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Short- and long-term consequences of venous thromboembolic disease

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Abstract

Venous thromboembolism (VTE) is a frequent disease, particularly in ill, elderly patients. Both immediate and longer-term mortality rates are significant, especially in patients presenting with pulmonary embolism, with chronic lung or heart disease or with malignancy. Survivors, even when adequately treated, may experience fatal or non-fatal recurrent episodes and/or may develop long-lasting and disabling sequelae such as post-thrombotic syndrome and chronic pulmonary hypertension. These complications usually arise within 2 years of the index episode but may occur even as much as 10 years later. In this setting, VTE should be considered a chronic disease.

Introduction

The term 'venous thromboembolism' (VTE) comprises two separate clinical entities: deep vein thrombosis (DVT) and pulmonary embolism (PE). These, despite their unrelated clinical features, represent different stages of the same disease.¹ The clinical relevance of this disorder is mainly related to the inherent risk of death from PE, although the potential for short- and long-term morbidity is substantial after non-fatal episodes.^{2,3}

The incidence of objectively confirmed VTE in the general population is between 1 and 2 per 1000 persons per year, with over half of the events being DVTs, and mostly first episodes.^{4,5}

The picture is worse for hospitalised patients as in this population, the frequency of VTE – without prophylaxis – may be higher than 50%.^{6,7} Irrespective of prophylaxis, around 1% of hospital inpatients develop PE, which is fatal in approximately half of cases.^{8,9} Furthermore, according to autopsy series, PE accounts for up to 10% of all in-hospital deaths, being an unexpected finding in most cases.¹⁰

Subjects developing DVT or PE may have one or more specific conditions that are commonly recognised

as risk factors for VTE – malignancy, recent surgery, immobilisation due to medical illness, family history of VTE, known coagulation disorders, chronic heart failure or lung disease. However, one-third to one-half of these patients suffer apparently idiopathic VTE.¹¹ Risk factors are usually further classified as **transient** (e.g. the presence of a plaster cast or a surgical procedure) or **persistent** (e.g. limb paralysis from a stroke or thrombophilia).

Suspected VTE should always be confirmed by means of objective testing, as clinical diagnosis is unreliable and treatment carries a significant risk of potentially fatal haemorrhagic events.¹² Currently, the diagnostic standards are contrast venography or ultrasonography for DVT¹³ and pulmonary angiography, ventilation/perfusion lung scanning or spiral computed tomography for PE.¹⁴ Fatal PE should be confirmed by autopsy.¹⁴

Established VTE (first episode) is usually treated with low-molecular-weight or unfractionated heparin(s) for at least 5 days, followed by vitamin K inhibitors for 3 months, or longer if the episode was idiopathic or associated with persistent risk factors such as malignancy or thrombophilic abnormalities.¹⁵ Patients with PE who are haemodynamically unstable should be administered thrombolytic drugs, while patients with absolute contraindications for anticoagulants (or with recurrent thromboembolism despite adequate anticoagulation) require vena cava filters.^{11,14,15} Patients with cancer appear to fare much better if they receive long-term treatment with low-molecular-weight heparin rather than vitamin K inhibitors.^{15,16}

Notwithstanding a prompt diagnosis and an adequate course of treatment, a variable proportion of patients with VTE experience complications (i.e. mortality, recurrence, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension). These usually arise within 2 years of the index episode but



they may occur even many years later. VTE should therefore be regarded as a chronic disease.^{2,14,17–20} This risk is particularly high and persisting in patients with idiopathic episodes or with permanent risk factors, but is not negligible in patients with transient risk factors.^{2,19}

Short-term mortality

More than 70% of cardiac arrests are caused by acute myocardial infarction or massive PE,²¹ and fatal PE is implicated in at least half of these cases.²² About 10% of patients with PE die within 1 hour of the onset of symptoms²³ and the 24-hour mortality rate has been estimated at 36%.¹⁷ During treatment, VTE-related mortality appears to be lower,^{19,24} although it remains high during the first weeks following the index event, especially in patients presenting with haemodynamically unstable PE.^{17,25,26} For instance, according to one quantitative review of 25 studies and about 5500 patients, the rate of fatal PE during anticoagulation was 0.5% in patients presenting with DVT and 2.3% in patients presenting with PE; following treatment, the respective figures were 0.3/100 patient-years and 0/265 patient-years, respectively (which may be explained by the fact that all fatal events in patients with PE occurred during the first 2 weeks of anticoagulant therapy).²⁴ Notably, the overall rate of death from PE was about four times higher in patients presenting with PE.²⁴ The in-hospital death rate in 249 patients with submassive and massive PE who received thrombolytic therapy was reported to be 9%.²⁵ In another study conducted in elderly inpatients with symptomatic DVT or PE, the overall short-term (first 2 weeks) mortality rates were 3.8% and 38.9%, respectively.²⁶ Likewise, in a population-based cohort study of 2218 patients with VTE, the 2-week cumulative mortality rate was 4.3% in those presenting with DVT, compared with 31.3% in those with PE.¹⁷ It is therefore likely that PE is a significant predictor of early death, compared with DVT alone.^{17,27}

Numerous randomised trials comparing different heparins for the initial treatment of VTE (mainly proximal DVT)

have evaluated mortality as an endpoint and have reported a frequency ranging between 1.4% and 10.6%, after 3 to 6 months of follow-up.^{27,28} Similarly, a 12.5% fatality rate after 6 months of follow-up was observed in a prospective registry of 4011 patients with VTE²⁹ and, in a cohort of 243 patients with non-massive PE, the observed total mortality was 17% after 6 months, with a recurrent fatal PE rate of 5%.³⁰ A retrospective population-based study corroborated these findings in patients with DVT, reporting a 3-month survival rate of 91.9%. However, when the analysis was restricted to patients with PE, the respective figure was strikingly lower at 62.8%.¹⁷ A similarly high mortality rate (40%) was observed in a randomised study of patients with cancer and VTE after 6 months of follow-up.¹⁶

Conditions that seem to be associated with a reduced short-term survival after VTE include: increasing age, malignancy, onset of VTE while confined in hospital or in a nursing home and a history of congestive heart failure or of chronic lung disease.¹⁷ Recently, right ventricular dysfunction (as assessed by echocardiography) and raised troponin concentrations have been proposed as prognostic markers of short-term adverse outcome in patients with PE, even if patients are haemodynamically stable.^{31,32} The combination of both elevated troponin and right ventricular enlargement increased by sevenfold the risk of death at 1 month in patients with haemodynamically unstable PE and remained a powerful predictor of poor outcome even in normotensive patients (hazard ratio 5.6, compared with the reference group).³³

Long-term mortality

Patients with VTE are also exposed to significant risk of long-term mortality, which persists for many years after the initial event and, in general, is higher than that in the general population.¹⁷ Indeed, even low-risk patients (e.g. those without malignancy, chronic medical illness, thrombophilia or history of previous VTE) have an overall mortality rate as high as 14% after 8 years of follow-up.³⁴

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A classic prospective cohort study conducted in 528 consecutive patients with a first episode of symptomatic proximal DVT reported an overall mortality of about 25% after 8 years of follow-up. The cumulative survival rate was 83.3% after 1 year, 79.9% after 2 years, 73.5% at 5 years and 69.3% at 8 years. Less than 10% of fatalities were accounted for by VTE, while the greater part was due to cancer (60%) or vascular deaths (14%). In particular, the presence of malignancy significantly increased the risk of death (risk ratio [RR] 7.1).² In another study that included patients with submassive and massive PE, the probability of survival was 92% at 1 year, 79% at 3 years and 56% at 10 years in patients discharged alive from hospital, and long-term mortality was significantly associated with age greater than 75 years (RR=2.7), persistent vascular pulmonary obstruction despite thrombolytic treatment (RR=2.2) and cancer (RR=2.0).²⁵ Finally, in one population-based cohort, the observed cumulative survival rates at 2, 5 and 8 years were 81.4%, 72.6%, and 65.2%, respectively, in patients with DVT and 53.6%, 47.4%, and 41.5%, respectively, in patients with PE.¹⁷

Predictors of reduced long-term survival are malignancy, increasing age, presentation with PE, tobacco smoking, onset of VTE while confined in hospital or in a nursing home and a history of congestive heart failure or chronic lung disease.¹⁷

Remarkably, several meta-analyses comparing the treatment of VTE with low-molecular-weight heparin *versus* that with unfractionated heparin showed a significant reduction of total mortality for the former.²⁸ This finding was attributed to a higher survival rate for patients with malignancy.³⁵ However, a randomised trial comparing low-molecular-weight heparins with vitamin K inhibitors for the secondary prevention of VTE in patients with cancer failed to show any differences in term of mortality between the study groups.¹⁶ Similarly, a longer course (6 months *versus* 6 weeks) of secondary prevention with oral anticoagulants did not seem to predict a higher survival.¹⁹

Recurrence

Despite adequate treatment, up to a quarter of patients with symptomatic DVT and/or PE will experience recurrent VTE within 5 years of the index thrombotic event.^{2,18,27,36,37}

The short-term (during anticoagulation) incidence of recurrent VTE has been assessed as a primary efficacy outcome in numerous randomised trials and meta-analyses. In general, the reported rate is about 5% at 3 months.²⁸ Similar figures have been reported by several prospective cohort studies.^{2,27,29}

Following anticoagulation, patients are still at a significant risk of recurrent VTE, evaluated in several prospective randomised or cohort studies. According to these investigations, the observed long-term rate of recurrence was approximately 10% after 6 to 12 months;^{2,18,19} 20% at 2 years,^{2,36} up to 24% at 5 years^{2,37} and about 30% after 8–10 years of follow-up (Figure 1).^{2,18}

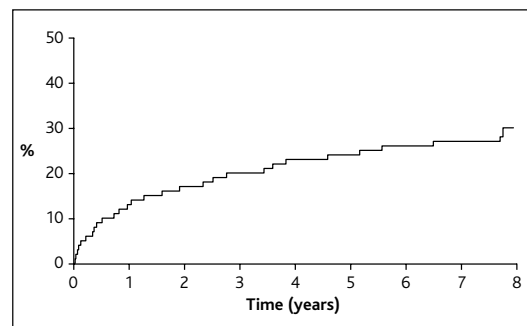


Figure 1. Cumulative incidence of recurrent venous thromboembolism in patients with proven DVT.² Reprinted with kind permission of Ferrara Storti Foundation, Pavia, Italy.

The risk of recurrent VTE appears to be higher during the first 2 years after the index thrombotic event^{2,18} and is increased in patients with malignancy,^{2,18,37} with a history of VTE³⁷ and those presenting with idiopathic episodes.^{36,38} Conversely, a history of surgery or of traumatic injuries is associated with a reduced incidence of recurrence.^{2,18,36,37} The risk of recurrent PE is higher in patients initially presenting with PE, as compared with DVT.¹⁷ The role of coagulation abnormalities is

disputed;^{2,36,38} as is that of the optimal (short *versus* long-term) duration of anticoagulation following the initial thrombotic episode.^{37,39} In particular, although a longer anticoagulation course is clearly protective against recurrence, the recurrence rate after withdrawal tends to rapidly catch up with its 'natural' course (e.g. that observed in patients who do not receive prolonged secondary prophylaxis).^{19,39} Notably, low-molecular-weight heparins, if used instead of vitamin K inhibitors for the secondary prevention of VTE, appear to halve the rate of recurrence in patients with cancer.¹⁶

Recent data indicate that patients with persistent venous obstruction (measured by ultrasound) and/or with abnormal D-dimer levels after the withdrawal of anticoagulants may be more prone to develop a VTE recurrence than subjects without such features.^{38,40}

Post-thrombotic syndrome

After an episode of symptomatic DVT of the lower extremity, patients may develop a typical pattern of symptoms, referred to as post-thrombotic syndrome (PTS). The clinical picture ranges from a mild presentation, with slight pain, swelling, skin discoloration and venous stasis, to a severe form featuring chronic pain, fixed oedema and, eventually, leg ulceration.³ Severe PTS is a chronic disease, imposing a substantial socioeconomic burden both on patients and on healthcare systems.³ The diagnosis of PTS is clinical and should be established based on a standardised and reproducible scale.³

The exact frequency and time of onset of PTS following objectively documented symptomatic DVT is uncertain – the former ranges between 20% and 80%.³ Three recent prospective, methodologically sound studies suggest that severe, disabling PTS arises in about 10% of patients within 2 years of a symptomatic episode of DVT.^{2,41,42}

The overall cumulative incidence of PTS, as estimated in a prospective cohort study of patients with symptomatic DVT administered standard treatment and wearing

compression stockings for 2 years, was 18%, 24.5% and 29.6% after 1, 2 and 5 years of observation, respectively. The respective figures for severe PTS, were 2.7% and 8.1% at 1 and 5 years (Figure 2).² Two prospective randomised trials have demonstrated that the use of elastic stockings, in addition to anticoagulants, can halve the incidence of PTS.^{41,42} In the first study, mild-to-moderate and severe PTS were observed in 20% and 11.5%, respectively, of patients wearing stockings and in 47% and 24%, respectively, of those without.⁴¹ In the second trial, the 2-year cumulative incidence of mild-to-moderate PTS was 24.5% in the stocking group *versus* 49.1% in the control group and that of severe PTS was 3.5% and 11.7%, respectively.⁴²

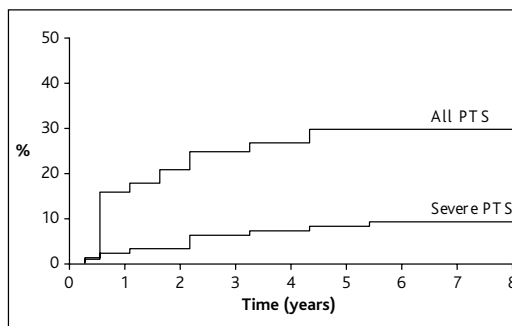


Figure 2. Cumulative incidence of overall and severe post-thrombotic syndrome, after a first episode of DVT, as assessed with a standardised scale.² Reprinted with kind permission of Ferrata Storti Foundation, Pavia, Italy.

The development of PTS appears to be associated with the occurrence of ipsilateral recurrent DVT but is apparently unrelated to the initial extent of DVT on venography.^{41,42}

Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTPH) is usually regarded as a rare complication of VTE, although associated with considerable morbidity and mortality.¹⁵ The incidence of CTPH was recently assessed in a long-term follow-up study of 223 patients with proven PE.²⁰ The cumulative incidence of symptomatic CTPH was 1.0% at 6 months, 3.1% at 1 year and 3.8% at 2 years. Interestingly, no new cases were detected beyond 2 years of observation.

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A history of previous PE, presentation with idiopathic PE, larger perfusion defects on pulmonary scans and younger age are all reported to be associated with the development of CTPH.²⁰

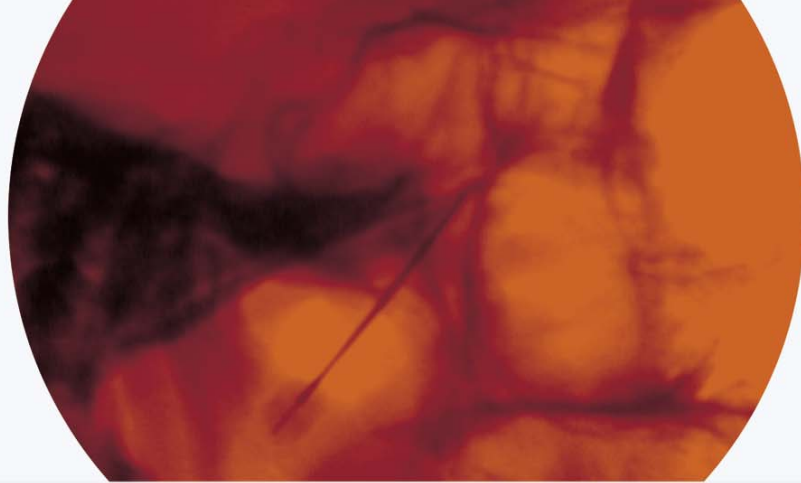
Selected patients with CTPH may benefit from pulmonary thromboendarterectomy but should nonetheless receive life-long vitamin K antagonists and a vena cava filter.¹⁵

Key Learning

- Patients with VTE are exposed to a significant and persistent risk of death from the onset of the disease and have a reduced life expectancy, compared with the general population
- Recurrent VTE is a life-threatening condition and exposes patients to a higher risk of long-term sequelae. Prolonged prophylaxis is useful but appears only to delay the onset of recurrence
- Severe post-thrombotic syndrome is a chronic, disabling condition that impairs patients' quality of life but may be effectively prevented by the use of elastic stockings
- Chronic thromboembolic pulmonary hypertension, although a less frequent complication of VTE, is a seriously disabling event and occurs more often in younger subjects. Treatment options include surgery, lifelong anticoagulation and vena cava filters

References

1. Huisman MV, Buller HR, ten Cate JW, *et al.* Unexpected high prevalence of silent pulmonary embolism in patients with proximal deep venous thrombosis. *Chest* 1989;**95**:498–502.
2. Prandoni P, Villalta S, Bagatella P, *et al.* The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997;**82**:423–8.
3. Bernardi E, Bagatella P, Frulla M, *et al.* Post-thrombotic syndrome: incidence, prevention and management. *Semin Vasc Med* 2001;**1**:71–80.
4. Anderson FA Jr, Wheeler HB, Goldberg RJ, *et al.* A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;**151**:933–8.
5. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;**353**:1386–9.
6. Geerts W, Pineo GF, Heit JA. Prevention of venous thromboembolism. The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;**126**:3385–4005.
7. Spyropoulos AC. Emerging strategies in the prevention of venous thromboembolism in hospitalized medical patients. *Chest* 2005;**128**:958–69.
8. Rasmussen MS, Wille-Jørgensen P, Jørgensen LN. Postoperative fatal pulmonary embolism in a general surgical department. *Am J Surg* 1995;**169**:214–16.
9. THRIFT Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992;**305**:567–74.
10. Alikhan R, Peters F, Wilmott R, *et al.* Fatal pulmonary embolism in hospitalised patients: a necropsy review. *J Clin Pathol* 2004;**57**:1254–7.
11. Kearon C. Epidemiology of venous thromboembolism. *Semin Vasc Med* 2001;**1**:7–25.
12. Levine MN, Raskob G, Beyth RJ, *et al.* Hemorrhagic complications of anticoagulant treatment. The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;**126**:2875–3105.
13. Kraaijenhagen RA, Lensing AWA, Lijmer JG, *et al.* Diagnostic strategies for the management of patients with clinically suspected deep-vein thrombosis. *Curr Opin Pulm Med* 1997;**3**:268–74.
14. Goldhaber SZ. Pulmonary embolism. *Lancet* 2004;**363**:1295–305.
15. Buller HR, Agnelli G, Hull RD, *et al.* Antithrombotic therapy for venous thromboembolic disease. The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;**126**:4015–285.
16. Lee AY, Levine MN, Baker RI, *et al.* Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;**349**:146–53.
17. Heit JA, Silverstein MD, Mohr DN, *et al.* Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999;**159**:445–53.
18. Heit JA, Mohr DN, Silverstein MD, *et al.* Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000;**160**:761–8.
19. Shulman S, Rhedin AS, Lindmarker P, *et al.* A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995;**332**:1661–5.
20. Pengo V, Lensing AWA, Prins MH, *et al.* Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004;**350**:2257–64.
21. Spohr F, Bottiger BW. Thrombolytics in CPR. Current advantages in cardiopulmonary resuscitation. *Minerva Anesthesiol* 2005;**71**:291–6.



22. Courtney DM, Kline JA. Prospective use of a clinical decision rule to identify pulmonary embolism as likely cause of outpatient cardiac arrest. *Resuscitation* 2005;**65**:57–64.
23. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest* 1995;**108**:978–81.
24. Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;**279**:458–62.
25. Meneveau N, Ming LP, Seronde MF, et al. In-hospital and long-term outcome after sub-massive and massive pulmonary embolism submitted to thrombolytic therapy. *Eur Heart J* 2003;**24**:1447–54.
26. Bosson JL, Labarere J, Sevestre MA, et al. Deep vein thrombosis in elderly patients hospitalized in subacute care facilities: a multicenter cross-sectional study of risk factors, prophylaxis, and prevalence. *Arch Intern Med* 2003;**163**:2613–8.
27. Douketis JD, Foster GA, Crowther MA, et al. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. *Arch Intern Med* 2000;**160**:3431–6.
28. Krishnan JA, Segal JB, Streiff MB, et al. Treatment of venous thromboembolism with low-molecular-weight heparin: a synthesis of the evidence published in systematic literature reviews. *Res Med* 2004;**98**:376–86.
29. Arcelus JL, Caprini JA, Monreal M, et al. The management and outcome of acute venous thromboembolism: a prospective registry including 4011 patients. *J Vasc Surg* 2003;**38**:916–22.
30. van Beek EJ, Kuijter PM, Buller HR, et al. The clinical course of patients with suspected pulmonary embolism. *Arch Intern Med* 1997;**157**:2593–8.
31. Grifoni S, Olivetto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation* 2000;**101**:2817–22.
32. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation* 2002;**106**:1263–8.
33. Scridon T, Scridon C, Skali H, et al. Prognostic significance of troponin elevation and right ventricular enlargement in acute pulmonary embolism. *Am J Cardiol* 2005;**96**:303–5.
34. Franzeck UK, Schalch I, Jager KA, et al. Prospective 12-year follow-up study of clinical and haemodynamic sequelae after deep vein thrombosis in low-risk patients (Zurich Study). *Circulation* 1996;**93**:74–9.
35. Green D, Hull RD, Brant R, et al. Lower mortality in cancer patients treated with low-molecular-weight versus standard heparin. *Lancet* 1992;**339**:1476.
36. Baglin T, Luddington R, Brown K, et al. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003;**362**:523–6.
37. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis incidence and risk factors. *Arch Intern Med* 2000;**160**:769–74.
38. Palareti G, Legnani C, Cosmi B, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation* 2003;**108**:313–8.
39. Ost D, Tepper J, Mihara H, et al. Duration of anticoagulation following venous thromboembolism: a meta-analysis. *JAMA* 2005;**294**:706–15.
40. Prandoni P, Lensing AW, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med* 2002;**137**:955–60.
41. Brandijes DPM, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal vein thrombosis. *Lancet* 1997;**349**:759–62.
42. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004;**141**:249–56.