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Thromboprophylaxis with dalteparin in medical patients: which patients benefit?

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Abstract: It is unclear whether thromboprophylaxis produces a consistent risk reduction in different subgroups of medical patients at risk from venous thromboembolism. We performed a retrospective, post hoc analysis of 3706 patients enrolled in the PREVENT study. Patients were at least 40 years old with an acute medical condition requiring hospitalization for at least 4 days and had no more than 3 days of immobilization prior to enrolment. Patients received either subcutaneous dalteparin (5000 IU) or placebo once daily. The primary end point was the composite of symptomatic deep vein thrombosis (DVT), pulmonary embolism, asymptomatic proximal DVT, or sudden death. Primary diagnosis subgroups were acute congestive heart failure, acute respiratory failure, infectious disease, rheumatological disorders, or inflammatory bowel disease. All patients, except those with congestive heart or respiratory failure, had at least one additional risk factor for venous thromboembolism. A risk reduction was shown in patients receiving dalteparin versus placebo. The relative risk (RR) was 0.73 in patients with congestive heart failure, 0.72 for respiratory failure, 0.46 for infectious disease, and 0.97 for rheumatological disorders. The RR was 0.52 in patients aged ≥ 75 years, 0.64 in obese patients, 0.34 for patients with varicose veins, and 0.71 in patients with chronic heart failure. No subgroup had a significantly different response from any other. Importantly, multivariate analysis showed that all patient groups benefited from thromboprophylaxis with dalteparin. Our findings, therefore, support the broad application of thromboprophylaxis in acutely ill hospitalized medical patients.

Key words: anticoagulants, dalteparin, deep vein thrombosis, low-molecular-weight heparin, thromboembolism

Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in hospitalized patients,^{1–5} including those with acute medical illnesses.^{6–8} Deep vein thrombosis (DVT) is reported to occur in approximately 10–26% of general medical patients.^{9,10} Pulmonary embolism (PE) causes approximately 10% of deaths in all hospitalized

patients.¹¹ Data from a recent registry demonstrate that medical patients at risk of VTE are much less likely to receive thromboprophylaxis than surgical patients.¹²

The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE Trial (PREVENT) was designed to assess the efficacy of the low-molecular-weight heparin dalteparin for the prevention of clinically important VTE in acutely ill medical patients. The primary results have been published previously.¹³ The present analysis examines the efficacy of dalteparin in subgroups of medical patients at risk of VTE. While the PREVENT study was not powered to detect a significant treatment effect in individual patient subgroups, this retrospective, post hoc analysis was undertaken to investigate whether there was consistency in the benefit of dalteparin thromboprophylaxis in the patient subgroups. In addition, this analysis examined whether certain groups of medical patients are at lower risk than others, and whether some subgroups do not benefit from thromboprophylaxis.

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Methods

PREVENT was a randomized, double-blind, placebo-controlled, multicentre, multinational 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 and has been described previously.^{13,14}

Patients were at least 40 years of age with an acute medical condition requiring anticipated hospitalization for 4 or more days and had no more than 3 days of immobilization preceding enrolment.

The patient subgroups according to primary diagnosis in PREVENT were: acute congestive heart failure (New York Heart Association class III or IV), acute respiratory failure that did not require ventilatory support, and other defined acute medical conditions (acute infectious disease, rheumatological disorders, or inflammatory bowel disease). Patients in the latter category also had to have at least one additional risk factor for DVT. The additional risk factors for DVT were: age \geq 75 years; cancer; previous DVT or PE; obesity (body mass index \geq 30 kg/m² for men and \geq 28.6 kg/m² for women); varicose veins and/or chronic venous insufficiency; hormone replacement therapy; history of chronic heart failure; chronic respiratory failure (defined as chronic oxygen supplementation, or pO₂ < 60 mmHg or pCO₂ > 45 mmHg); or myeloproliferative syndrome. Patients could have more than one primary diagnosis or additional risk factor.

The study was conducted in accordance with the Declaration of Helsinki and local regulations. Written

informed consent was obtained from patients, and independent ethics committees approved the protocol.

The primary end point was the composite of objectively verified symptomatic DVT, symptomatic PE, asymptomatic proximal DVT, or sudden death by day 21. All patients underwent compression ultrasound (CUS) examination for asymptomatic proximal DVT.¹⁵ The CUS results were ascertained in a blinded fashion by a core laboratory.

Subgroup analyses were performed on the primary end point and subgroups of patients were categorized according to their diagnosis or risk factor characteristics recorded at baseline. Statistical analysis was performed on the intention-to-treat population with observed events, using a Cochran–Mantel–Haenszel test. The Breslow–Day test was used to test for the homogeneity of strata. Two-sided 95% confidence intervals (95% CI) were calculated for the relative risk between the two treatment groups. The a priori statistical plan stipulated that 95% CI would not be calculated if fewer than five patients in the treatment group experienced an event.

Results

Overall findings from the PREVENT study

The original analysis and publication showed that a total of 3706 patients were enrolled at 219 centres in 26 countries.¹³ Baseline characteristics were similar in the placebo and dalteparin groups (Table 1). The most common reasons for inclusion were acute congestive heart failure, acute respiratory failure, or infectious

Table 1 Patient characteristics at baseline.

	Dalteparin <i>n</i> = 1848	Placebo <i>n</i> = 1833
Age; mean (SD), years	68.5 (11.1)	68.5 (11.7)
Male, <i>n</i> (%)	884 (47.8)	888 (48.4)
BMI; mean (SD), kg/m ²	27.4 (5.9)	27.5 (6.0)
Primary diagnosis, <i>n</i> (%)		
Acute congestive heart failure	965 (52.2)	940 (51.3)
Acute respiratory failure	561 (30.4)	560 (30.6)
Acute condition	749 (40.5)	781 (42.6)
Infectious disease	673 (36.4)	687 (37.5)
Rheumatological disorder	200 (10.8)	198 (10.8)
Inflammatory bowel disease	10 (0.5)	8 (0.4)
Risk factors, <i>n</i> (%)		
Chronic heart failure	925 (50.1)	946 (51.6)
Age \geq 75 years	611 (33.1)	615 (33.6)
Obesity	558 (30.2)	560 (30.6)
Varicose veins	487 (26.4)	530 (28.9)
Chronic respiratory failure	176 (9.5)	183 (10.0)
Cancer	85 (4.6)	105 (5.7)
Previous VTE	62 (3.4)	80 (4.4)
Hormone therapy	33 (1.8)	30 (1.6)
Myeloproliferative syndrome	5 (0.3)	9 (0.5)

Patients could have more than one reason for inclusion.

SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism.

disease. The prevalence of the primary composite outcome 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 to 0.80; $p = 0.0015$).

Subgroup findings in the PREVENT study

The point estimates varied slightly from one subgroup to another. However, all of the relative risks were consistently lower in patients who received prophylaxis compared with those who did not receive prophylaxis, in both the primary diagnosis (Table 2) and risk factor (Table 3) subgroups.

The prevalence of the primary end point in patients with acute congestive heart failure was 3.07% in the dalteparin group versus 4.23% in the placebo group (relative risk: 0.73; 95% CI: 0.44 to 1.21). In the dalteparin group, the primary end point occurred in 3.62% of patients with acute respiratory failure compared with 5.06% in the placebo group (relative risk: 0.72; 95% CI: 0.38 to 1.34). This represents a relative risk reduction of 28%. In patients with acute infectious disease, the prevalence of the primary end point was 2.90% in the dalteparin group versus 6.30% in the placebo group, a relative risk reduction of 54% (relative risk: 0.46; 95% CI: 0.25 to 0.84). The prevalence of the primary end point in patients with rheumatological disorder was 3.43% in the dalteparin group versus 3.55% in the placebo group (relative risk: 0.97; 95% CI: 0.32 to 2.94).

In patients aged ≥ 75 years, the prevalence of the primary end point was 4.15% in the dalteparin group versus 8.03% in the placebo group, a risk reduction of 48% (relative risk: 0.52; 95% CI: 0.31 to 0.87). The prevalence of the primary end point in obese patients was 2.79% in the dalteparin group versus 4.34% in the placebo group, a risk reduction of 36% (relative risk: 0.64; 95% CI: 0.32 to 1.28). In the subgroup of patients with varicose veins, the prevalence of the primary end point was 2.44% in the dalteparin group versus 7.11% in the placebo group, a risk reduction of 66% (relative risk: 0.34; 95% CI: 0.17 to 0.69). The prevalence of the primary end point in patients with chronic heart failure was 3.32% in the dalteparin group versus 4.70% in the placebo group (relative risk: 0.71; 95% CI: 0.43 to 1.15).

The subgroup confidence intervals of the relative risks were overlapping and the tests of homogeneity showed non-significance, as illustrated in Figure 1. Multivariate analysis (details not shown) confirmed the findings of the univariate analysis.

Discussion

This study has shown a consistent reduction in the risk of VTE among the various patient subgroups enrolled in PREVENT. The PREVENT study was not powered to detect a significant difference in the prevalence of

Table 2 Incidence and relative risk of the primary end point in the primary diagnosis subgroups.

Primary diagnosis subgroups	Dalteparin n/N (%)	Placebo n/N (%)	Relative risk (95% CI)
Acute congestive heart failure (NYHA class III or IV)	25/814 (3.07)	33/781 (4.23)	0.73 (0.44–1.21)
Acute respiratory failure	16/442 (3.62)	22/435 (5.06)	0.72 (0.38–1.34)
Other acute medical conditions	18/605 (2.98)	35/617 (5.67)	0.52 (0.30–0.92)
Infectious disease	15/517 (2.90)	33/524 (6.30)	0.46 (0.25–0.84)
Rheumatological disorder	6/175 (3.43)	6/169 (3.55)	0.97 (0.32–2.94)
Inflammatory bowel disease	0/6 (0)	1/8 (12.50)	–

Patients could have more than one primary diagnosis.

Table 3 Incidence and relative risk of the primary end point in the risk factor subgroups.

Risk factor subgroups	Dalteparin n/N (%)	Placebo n/N (%)	Relative risk (95% CI)
Age ≥ 75 years	20/482 (4.15)	38/473 (8.03)	0.52 (0.31–0.87)
Cancer	2/65 (3.08)	6/72 (8.33)	0.37 (–)
Previous VTE	2/48 (4.17)	8/62 (12.90)	0.32 (–)
Obesity	13/466 (2.79)	20/461 (4.34)	0.64 (0.32–1.28)
Varicose veins	10/410 (2.44)	31/436 (7.11)	0.34 (0.17–0.69)
Hormone therapy	0/23 (0)	1/22 (4.55)	–
Chronic heart failure	26/784 (3.32)	37/788 (4.70)	0.71 (0.43–1.15)
Myeloproliferative syndrome	0/4 (0)	1/7 (14.29)	–
Chronic respiratory failure	4/129 (3.10)	6/139 (4.32)	0.72 (–)

Patients could have more than one risk factor.
VTE, venous thromboembolism.

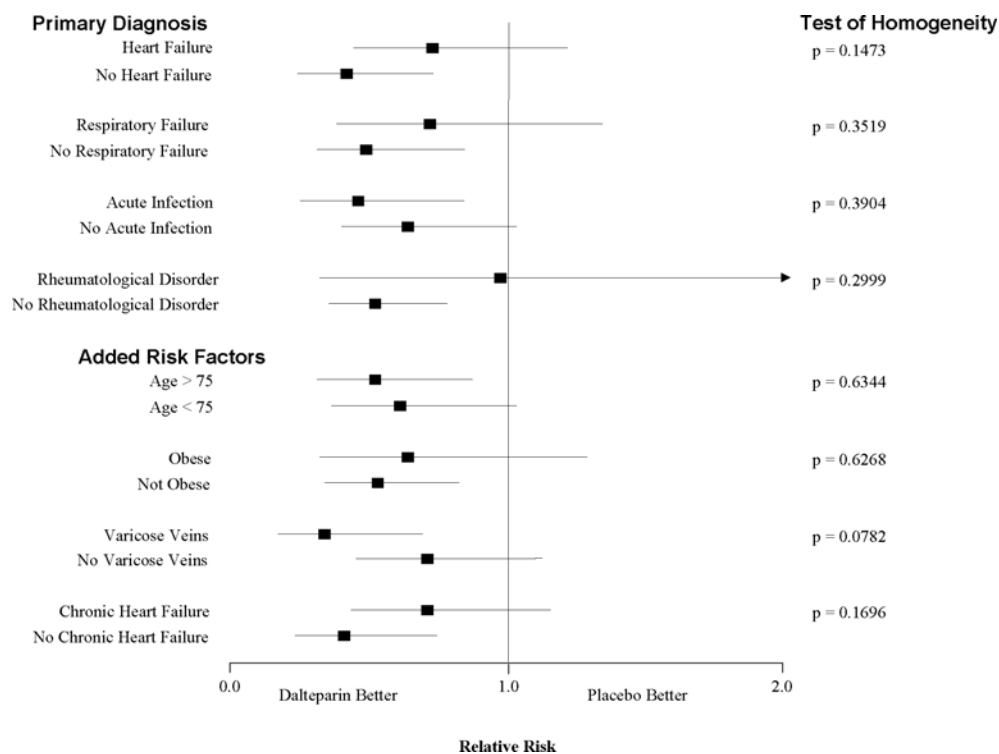


Figure 1 Venous thromboembolism in acutely ill medical patients, presented as relative risk and 95% CI. Subgroups with fewer than five events in the treatment groups are not illustrated.

VTE in the individual subgroups. Therefore, the reason why many of the subgroups did not have significant responses may be due to an insufficient sample size and hence there still could be differences in response to dalteparin. As a result, the data from the at-risk subgroups of patients from the PREVENT study were examined to evaluate whether the overall risk reduction in VTE reflected a consistent risk reduction across the various subgroups. Although the point estimates varied slightly from one subgroup to another, all of the relative risks consistently demonstrated a risk reduction in VTE in favour of thromboprophylaxis with dalteparin.

The non-significant *p*-values for the test of homogeneity indicate that no single group was significantly different in response from any other group. Similarly, the benefit of thromboprophylaxis with dalteparin was evident across the risk factor subgroups, and the overall relative risk reduction of 45% observed in the study is likely to apply to all the categories of patients included in PREVENT. Importantly, our analyses did not identify a group of patients that failed to benefit from dalteparin administration. This study found that obesity did not significantly affect the efficacy of dalteparin, while the outcome was affected by age, with patients aged over 75 years deriving greater benefit than younger patients. This may have been due to a relatively lower frequency of events in the obesity groups when compared with the groups of elderly patients, as indicated by the point estimates which

were similar (0.64 and 0.52 respectively). The relationship between both obesity and age has been examined in greater detail in a study we published previously. This study examined weight and age in five categories and showed dalteparin of 5000 IU once daily was safe and effective in the prevention of VTE in these patients.¹⁶ The present study confirms that all patient groups benefited from dalteparin administration in terms of a reduction in VTE risk. Apart from our analysis showing a lack of any effect in rheumatology patients, these results are consistent with the recently reported subgroup analysis of the MEDENOX study, which was a smaller placebo-controlled study in a similar population of medical patients that relied mainly on venographic outcomes.¹⁷

PREVENT builds upon observations from previous studies that reported a reduction in the prevalence of asymptomatic venous thrombosis comprising mostly distal (calf vein) DVT, the clinical relevance of which is uncertain.^{18,19} In PREVENT, the overall reduction in the prevalence of VTE was largely due to prevention of asymptomatic proximal DVT.¹³ Both symptomatic and asymptomatic proximal DVT are widely accepted as clinically relevant, and are closely linked to the risk of PE.²⁰⁻²² Retrospective analysis of data from PREVENT showed that asymptomatic proximal DVT is associated with increased mortality,²³ which underscores its clinical relevance and supports targeting of asymptomatic proximal DVT as an appropriate end point in clinical trials of thromboprophylaxis.

The results of our analysis show that dalteparin was effective in all patient subgroups, whether defined by the primary diagnosis or by the secondary, added risk factors. These findings clearly show the homogeneity of the benefits of thromboprophylaxis with dalteparin, and support the recommendation for broad utilization of antithrombotic prophylaxis in acutely ill hospitalized medical patients.

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