Efficacy and Safety of Fixed Low-Dose Dalteparin in Preventing Venous Thromboembolism Among Obese or Elderly Hospitalized Patients

A Subgroup Analysis of the PREVENT Trial

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Background: We were concerned that a fixed rather than a weight-based dosing regimen of dalteparin sodium to prevent venous thromboembolism (VTE) might result in decreased efficacy in obese patients and decreased safety in elderly patients.

Methods: We retrospectively performed subgroup analyses using the database from the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients (PREVENT) Trial, a study of 3706 hospitalized, medically ill patients randomized to receive either dalteparin sodium, 5000 U/d, or placebo. The primary end point was a composite of symptomatic VTE, fatal pulmonary embolism, sudden death, or asymptomatic proximal deep venous thrombosis by day 21. Obesity was defined as a body mass index (calculated as weight in kilograms divided by the square of height in meters) of 30 or greater for men and 28.6 or greater for women.

Results: Overall, 1118 patients (30.4%) were obese and 1226 (33.3%) were 75 years or older. In obese patients, the primary end point occurred in 2.8% of the dalteparin and in 4.3% of the placebo groups (relative risk, 0.64; 95% confidence interval [CI], 0.32-1.28). In patients 75 years or older, the primary end point was reported in 4.2% of the dalteparin and in 8.0% of the placebo groups (relative risk, 0.52; 95% CI, 0.31-0.87). The dalteparin effect for the primary end point (odds ratio, 0.51; 95% CI, 0.32-0.82) was not attenuated when adjusted for age, sex, obesity, history of VTE, and varicose veins. Dalteparin was not associated with an increase in major hemorrhage by day 21 in obese (0% vs 0.7% placebo; $P>.99$) and in elderly (1.1% vs 0.7%; $P=.12$) patients.

Conclusion: Our findings suggest that a fixed low dose of dalteparin sodium of 5000 U/d is effective and safe in preventing VTE in obese and elderly hospitalized medical patients.

Arch Intern Med. 2005;165:341-345

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Financial Disclosure: Dr Vaitkus was an employee of Pharmacia Corp during this study. Dr Cohen was a consultant for Pfizer Inc, Sanofi-Synthelabo Inc, AstraZeneca, Aventis, and Mitsubishi Pharma Corp. Dr Goldhaber was a consultant for Pfizer Inc.

OBESITY IS AN ESTABLISHED risk factor for venous thromboembolism (VTE)[1-4] and represents a major health problem, especially in the United States, where the prevalence has reached 30% in the past decade.[5,6] Increasing age is also a risk factor for VTE, and risk approximately doubles with each subsequent decade.[7-10] The US population is aging,[11] and an increasing proportion of hospitalized patients is elderly.[12]

Dalteparin sodium, a low-molecular-weight heparin (LMWH), is used in fixed low doses to prevent VTE in surgical patients.[13-15] In the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients (PREVENT) Trial, a fixed dose of 5000 U of dalteparin sodium reduced VTE events by 45% (relative risk [RR], 0.55; 95% confidence interval [CI], 0.38-0.80) in patients 40 years or older who required hospitalization with an acute medical condition.[16] We were concerned that a fixed rather than a weight-based dosing regimen of dalteparin might result in decreased efficacy in obese patients because of increased plasma drug distribution.[17-21] We were also concerned about the possibility of decreased safety in elderly patients because of decreased drug clearance.[22,23]

METHODS

We retrospectively analyzed data from the PREVENT Trial, a study of 3706 hospitalized, medically ill patients, with a projected hospitalization of 4 or more days, who had been randomized to receive either dalteparin sodium, 5000 U/d, or placebo in a double-blinded fashion.[24] Obesity was defined as a body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) of 30

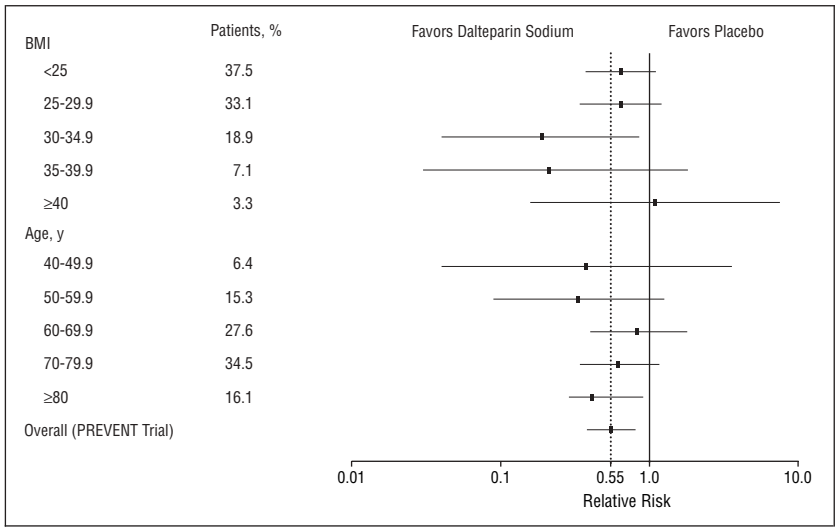

Figure. Effect of dalteparin sodium on prevention of the primary end point in body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) and age subgroups, presented as relative risk (logarithmic axis) and 95% confidence intervals.

Table 1. Baseline Characteristics*

Characteristic	Obese (n = 1118)	Nonobese (n = 2563)	*P* Value
Men	396 (35.4)	1376 (53.7)	<.001
Women	722 (64.6)	1187 (46.3)	
Age <75 y	848 (75.8)	1607 (62.7)	<.001
Age ≥75 y	270 (24.2)	956 (37.3)	
Race			
White	1025 (91.7)	2366 (92.3)	.91
Black	17 (1.5)	35 (1.4)	
Other	70 (6.3)	151 (5.9)	
Unknown	6 (0.5)	11 (0.4)	
Weight, kg	90.8 ± 16.6	68.4 ± 13.5	<.001
Median	89.5	68.0	
BMI	33.8 ± 4.9	24.6 ± 3.8	<.001
Median	32.9	24.7	
Primary diagnosis			
Acute CHF, NYHA class III or IV	581 (52.0)	1324 (51.7)	.86
Acute respiratory failure	293 (26.2)	828 (32.3)	<.001
Infectious disease	378 (33.8)	982 (38.3)	.009
Acute rheumatic disease	41 (3.7)	44 (1.7)	<.001
Acute arthritis (leg)	62 (5.5)	62 (2.4)	<.001
Acute lumbago/sciatica	78 (7.0)	120 (4.7)	.004
Acute inflammatory bowel disease	8 (0.7)	10 (0.4)	.19
Comorbidities			
Chronic heart failure	612 (54.7)	1259 (49.1)	.002
Varicose veins	398 (35.6)	619 (24.2)	<.001
Cancer	32 (2.9)	158 (6.2)	<.001
Chronic respiratory failure	91 (8.1)	268 (10.5)	.03
History of VTE	48 (4.3)	94 (3.7)	.37
Hormone therapy	21 (1.9)	42 (1.6)	.61
Long-term aspirin use (any dose)	455 (40.7)	1073 (41.9)	.49

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CHF, congestive heart failure; NYHA, New York Heart Association; VTE, venous thromboembolism.

*Data are given as number (percentage) of patients or mean ± SD value unless otherwise specified.

or greater for men and 28.6 or greater for women[25]; elderly was defined as 75 years or older.[25]

Inclusion criteria for the PREVENT Trial were acute congestive heart failure (New York Heart Association III and IV), acute respiratory failure that did not require ventilatory support, infectious disease, acute rheumatic disease, or inflammatory bowel disease. In patients with infectious, rheumatic, or inflammatory bowel disease, at least 1 additional VTE risk factor had to be present: chronic congestive heart failure, 75 years or older, obesity, varicose veins, chronic respiratory failure (defined as chronic oxygen supplementation, P_{O_2} <60 mm Hg, or P_{CO_2} >45 mm Hg), cancer, history of VTE, hormone therapy, or myeloproliferative syndrome. The main exclusion criteria were major surgery within the previous month, immobilized lower extremity due to trauma, acute stroke within 3 months, an increased bleeding risk, a platelet count less than 100×10^9/L, creatinine level higher than 2 mg/dL (>176.8 µmol/L), hepatic disease, immobility for longer than 3 days, coagulopathy, pregnancy, or a life expectancy of less than 1 month.

The primary end point of the PREVENT Trial was a composite of symptomatic VTE, fatal pulmonary embolism, sudden death, or asymptomatic proximal deep venous thrombosis by compression ultrasound at day 21. Overall, 2991 of the 3706 patients were evaluable for the primary end point.[24] Compression ultrasound was performed bilaterally, from the common femoral to the distal popliteal vein. In the presence of symptoms or signs of deep vein thrombosis (DVT), the calf deep veins were also examined. Secondary end points of the PREVENT Trial were all-cause mortality by days 21 and 90, symptomatic or asymptomatic proximal DVT at day 21, major and minor bleeding at day 21, and thrombocytopenia by day 21. All asymptomatic DVT end points were centrally adjudicated by a core ultrasound laboratory, blinded to group assignment; other symptomatic end points were centrally adjudicated by a clinical event committee.

Major bleeding was defined as bleeding that was fatal, intracranial, intraocular, spinal/epidural, retroperitoneal, or associated with a hemoglobin loss of 2 g/dL or greater or a transfusion of 2 U or more of blood or significant medical or surgical intervention.

Dichotomous data comparing obese vs nonobese and elderly vs younger patients were evaluated with a χ^2 test, and continuous variables were evaluated with an unpaired, 2-tailed *t* test. We used the Bonferroni correction for multiple univariate comparisons and defined a *P* value of less than .002 as significant. We calculated incidence and RR with 95% CIs of the primary end point for dalteparin vs placebo in obese and nonobese patients as well as in patients 75 and older and younger than 75 years. Relative risk was also calculated in predefined age and BMI subgroups (**Figure**). We calculated interaction between the daltepa-

rin effect for the primary end point and obesity using a logistic regression model with the factors treatment, obesity, and interaction term. Multivariate logistic regression analysis was performed to model the treatment effect of dalteparin for the primary end point while adjusting for obesity, age, and sex. A personal history of VTE and presence of varicose veins were univariate predictors of the primary end point; we therefore included these variables in the multivariate analysis.

RESULTS

Obesity was present in 1118 patients (30.4%), one third of men and two thirds of women (**Table 1**). Most obese patients were younger than nonobese patients. Acute arthritis, acute lumbago/sciatica, chronic heart failure, and varicose veins were more common in obese patients. Acute respiratory failure and cancer were less common in obese than in nonobese patients.

In obese patients, the primary end point occurred in 2.8% (95% CI, 1.3%-4.3%) and 4.3% (95% CI, 2.5%-6.2%) of the dalteparin and placebo groups, respectively (RR, 0.64; 95% CI, 0.32-1.28). In nonobese patients, the primary end point was reported in 2.8% (95% CI, 1.8%-3.8%) and 5.2% (95% CI, 3.9%-6.6%) of the dalteparin and placebo groups, respectively (RR, 0.53; 95% CI, 0.34-0.82).

In patients 75 years or older, the primary end point occurred in 4.2% (95% CI, 2.4%-5.9%) and 8.0% (95% CI, 5.6%-10.5%) of the dalteparin and placebo groups, respectively (RR, 0.52; 95% CI, 0.31-0.87). In patients younger than 75 years, the primary end point was reported in 2.1% (95% CI, 1.3%-3.0%) and 3.5% (95% CI, 2.4%-4.6%) of the dalteparin and placebo groups, respectively (RR, 0.61; 95% CI, 0.36-1.03).

Except for patients with a BMI of 40 or greater, dalteparin was effective in reducing the primary end point in the BMI and age subgroups (Figure).

The proportion of patients who had components of the primary end point was similar in obese and nonobese patients (**Table 2**). Compared with younger patients, elderly patients more often had symptomatic pulmonary embolism and both symptomatic and asymptomatic proximal DVT.

Logistic regression analysis modeling the probability of the primary end point indicated no interaction between dalteparin efficacy and the presence of obesity ($P=.63$). When weight was modeled as a continuous variable, no statistically significant interaction between weight and dalteparin efficacy was observed ($P=.97$). The dalteparin effect for the primary end point persisted (adjusted odds ratio, 0.51; 95% CI, 0.32-0.82; $P=.006$) when adjusted for univariately significant predictors of the primary end point, including age, history of VTE, sex, obesity, and varicose veins.

Dalteparin was not associated with an increase in mortality by day 21 in obese patients (4.6% vs 2.7% placebo; $P=.14$) and elderly patients (6.7 vs 5.7% placebo; $P=.62$) or major hemorrhage by day 21 in obese patients (0% vs 0.7% placebo; $P>.99$) and elderly patients (1.1% vs 0.7%; $P=.12$) (**Table 3** and **Table 4**).

COMMENT

A fixed low dose of dalteparin sodium of 5000 U/d was similarly effective in obese and in nonobese and in elderly and younger hospitalized patients in preventing VTE by day 21. Dalteparin was also safe in obese and elderly patients. In these subgroups, we did not observe a significant difference in mortality or major hemorrhage by day 21 between the treatment and placebo groups.

Table 2. Components of the Primary End Point, According to Body Mass Index and Age*

End Point Component	Obese (n = 1118)	Nonobese (n = 2563)	Age <75 y (n = 2455)	Age ≥75 y (n = 1226)
Sudden death	4/1107 (0.36)	4/2529 (0.16)	5/2422 (0.21)	3/1214 (0.25)
PE: fatal	0/1107	2/2529 (0.08)	2/2422 (0.08)	0/1214
PE: symptomatic	3/1080 (0.28)	8/2419 (0.33)	4/2351 (0.17)	7/1148† (0.61)
DVT: distal, symptomatic	3/1080 (0.28)	4/2418 (0.17)	3/2350 (0.13)	4/1148 (0.35)
DVT: proximal, symptomatic	23/922 (2.49)	66/2070 (3.19)	45/2038 (2.21)	44/954‡ (4.61)
DVT: proximal, asymptomatic	22/917 (2.40)	58/2043 (2.84)	39/2019 (1.93)	41/941§ (4.36)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
*Data are given as number/total number (percentage).
†$P=.048$.
‡$P=.001$.
§$P<.001$ (the Fisher exact test for differences in end points between patients aged <75 and ≥75 years).

Table 3. Adverse Events According to the Presence or Absence of Obesity

	Nonobese			Obese		
Adverse Event	Dalteparin Sodium (n = 1290)	Placebo (n = 1273)	*P* Value	Dalteparin Sodium (n = 558)	Placebo (n = 560)	*P* Value
Mortality, %						
Day 21	5.5	6.0	.54	4.6	2.7	.14
Day 90	14.3	13.7	.94	9.9	8.6	.36
Hemorrhage, %						
Major day 21	1.6	0.3	.07	0	0.7	>.99
Minor day 21	2.5	1.8	.31	1.4	0.7	.22
Thrombocytopenia, %						
Day 21	1.5	1.0	.79	0.9	0.9	>.99

Table 4. Adverse Events According to Age

Adverse Event	Age <75 y			Age ≥75 y		
	Dalteparin Sodium (n = 1237)	Placebo (n = 1218)	*P* Value	Dalteparin Sodium (n = 611)	Placebo (n = 615)	*P* Value
Mortality, %						
Day 21	3.4	3.0	.88	6.7	5.7	.62
Day 90	8.1	8.4	.56	16.1	13.9	.41
Hemorrhage, %						
Major day 21	0.5	0.3	.69	1.1	0.7	.12
Minor day 21	1.7	0.3	.02	2.2	2.2	>.99
Thrombocytopenia, %						
Day 21	0.6	0.6	>.99	1.8	1.3	.55

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Low-molecular-weight heparins[22,26] reduce VTE in hospitalized medically ill patients. The prevalence of obesity in the PREVENT Trial is comparable to that reported among adults in the United States,[5] even though patients were enrolled from 23 countries. Markedly obese patients were well represented, with a BMI of 35 or greater in more than 10% of the PREVENT Trial patients.

In 3706 medically ill patients, the relative treatment effect of dalteparin was not attenuated when adjusted for age, sex, and obesity. While the absolute risk was similar in placebo-treated obese (4.3%) and nonobese (5.2%) patients, dalteparin was effective in obese patients, with an RR reduction of 36%. Although the absolute VTE risk was twice as high in placebo-treated patients 75 years or older (8.0%) compared with patients younger than 75 years (3.5%), dalteparin reduced VTE events by 48% in this population. Similarly, hospitalized medically ill patients 75 years or older in the MEDENOX study[27] had a greater benefit from 40 mg/d of enoxaparin sodium prophylaxis compared with younger patients. Dalteparin was effective in reducing VTE in all

age subgroups and in patients with a BMI of up to 40. A fixed low dose of dalteparin in patients with a BMI of 40 or greater may not be appropriate, particularly in the presence of additional VTE risk factors.

The overall 5% incidence of the primary end point in the placebo group of the PREVENT Trial indicates that the patients were at moderate VTE risk according to the classification by the Thromboembolic Risk Factors Consensus Group.[28] Whether weight-adjusted dosing rather than a fixed low dose of dalteparin should be used in older and obese medically ill patients with recent surgery, trauma, or thrombophilia remains unanswered because these patients were excluded from our trial. In the PREVENT Trial, patients with creatinine levels up to 2 mg/dL (176.8 µmol/L) were enrolled. It is likely that many elderly patients with renal dysfunction were included because, in this age group, renal function may decline even if the serum creatinine level remains within the normal range. Because creatinine clearance was not directly measured, the efficacy and safety of dalteparin according to various degrees of renal dysfunction was not assessed. Compression ultrasonography has limitations in diagnosing distal and asymptomatic proximal DVT. This may have affected the reported DVT rate, particularly in obese patients.

In conclusion, our findings suggest that the effectiveness and safety of dalteparin in preventing VTE among hospitalized patients with acute medical illness are not significantly affected by age or BMI. Because this study was a retrospective subgroup analysis of a randomized controlled trial, no definite conclusions can be drawn regarding the efficacy and safety of dalteparin in hospitalized obese and elderly patients. Future randomized controlled VTE prevention trials are warranted that specifically enroll these high-risk patients.

Accepted for Publication: September 2, 2004.

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Funding/Support: This study was sponsored by Pfizer Inc, New York, NY.

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