

# Preventing Venous Thromboembolism



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Venous thromboembolism (VTE) is a silent, difficult-to-diagnose disease that is a major cause of morbidity and mortality worldwide. At a symposium in Singapore sponsored by sanofi-aventis, Dr Alexander Cohen, an eminent vascular physician and epidemiologist, highlighted the burden of VTE in Asia and delineated evidence-based best practice in VTE prevention and management for medical and surgical patients.

In countries of the European Union, more than one million VTE events or deaths are estimated to occur per year, with VTE mortality exceeding the combined death tolls of AIDS, breast cancer, prostate cancer and road transport accidents. Epidemiological data from the United States of America indicates similar prevalence, with 900,000 VTE events reported each year. Most VTE-related deaths happen in the hospital setting, or within three months of hospitalization; only a third of such deaths occur due to community-acquired VTE.

Importantly, most fatal VTE events are unsuspected and undiagnosed before death. Similarly, pulmonary embolism (PE) is diagnosed two-and-a-half times more frequently post-mortem than prior to death, indicating that substantially more deaths occur due to PE than are diagnosed and treated.<sup>1-4</sup>

**Table 1. ENDORSE: patients at risk for VTE<sup>5</sup>**

Country	Number of surgical patients	Proportion of surgical patients at-risk
UK	2091	65%
USA	4061	78%
India	1110	61%
Pakistan	748	44%
Thailand	1001	62%
Bangladesh	962	48%

The incidence of asymptomatic and symptomatic VTE in Asian patients is similar to that observed in Western countries. ENDORSE, a global observational study of VTE risk and prophylaxis in the acute care hospital setting, which involved 68,183 patients from 358 hospitals in 32 countries, showed that the risk of thrombosis were almost exactly the same in different parts of the world (Table 1).<sup>5</sup>

Furthermore, the incidence of deep vein thrombosis (DVT) observed in multinational epidemiological studies conducted in Asia, including AIDA (Assessment, Incidence of DVT in Asia) and SMART (Surgical Multinational Asian Registry in Thrombosis) appear similar to those reported in Western studies, also they overlap the range of incidences observed in Western studies. More importantly, the reported incidences of confirmed symptomatic PE and fatal PE reported in AIDA and SMART are very close to those reported in Western nations.<sup>6,7</sup>

## VTE Prophylaxis in Surgical Patients

Appropriate prophylactic measures to prevent VTE and adherence to guidelines can significantly reduce the burden of VTE, noted Dr Cohen. In a systemic review that evaluated 79 safety practices or interventions, appropriate use of VTE prophylaxis ranked highest among safety practices that reduce adverse patient outcomes and decrease overall costs. "Thromboprophylaxis is the number one ranked intervention, based on safety, morbidity and mortality," reiterated Dr Cohen.<sup>8</sup>

VTE can be prevented by medical interventions, heparin, for example, reduces total mortality and fatal PE. In randomized clinical trials involving general, orthopaedic and urology surgery patients, perioperative administration of subcutaneous heparin resulted in a significant 21% relative risk reduction in total mortality. Importantly, heparin therapy did not increase the incidence of fatal bleeding, which is a common concern.<sup>8</sup>

The evidence-based American College of Chest Physicians (ACCP) guidelines for VTE prevention recommend thromboprophylaxis measures for patients undergoing major surgery (Table 2). For patients undergoing hip or knee arthroplasty or hip fracture surgery, ACCP recommends thromboprophylaxis for at least 10 days (Grade 1A evidence). ACCP does not recommend the use of aspirin alone as thromboprophylaxis for any patient group.<sup>9</sup>

Cancer patients' risk of VTE is six-fold greater than that of non-cancer patients, and cancer patients undergoing surgery have at least double the risk of DVT and more than three times the risk of fatal PE compared to patients without malignancies.<sup>9,10</sup> Prolonged

**Table 2. ACCP thromboprophylaxis recommendations**

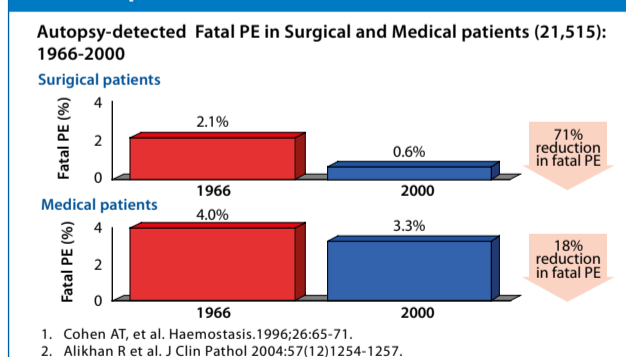
Patient Category	Recommended Prophylaxis	Evidence Grade	
Surgery Patients	Low Risk General Surgery with no additional thromboembolic risk factors	Early and Frequent ambulation	1A
	Moderate risk general surgery (Benign disease)	LMWH, low-dose unfractionated heparin (LDUH) or fondaparinux	1A
	Higher risk general surgery patients (Major procedure for cancer)	LMWH, LDUH tid, or fondaparinux	1A
High risk general surgery (Multiple VTE risk factors)	To add on optimal use of a mechanical method (i.e. graduated compression stockings (GCS) and/or intermittent pneumatic compression (IPC)) on top of pharmacological method (LMWH, LDUH tid, or fondaparinux)		1C
	Elective total hip or knee arthroplasty	LMWH (at the usual high-risk doses), fondaparinux, or adjusted dose vitamin K antagonist (VKA) for at least 10 days	1A
Medical Patients	General medical patients	LDH, LMWH, fondaparinux	1A

VTE prophylaxis with enoxaparin in patients undergoing cancer surgery has achieved significant reductions in VTE and proximal DVT. In addition, a meta-analysis has confirmed that LMWH treatment therapy is associated with reduced mortality compared to LDUH in cancer surgery patients.<sup>11,12</sup>

## VTE Prophylaxis in Medical Patients

Medical thromboprophylaxis has been consistently found to significantly reduce VTE in medical patients.<sup>13-15</sup> Interestingly, close to 60% of the attributable risk for DVT/PE is medical, with 60% to 80% of all deaths due to PE occurring in medical patients.<sup>16</sup> Furthermore, while a 71% reduction in fatal PE events was reported in surgical patients between 1966 and 2000, there was only an 18% drop in the incidence of PE in medical patients over the same period (Figure 1). This underscores the need to implement effective thromboprophylaxis measures in all at-risk medical patients.<sup>17-18</sup>

**Figure 1. Autopsy-detected fatal PE in surgical and medical patients (21,515) 1966-2000.**



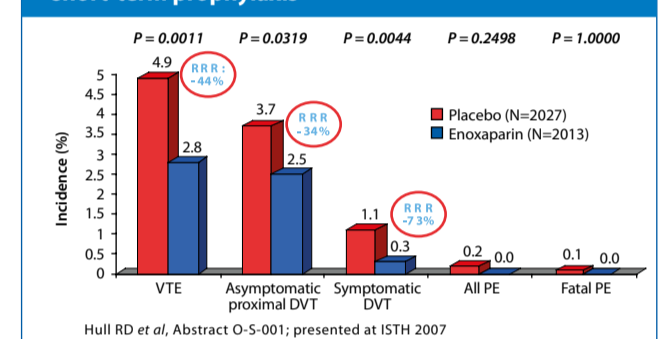
The recommended therapeutic options for thromboprophylaxis in general medical patients include LDUH, LMWH and fondaparinux (all Grade 1A; see Table 2).<sup>9</sup> Comparing the effects of LMWH and unfractionated heparin in these patients, Dr Cohen noted that although there were no substantial differences in the incidences of DVT or clinical PE with LMWH versus unfractionated heparin prophylaxis, the incidence of major bleeding with LMWH was almost half that of unfractionated heparin.<sup>19</sup>

Enoxaparin 40 mg once daily, administered subcutaneously, has proven effective and safe, reducing the risk of VTE by 63% in at-risk medical patients, with an absolute risk reduction of 9.4%.<sup>14</sup> In the EXCLAIM trial, extended duration prophylaxis with enoxaparin reduced the rate of VTE by 44% and was found to be superior to short-term prophylaxis in acutely-ill medical patients with recent reduced mobility (Figure 2). The benefit of enoxaparin was con-

sistent across all primary diagnoses and major risk factors, with no significant difference in fatal bleeding or overall mortality.<sup>20</sup>

Expressing his concern over non-compliance to clinical practice guidelines recommended for VTE prophylaxis, Dr Cohen remarked that VTE is a 'Cinderella disease' that is often not perceived to be a problem, as it is usually not the primary medical concern. Dr Cohen attributed poor compliance with VTE prophylaxis to lack of awareness of guidelines and evidence, a mistaken perception of lack of efficacy of thromboprophylaxis, concern about bleeding risks, and perceived difficulties in risk assessment.

**Figure 2. Efficacy of extended duration enoxaparin vs short-term prophylaxis**



I believe that opinion leaders can play an important role in improving thromboprophylaxis compliance, said Dr Cohen. In addition, the development of clinical-decision support tools such as risk-assessment models and regional and practice-specific simplified guidelines would also contribute to improving thromboprophylaxis compliance. The very low rate of prophylaxis use in Asian patients, despite the high risk of VTE, is a grave cause for concern, continued Dr Cohen, and warrants a much needed improvement of awareness and patient care in Asia.

## In Summary

VTE is a common disease and a major cause of death. Most VTE-associated deaths occur due to sudden PE or following undiagnosed and untreated VTE. Many of these events and deaths are preventable with available effective prophylaxis. Prevention remains the mainstay of VTE management. This is of particular importance in the medical setting where the implementation of prophylaxis remains suboptimal.

## References

- Cohen AT et al. Thrombosis and Haemostasis. 2007;98:756-64.
- Eurostat statistics on health and safety 2001 (<http://epp.eurostat.ec.eu.int>)
- Hirsh J et al. Circulation. 1996;93:2212-45.
- Heit J et al. J Thromb Haemost. 2005;3:1611-17.
- Cohen AT et al. Lancet. 2008;371:387-94.
- Piovella F et al. J Thromb Haemost. 2005;3:2664-70.
- Leizorovicz A et al. J Thromb Haemost. 2005;3:28-34.
- Collins R et al. N Engl J Med. 1988;318:1162-73.
- Geerts WH et al. Chest. 2004;126:3385-4005.
- Cohen AT et al. Thromb Haemost. 2005;94:750-9.
- Bergqvist D et al. N Engl J Med. 2002;346:975-80.
- Hettiarachchi RJ et al. Thromb Haemost. 1999;82:947-52.
- Samama MM et al. N Engl J Med. 1999;341:793-800.
- Leizorovicz A et al. Circulation. 2004;110:874-9.
- Cohen AT et al. BMJ. 2006;332:325-9.
- Heit JA et al. Arch Intern Med. 2002;162:1245-8.
- Cohen AT et al. Haemostasis. 1996;26:65-71.
- Alikhan R et al. J Clin Pathol. 2004;57:1254-7.
- Mismetti P et al. Thromb Haemost. 2000;83:14-19.
- Hull RD et al. J Thromb Thrombolysis. 2006;22:31-8.

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