141:249-56.
2. Ginsberg JS et al Arch Intern Med 2001; 161:2105-9.
3. Brandjes DP et al Lancet 1997; 349:759-62.
4. Aschwanden M et al J Vasc Surg 2008; 47:1015-21.
5. Henke P et al J Vasc Surg 2010; 52:37S-38S.

Arguments

- **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)
  - This resulted in a large number of recommendations based on high level of evidence for preventing DVT, PE or recurrent VTE
  - Such an approach provides clinically important distinctions to guide clinicians