Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients

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Summary

The clinical importance of asymptomatic proximal and distal deep vein thrombosis (DVT) remains uncertain and controversial. The aim of this retrospective, post-hoc analysis was to examine mortality and risk factors for development of proximal DVT in hospitalized patients with acute medical illness who were recruited into a randomized, prospective clinical trial of thromboprophylaxis with dalteparin (PREVENT). We analyzed 1738 patients who had not sustained a symptomatic venous thromboembolic event by Day 21 and who had a complete compression ultrasound of the proximal and distal leg veins on Day 21. We examined the 90-day mortality rates in patients with asymptomatic proximal DVT (Group I, N = 80), asymptomatic distal DVT (Group II, N = 118) or no DVT (Group III, N = 1540). The 90-day mortality rates were 13.75%, 3.39%, and 1.92% for Groups I–III, respectively. The difference in mortality between Group I and Group III was significant (hazard ratio 7.63, 95% CI = 3.8–15.3; p < 0.0001), whereas the difference between Groups II and III did not reach significance (hazard ratio 1.36, 95% CI = 0.41–4.45). The association of asymptomatic proximal DVT with increased mortality remained highly significant after adjusting for differences in baseline demographics and clinical variables. Risk factors significantly associated with the development of proximal DVT included advanced age (p = 0.0005), prior DVT (p = 0.001), and varicose veins (p = 0.04). In conclusion, the high mortality rate in patients with asymptomatic proximal DVT underscores its clinical relevance and supports targeting of asymptomatic proximal DVT as an appropriate endpoint in clinical trials of thromboprophylaxis.

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is often undetected and asymptomatic in hospitalized patients. Prophylaxis may be the most effective means of reducing the morbidity and mortality associated with this condition (1, 2).

Proximal DVT is more commonly associated with PE than distal DVT (3–9), but the relative risk of death associated with asymptomatic proximal versus distal DVT continues to be a source of controversy and uncertainty. The recently completed **Pr**ospective **E**valuation of Dalteparin Efficacy for Prevention of **VTE** in Immobilized Patie**n**ts **T**rial (PREVENT) investigated the efficacy and safety of a low-molecular-weight heparin, dalteparin, for the prevention of VTE in groups of acutely ill hospitalized patients with risk factors for VTE. The objectives of this post hoc retrospective analysis of PREVENT data were: 1) to compare the mortality rates in patients with asymptomatic proximal DVT, asymptomatic distal DVT, or no DVT, and 2) to identify risk factors for development of proximal DVT.

Materials and methods

We conducted a retrospective, post-hoc analysis of patients enrolled in the PREVENT study. PREVENT was a randomized, double-blind, placebo-controlled, multicenter, multinational

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trial of once-daily dalteparin (5000 IU subcutaneous) or placebo for 14 days, with a follow-up period of 90 days, for the prevention of VTE in acutely ill hospitalized patients. The methods have been described in detail previously (10, 11).

Patients were at least 40 years of age with an acute medical condition requiring a projected hospitalization for 4 or more days and had had no more than 3 days of prior immobilization. The major diagnostic subgroups in PREVENT included acute congestive heart failure (New York Heart Association [NYHA] class III or IV), acute respiratory failure that did not require ventilatory support or other acute medical conditions. Patients in the latter group had to have at least one of the following additional risk factors: age ≥75 years, cancer, previous DVT or PE, obesity (body mass index ≥30 kg/m^2 for men and ≥28.6 kg/m^2 for women), varicose veins and/or chronic venous insufficiency, hormone replacement therapy, history of chronic heart failure, chronic respiratory failure, or myeloproliferative syndrome.

The primary endpoint of PREVENT was the composite of objectively verified symptomatic DVT, PE, asymptomatic proximal DVT, and sudden death by Day 21. Symptomatic VTE required imaging confirmation (e.g., compression ultrasound or venography for DVT, lung scans or angiography for PE). Patients who did not have confirmed symptomatic VTE by Day 21 underwent compression ultrasound examination of the lower extremity. The compression ultrasound was performed in both legs on a centimeter-by-centimeter basis, was recorded on videotape, and forwarded to a core reading lab for blinded evaluation. The principal criterion for diagnosis of DVT was failure of a vein to compress completely upon the application of pressure. If both a proximal and distal DVT were identified, the patient was assigned to the proximal-DVT group.

The present report includes patients for whom a technically adequate (i.e., including proximal and distal veins) Day-21 compression ultrasound was available and for whom the vital status at Day 90 was known.

The management of patients with DVT, either proximal or distal, was left to the discretion of the treating physicians and was not dictated by the protocol. Data on patient management following the diagnosis of DVT were not collected.

Correlations were calculated using univariate and multivariate models (stepwise logistic regression analyses). For multivariate analysis, death was the dependent variable and the independent variables included baseline demographic and clinical characteristics (including all of the qualifying diagnostic categories), and the presence of proximal or distal DVT.

Results

A total of 3706 patients were enrolled at 219 centers in 26 countries (11). The incidence of the primary composite endpoint was 2.77% in the dalteparin group and 4.96% in the placebo group, a risk reduction of 45% (relative risk 0.55; 95% CI 0.38 – 0.80; p = 0.0015).

Of patients alive on Day 21 who had not sustained a symptomatic, verified event, 1738 had an adequate compression ultrasound of both the proximal and distal veins and constitute the

Table 1: Baseline characteristics.

	Proximal DVT	Distal DVT	No DVT
	N = 80	N = 118	N = 1540
Mean age, years	73.0	74.7	67.4
Male, n (%)	43 (53.8)	51 (43.2)	749 (48.6)
Race, n (%)			
White	73 (91.3)	111 (94.1)	1454 (94.6)
Black	0	2 (1.7)	28 (1.8)
Asian	0	1 (0.8)	4 (2.6)
Other	7 (8.8)	4 (3.4)	51 (3.3)
Mean weight, kg	72.4	69.6	75.1
Primary diagnosis, n (%)			
Congestive Heart Failure	49 (61.3)	59 (50.0)	922 (59.9)
Respiratory failure	31 (38.8)	45 (38.1)	529 (34.4)
Additional risk factors, n (%)			
Chronic heart failure	49 (61.3)	59 (50.0)	922 (59.9)
Chronic respiratory failure	7 (8.8)	14 (11.9)	133 (8.6)
Obesity	15 (18.8)	30 (25.2)	430 (28.0)
Prior VTE	8 (10.0)	4 (3.4)	60 (3.9)
Cancer	5 (6.3)	6 (5.1)	67 (4.4)
Varicose veins	28 (35.0)	32 (27.1)	414 (26.9)
Hormone therapy	1 (1.3)	1 (0.9)	25 (1.6)
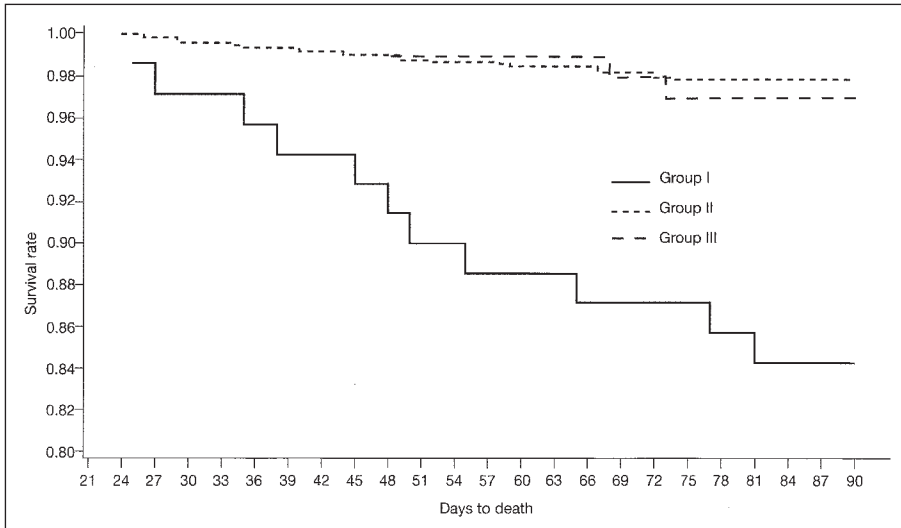
Figure 1: Kaplan-Meier survival curves illustrating the cumulative survival from Day 21 to Day 90 of patients with asymptomatic proximal DVT (Group I), asymptomatic distal DVT (Group II), and no DVT (Group III).

population for this analysis. Of these 1738 patients, 80 (27 dalteparin and 53 placebo) had asymptomatic proximal DVT (Group I), 118 (54 dalteparin and 64 placebo) had asymptomatic distal DVT (Group II), and 1540 (778 dalteparin and 762 placebo) had no DVT (Group III). Baseline characteristics are summarized in Table 1.

Eleven Group I patients (13.8%) had died by Day 90 compared with 4 Group II patients (3.4%) and 30 Group III patients (1.9%) with no DVT (p < 0.001 Group I versus Group III; p = 0.0014 Group I versus Group II; p = 0.29 Group II versus Group III). The hazard ratio for mortality in Group I versus Group III was 7.63 (95% CI = 3.8–15.3). The hazard ratio for mortality in Group II versus Group III was 1.36 (95% CI = 0.41–4.45). Among patients with proximal DVT, 2 patients receiving dalteparin died (7.4%) and 9 patients in the placebo group died (17%).

The survival curves for the three groups are illustrated in Figure 1. The curves separate early and the difference in cumulative mortality progresses through the observation period. The adjudicated causes of death between Day 21 and Day 90 are summarized in Table 2. In multivariate analysis, only two variables were associated with a significantly increased risk of death: asymptomatic proximal DVT (p < 0.0001) and age >75 (p = 0.0051). The individual clinical variables that were significantly associated with the development of proximal DVT included age ≥75 (p = 0.0005), prior DVT (p = 0.001), and varicose veins (p = 0.04).

Discussion

We have demonstrated that, in an acutely ill, immobilized medical population, the presence of compression ultrasound-identified asymptomatic proximal DVT was associated with a high 90-day mortality. No previous study has linked the presence of asymptomatic proximal DVT to mortality. The Group I mortality rate of 13.8% was comparable to the 12.5% mortality rate observed in high risk patients with symptomatic proximal DVT in the PREPIC study (12) and the 17.4% 90-day mortality rate previously reported in a large study of patients with PE (13). In contrast in the present study, the observed increase in 90-day

mortality in the presence of asymptomatic distal DVT did not reach statistical significance.

The association between asymptomatic proximal DVT and 90-day mortality persisted in univariate and multivariate analyses. Therefore, though there were differences in baseline characteristics among the three groups of patients (e.g. in the prevalence of underlying diagnoses), these did not account for the difference in 90-day mortality. However, other unidentified baseline characteristics could confound the results.

The finding that asymptomatic proximal DVT is associated with a high mortality rate supports the use of asymptomatic proximal DVT as an appropriate endpoint in clinical trials of thromboprophylaxis. Furthermore, this emphasizes the critical importance of prevention of VTE because it is not routine practice to conduct surveillance imaging in asymptomatic patients.

Though our study did not demonstrate a significant difference in mortality between Groups II and III, this cannot be construed as proof that distal DVTs are benign. There was a numerical increase in mortality among patients with distal DVTs compared with patients without DVT. It would require a substantially

Table 2: Adjudicated cause of death from Day 21 to Day 90. The percentages in parentheses are the percentage of deaths within each group.

	Group I N (%)	Group II N (%)	Group III N (%)
Sudden death	0	0	5 (16.7)
Likely VTE related	0	0	1 (3.3)
Fatal bleed	0	0	1 (3.3)
Vascular death	4 (36.4)	0	13 (43.3)
Cancer related	3 (27.3)	1 (25)	3 (10)
Other causes of death	4 (36.4)	2 (50)	6 (20)
Not assessable	0	0	1 (3.3)
Missing	0	1 (25)	0

larger sample size to adequately address whether or not this represents a significant increase in mortality.

We also identified advanced age, prior history of VTE, and varicose veins as the most potent predictors of patients who develop proximal DVT.

There are several limitations to the present study. Compression ultrasound is more accurate for the diagnosis of proximal DVT than it is for diagnosing distal DVT (14). Thus, our observations with respect to distal DVTs are less certain than our observations with respect to proximal DVTs. However, we included in the present analysis only those patients who had had a technically adequate compression ultrasound of both proximal and distal veins, and we ensured the uniformity of ultrasonographic criteria by using a core lab.

The association between proximal DVT and subsequent mortality does not necessarily establish causality. Although a blinded endpoints committee adjudicated the causes of death, we cannot be certain of the precise contribution of VTE to the observed fatalities. DVT or PE as a causative or contributing factor to deaths in this population with significant cardiac or pulmonary disease was not systematically evaluated. Without autopsy data, it would be nearly impossible to ascertain the precise frequency of PE. Furthermore, the association of proximal DVT and increased mortality could reasonably be interpreted in several ways. Plausible explanations include that the proximal DVT's directly contributed to increased mortality via their propensity to embolize or, alternatively, that developing a DVT is a marker for severe underlying illness.

Asymptomatic proximal DVT is often used as an endpoint in clinical trials of VTE prophylaxis. Our study demonstrated the clinical importance of asymptomatic proximal DVT as a marker of high mortality risk and thus provides evidence supporting the use of asymptomatic proximal DVT as an endpoint in preventive studies.

Appendix

Steering Committee — A Leizorovicz (Chairman), SZ Goldhaber (Co-chairman), AT Cohen, A Eldor, C-G Olsson, AG Turpie; *Clinical Endpoint Committee* — J Weitz (Chairman), R Becker, M Gent, J Ginsburg, J Heit; *Core Laboratory Site for Ultrasound* — A Leizorovicz (Administrative Director), Z Akkal, M Alves, F Becker (Scientific Director), H Boulet, B Fevrier, A Junod, C Noize-Pin, N Visele; *Independent Data-Monitoring Committee* B Davidson (Chairman), T Fleming, MM Samama.

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