ORIGINAL ARTICLE

Low-Molecular-Weight Heparin and Mortality in Acutely Ill Medical Patients

Ajay K. Kakkar, M.B., B.S., Ph.D., Claudio Cimminiello, M.D., Samuel Z. Goldhaber, M.D., Rajiv Parakh, M.D., Chen Wang, M.D., Ph.D., and Jean-François Bergmann, M.D., for the LIFENOX Investigators*

ABSTRACT

BACKGROUND

Although thromboprophylaxis reduces the incidence of venous thromboembolism in acutely ill medical patients, an associated reduction in the rate of death from any cause has not been shown.

METHODS

We conducted a double-blind, placebo-controlled, randomized trial to assess the effect of subcutaneous enoxaparin (40 mg daily) as compared with placebo — both administered for 10±4 days in patients who were wearing elastic stockings with graduated compression — on the rate of death from any cause among hospitalized, acutely ill medical patients at participating sites in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia. Inclusion criteria were an age of at least 40 years and hospitalization for acute decompensated heart failure, severe systemic infection with at least one risk factor for venous thromboembolism, or active cancer. The primary efficacy outcome was the rate of death from any cause at 30 days after randomization. The primary safety outcome was the rate of major bleeding during and up to 48 hours after the treatment period.

RESULTS

A total of 8307 patients were randomly assigned to receive enoxaparin plus elastic stockings with graduated compression (4171 patients) or placebo plus elastic stockings with graduated compression (4136 patients) and were included in the intention-to-treat population. The rate of death from any cause at day 30 was 4.9% in the enoxaparin group as compared with 4.8% in the placebo group (risk ratio, 1.0; 95% confidence interval [CI], 0.8 to 1.2; P=0.83). The rate of major bleeding was 0.4% in the enoxaparin group and 0.3% in the placebo group (risk ratio, 1.4; 95% CI, 0.7 to 3.1; P=0.35).

CONCLUSIONS

The use of enoxaparin plus elastic stockings with graduated compression, as compared with elastic stockings with graduated compression alone, was not associated with a reduction in the rate of death from any cause among hospitalized, acutely ill medical patients. (Funded by Sanofi; LIFENOX ClinicalTrials.gov number, NCT00622648.)

From the Thrombosis Research Institute and University College London, London (A.K.K.); the Medical Department, Ospedale Civile di Vimercate, Vimercate, Italy (C.C.); Brigham and Women's Hospital and Harvard Medical School, Boston (S.Z.G.); Medanta–Medicity, Gurgaon, Haryana, India (R.P.); the Beijing Institute of Respiratory Medicine, Chaoyang District, and Beijing Hospital, Ministry of Health, Dongcheng District, Beijing (C.W.); and Hôpital Lariboisière, Assistance Publique–Hôpitaux de Paris, University of Paris Diderot, Paris (J.-F.B.). Address reprint requests to Dr. Kakkar at the Thrombosis Research Institute, Manresa Rd., Emmanuel Kaye Bldg., Chelsea, London SW3 6LR, United Kingdom, or at akkakkar@tri-london.ac.uk.

*A complete list of the LIFENOX investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;365:2463-72.

Venous thromboembolism is an important complication in hospitalized patients.[1-4] It is estimated that if thromboprophylaxis is not administered, objectively diagnosed deep-vein thrombosis — with the potential for fatal pulmonary embolism — will develop in 10 to 20% of medical patients and in 40 to 60% of patients undergoing major orthopedic surgery.[5] A retrospective review of 6833 autopsies showed that 81% of fatal cases of pulmonary embolism occurred in nonsurgical patients.[6]

Pharmacologic thromboprophylaxis has been proved to reduce the incidence of venous thromboembolism in both surgical patients and acutely ill medical patients.[5,7-9] In surgical patients, thromboprophylaxis has been shown to reduce the incidence of fatal pulmonary embolism and the rate of death from any cause[10,11]; in medical patients, studies have shown that thromboprophylaxis is associated with reductions in the rate of venous thromboembolic events, including asymptomatic deep-vein thrombosis assessed as part of a composite study end point.[7-9] A meta-analysis of five studies involving medical patients indicated that prophylaxis may be associated with a reduction in the rate of fatal pulmonary embolism but not in the rate of death from any cause.[12] Screening for asymptomatic deep-vein thrombosis, with subsequent treatment of the condition, may favorably alter the natural history of venous thromboembolism, thereby masking potential reductions in mortality associated with thromboprophylaxis.

The fact that thromboprophylaxis is used more frequently in hospitalized surgical patients than in acutely ill medical patients,[13-15] even though current guidelines clearly recommend its use in both patient populations,[5,16] may reflect a lack of evidence for a mortality reduction associated with pharmacologic prophylaxis in acutely ill medical patients.

In this trial, we evaluated the effect of pharmacologic thromboprophylaxis on the rate of death from any cause in acutely ill medical patients. Patients were randomly assigned to receive the low-molecular-weight heparin enoxaparin or placebo, with both groups assigned to wear elastic stockings with graduated compression.

METHODS

STUDY OVERSIGHT

We conducted this international, multicenter, randomized, double-blind, parallel-group study at 193 sites in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia. Recruitment began in January 2008 and was completed in September 2010. The study was conducted in accordance with the principles of the Declaration of Helsinki, including all the applicable amendments set forth by the World Medical Assembly, and with the International Conference on Harmonization guidelines for Good Clinical Practice. The study was approved by the research ethics committee at each participating site. Ethical approval was also obtained from the Comité de Protection des Personnes Île-de-France XI. A steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed and led the trial and planned the analyses. Funding and study drugs were provided by the sponsor (Sanofi). The data were gathered by the sponsor and were maintained and analyzed by an independent contract research organization. The steering committee had full access to the data. The first author wrote the first draft of the manuscript, and subsequent drafts were prepared with input from the coauthors, all of whom approved the submission of the final version of the manuscript. An independent data and safety monitoring committee (see the Supplementary Appendix) performed prespecified interim analyses after approximately 10%, 25% (for safety), 50%, and 75% (for both safety and efficacy) of the patients had completed the 30-day follow-up period, with stopping rules based on the Lan–DeMets type of O'Brien–Fleming stopping boundary. The study was conducted in accordance with the research protocol, which, along with the statistical analysis plan, is available at NEJM.org.

STUDY POPULATION

We enrolled men and women, 40 years of age or older, who were hospitalized within 48 hours before randomization for at least one of the following conditions: acute decompensation of heart failure; active cancer (defined as histologically confirmed cancer with an initial diagnosis within the previous 6 months or with a recurrence or metastasis within the previous 6 months), unless the hospitalization was a planned hospitalization for chemotherapy; or severe systemic infection in addition to at least one of the following conditions: chronic pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary fibrosis, or the pulmonary restrictive syndrome), obesity (a body-mass index [the weight in kilograms divided by

the square of the height in meters] ≥30), a personal history of venous thromboembolism, or an age of 60 years or older. In addition, eligible patients were required to have an anticipated duration of hospitalization of at least 6 days and an American Society of Anesthesiologists health status score of 3 or less (on a scale of 1 to 6, with higher scores indicating more severe illness) or, for patients with cancer, an Eastern Cooperative Oncology Group performance status score of 2 or less (on a scale of 0 to 5, with higher scores indicating greater severity of illness). All eligible patients were also required to provide written informed consent. The exclusion criteria are listed in the Supplementary Appendix.

STUDY DESIGN

Patients were randomly assigned to receive a subcutaneous injection with either enoxaparin, at a dose of 40 mg (Lovenox [United States] or Clexane [outside the United States], Sanofi), or placebo (0.9% saline) once every 24±4 hours during hospitalization, for 6 to 14 days (10±4 days). The investigators assigned the patients to a group in the sequential order of the treatment numbers available at the site. The treatment-code list of random permuted blocks was generated by an independent contract research organization and was stratified according to center. Patients who were discharged before the completion of the treatment period continued to receive the study medication at home. Knee-high elastic stockings (Ganzoni) that provided graduated pressure from 15 mm Hg (at the ankle) to 10 mm Hg (at the knee) were provided to both groups. The investigators, patients, and research personnel, as well as the members of the steering committee and of the data and safety monitoring committee, were unaware of the group assignments.

The study drug was discontinued in the event of an intercurrent illness or adverse event (e.g., creatinine clearance of <30 ml per minute or thrombocytopenia with a platelet count of <50,000 per cubic millimeter), definite venous thromboembolism requiring anticoagulant treatment, or proven heparin-induced thrombocytopenia.

OUTCOMES

The primary efficacy outcome was the rate of death from any cause between the time of randomization and day 30. Secondary efficacy outcomes were the rates of death from any cause between the time of randomization and day 14 and between the time of randomization and day 90; the rate of cardiopulmonary death (sudden death or death due to acute myocardial infarction, heart failure, pulmonary failure, or pulmonary embolism) at days 14, 30, and 90 after randomization; and the composite of the rate of sudden death or pulmonary embolism at days 14, 30, and 90 after randomization.

The main safety outcome was the rate of major hemorrhagic events during the treatment period. Other safety outcomes were clinically relevant nonmajor bleeding, minor bleeding, serious adverse events, nonserious adverse events, and adverse events of special interest, including thrombocytopenia and heparin-induced thrombocytopenia, occurring during the entire observation period (from receipt of informed consent until day 90). A major hemorrhage was defined as overt bleeding associated with one of the following: death; the need for transfusion of at least 2 units of packed red cells or whole blood; a fall in the hemoglobin level of 20 g or more per liter; the requirement for a major therapeutic intervention (e.g., surgery) to stop or control bleeding; or a bleeding site that was retroperitoneal, intracranial, or intraocular.[17] Clinically relevant nonmajor bleeding was defined as a nonmajor hemorrhage leading to discontinuation of the study drug or to hospitalization. A minor hemorrhage was defined as overt bleeding that did not meet the criteria for major hemorrhage but was associated with clinical features defined in the protocol.

STATISTICAL ANALYSIS

We estimated that with 3944 patients in each group, the study would have 90% power to show a 25% reduction with enoxaparin in the relative risk of death from any cause at 30 days, assuming a rate of death of 7% in the placebo group, at a two-sided alpha level of 0.05. Assuming that we would not be able to evaluate data from 5% of the patients, we estimated that we would have to enroll 8300 patients.

The primary population for the efficacy analyses comprised all patients who underwent randomization (intention-to-treat population). The safety analyses were performed on data from all patients who received at least one dose of a study drug. For the primary efficacy analysis, the incidence of death from any cause within 30 days after randomization was compared between the two study groups with the use of a chi-square test. Time-to-event analyses were performed with

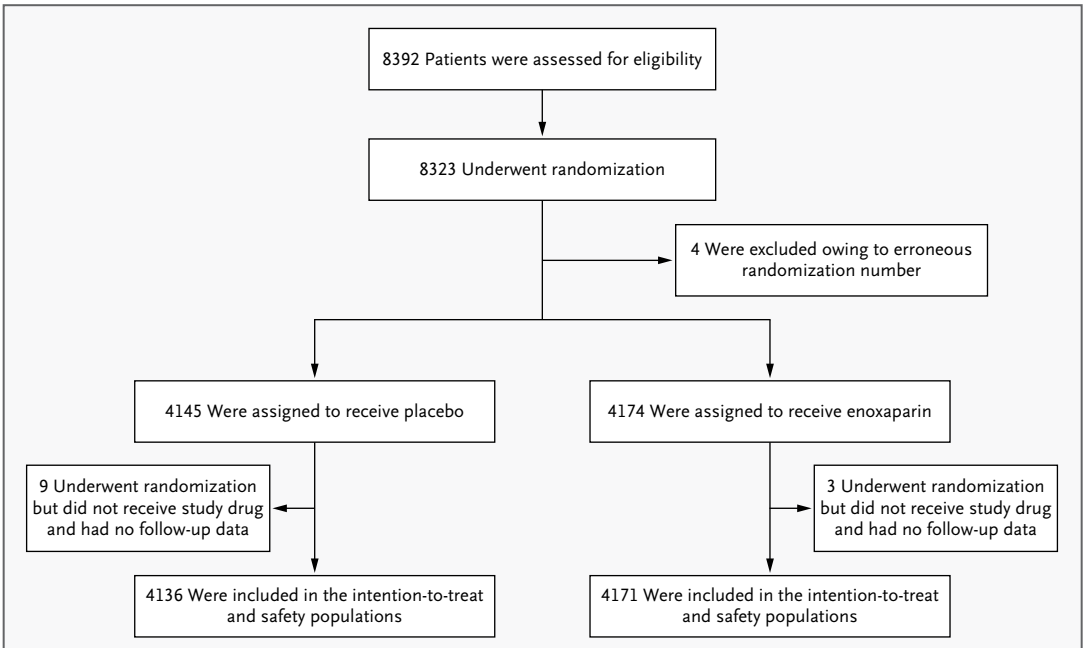


Figure 1. Screening, Randomization, and Follow-up.

the use of a log-rank test. Kaplan–Meier curves were used to show the probability of events over time. All analyses were performed with the SAS software package, version 9.1 (SAS Institute).

RESULTS

PATIENTS

A total of 8392 patients were assessed for eligibility, of whom 8323 were randomly assigned to a study group (Fig. 1). A total of 16 patients (0.2%) were subsequently excluded either because they had been given an erroneous randomization number (4 patients) or because they did not receive the study drug and had no follow-up data (12 patients). The final intention-to-treat population included 8307 patients, of whom 2071 were enrolled in China (24.9%), 4050 in India (48.8%), 383 in Korea (4.6%), 292 in Malaysia (3.5%), 396 in Mexico (4.8%), 585 in the Philippines (7.0%), and 530 in Tunisia (6.4%).

Table 1 shows the baseline characteristics of the patients. The mean (±SD) age was 65±12 years, and 37.3% of the patients (3096 of the 8307 patients in the intention-to-treat population) were women. More than half (64.4%; 5346 of the 8300 patients with data on the primary reason for hospitalization) were hospitalized for severe systemic infection (49.8% of whom also had chronic pulmonary disease).

The median duration of hospitalization was 9 days in both groups. The median duration of treatment was 6 days in both groups, with 93.9% of the patients receiving 6 to 14 days of treatment. The median duration of the use of elastic stockings with graduated compression was 6 days in the enoxaparin group and 7 days in the placebo group. A total of 39 patients (0.5%) were lost to follow-up at day 30 (20 in the enoxaparin group and 19 in the placebo group), and 76 (0.9%) were lost to follow-up at day 90 (39 in the enoxaparin group and 37 in the placebo group).

EFFICACY OUTCOMES

The rate of death from any cause at 30 days was 4.9% in the enoxaparin group and 4.8% in the placebo group (risk ratio, 1.0; 95% confidence interval [CI], 0.8 to 1.2; P=0.83) (Table 2 and Fig. 2). With a rate of death in the placebo group of 4.8% rather than the 7% originally anticipated, our study had 77% power to detect a 25% reduction in the rate of death from any cause and 57% power to detect a 20% reduction. The incidence of death from cardiopulmonary causes (including sudden death and death due to acute myocardial infarction, heart failure, pulmonary failure, or pulmo-

Table 1. Baseline Characteristics and Primary Reason for Hospitalization in the Intention-to-Treat Population.*

Variable	Placebo (N=4136)	Enoxaparin (N=4171)
Baseline characteristic		
Age — yr	65.3±12.2	65.6±12.0
Female sex — no. (%)	1528 (36.9)	1568 (37.6)
Body-mass index†	23.3±5.4	23.4±5.4
Renal impairment — no./total no. (%)		
Any	1452/4057 (35.8)	1454/4097 (35.5)
Severe‡	202/4057 (5.0)	178/4097 (4.3)
Selected risk factors for venous thromboembolism — no./total no. (%)		
Age ≥75 yr	1030/4136 (24.9)	1079/4171 (25.9)
Personal history of venous thromboembolism	21/4135 (0.5)	27/4168 (0.6)
Family history of venous thromboembolism	5/4134 (0.1)	4/4166 (0.1)
Active cancer	239/4136 (5.8)	250/4170 (6.0)
Body-mass index ≥30†	429/4084 (10.5)	431/4111 (10.5)
Coagulation disorder	3/4134 (0.1)	2/4168 (<0.1)
Hospitalization within previous 3 months for acute medical illness	390/4135 (9.4)	377/4168 (9.0)
Primary reason for hospitalization — no./total no. (%)		
Heart failure	1297/4134 (31.4)	1280/4166 (30.7)
NYHA Class I or II	210/4134 (5.1)	206/4166 (4.9)
NYHA Class III or IV	1069/4134 (25.9)	1055/4166 (25.3)
NYHA class not determined	18/4134 (0.4)	19/4166 (0.5)
Severe systemic infection	2336/4134 (56.5)	2383/4166 (57.2)
Active cancer	170/4134 (4.1)	195/4166 (4.7)
Heart failure and severe systemic infection	262/4134 (6.3)	253/4166 (6.1)
Heart failure and active cancer	5/4134 (0.1)	7/4166 (0.2)
Severe systemic infection and active cancer	62/4134 (1.5)	45/4166 (1.1)
Heart failure, severe systemic infection, and active cancer	2/4134 (<0.1)	3/4166 (0.1)
None of the above	25/4136 (0.6)	24/4171 (0.6)

* Plus–minus values are means ±SD. There were no significant differences between the two study groups in any of the baseline characteristics (P>0.05 for all comparisons). NYHA denotes New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Renal impairment was classified as severe if the creatinine clearance was 30 ml per minute or less.

nary embolism) and the composite of the rate of sudden death or pulmonary embolism at 30 days did not differ significantly between the groups (Table 2).

The most common cause of death by day 30 was pulmonary failure, which occurred in 2.1% of the patients in the enoxaparin group and in 1.8% of the patients in the placebo group (Table 2). Deaths due to cancer occurred in 0.5% of the patients in the enoxaparin group and in 0.8% of the patients in the placebo group, and the rate of sudden death was 0.7% in both groups. Three patients in the enoxaparin group (0.1%) died from a hemorrhage, and one patient in each group died from a pulmonary embolism. No autopsies were performed in either group. Multivariate logistic regression identified the following variables as factors that were independently associated with increased mortality at day 30: a diagnosis of active cancer (odds ratio, 4.0; 95% CI, 2.8 to 5.8; P<0.001), chronic pulmonary disease (odds ratio, 1.3; 95% CI, 1.1 to 1.7; P=0.02), two or more acute illnesses (odds ratio, 1.6; 95% CI, 1.2 to 2.3; P=0.003), and renal impairment (odds ratio, 2.0; 95% CI, 1.6 to 2.4; P<0.001).

The hazard rate (i.e., a rate that is derived from a time-to-event analysis) for death from any cause at day 90 was 8.4% in the enoxaparin group

Table 2. Efficacy Outcomes and the Characteristics and Primary Causes of Death.*

Variable	Placebo (N=4136)	Enoxaparin (N=4171)	Risk Ratio for Enoxaparin vs. Placebo (95% CI)	P Value†
	no. of patients (%)			
Efficacy outcomes				
14-day mortality				
Death from any cause	119 (2.9)	121 (2.9)	1.0 (0.8–1.3)	0.95
Cardiopulmonary death	93 (2.2)	86 (2.1)	0.9 (0.7–1.2)	0.56
Sudden death or pulmonary embolism	27 (0.7)	20 (0.5)	0.7 (0.4–1.3)	0.29
30-day mortality				
Death from any cause	199 (4.8)	205 (4.9)	1.0 (0.8–1.2)	0.83
Cardiopulmonary death	135 (3.3)	141 (3.4)	1.0 (0.8–1.3)	0.77
Sudden death or pulmonary embolism	29 (0.7)	29 (0.7)	1.0 (0.6–1.7)	0.97
90-day mortality‡				
Death from any cause	355 (8.6)	348 (8.4)	1.0 (0.8–1.1)	0.71
Cardiopulmonary death	214 (5.3)	211 (5.1)	1.0 (0.8–1.2)	0.82
Sudden death or pulmonary embolism	40 (1.0)	43 (1.1)	1.1 (0.7–1.6)	0.77
Characteristics of deaths recorded at day 30§				
Abrupt				
Explained	67 (1.6)	75 (1.8)		
Unexplained	22 (0.5)	24 (0.6)		
Insidious				
Explained	92 (2.2)	94 (2.3)		
Unexplained	15 (0.4)	9 (0.2)		
Primary adjudicated reason for death at day 30				
Sudden death	28 (0.7)	28 (0.7)		
Acute myocardial infarction	4 (0.1)	3 (0.1)		
Stroke	2 (<0.1)	3 (0.1)		
Heart failure	26 (0.6)	23 (0.6)		
Cancer	33 (0.8)	22 (0.5)		
Pulmonary failure	76 (1.8)	86 (2.1)		
Multiorgan failure	6 (0.1)	9 (0.2)		
Sepsis	8 (0.2)	10 (0.2)		
Accident or trauma	0	1 (<0.1)		
Pulmonary embolism	1 (<0.1)	1 (<0.1)		
Hemorrhage	0	3 (0.1)		
Unclassified	15 (0.4)	16 (0.4)		

* Sudden death, defined as an unexpected death occurring in a short period (<1 hour after onset of symptoms) in a patient in whom there was no previous diagnosis of a fatal condition, was an adjudicated event. Abrupt death, as reported by the investigator, was a nonadjudicated event.

† The P values at day 14 and day 30 were calculated with the use of a chi-square test; the P values at day 90 were calculated with the use of a log-rank test.

‡ Hazard rates (i.e., rates derived from a time-to-event analysis) and hazard ratios, rather than percentages and risk ratios, are provided for 90-day outcomes.

§ Information was not available on the characteristics of three deaths in each group.

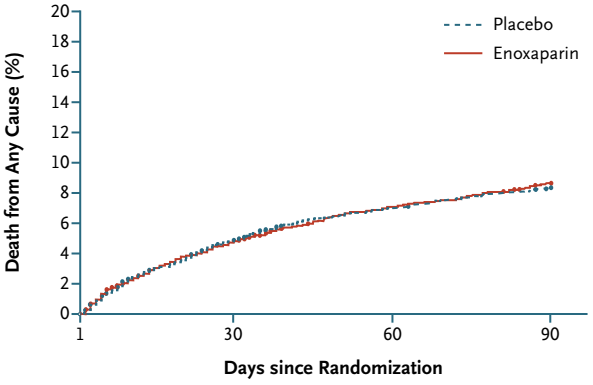
(with death occurring in 348 of 4171 patients) and 8.6% in the placebo group (with death occurring in 355 of 4136 patients) (hazard ratio, 1.0; 95% CI, 0.8 to 1.1; P=0.71) (Table 2); the hazard rates for cardiopulmonary deaths were 5.1% and 5.3% in the two groups, respectively. Up to day 90, there was clinical suspicion of venous thromboembolism in 0.5% of the pa-

tients in the enoxaparin group (22 of 4072 patients) and in 0.7% of the patients in the placebo group (27 of 4044 patients). The diagnosis was confirmed by objective testing in 0.2% of the patients in the enoxaparin group and in 0.1% of the patients in the placebo group.

SAFETY OUTCOMES AND ADVERSE EVENTS

Major bleeding events during the treatment period and up to 48 hours after the treatment period were reported in 16 patients in the enoxaparin group (0.4%) and in 11 patients in the placebo group (0.3%) (risk ratio with enoxaparin, 1.4; 95% CI, 0.7 to 3.1; P=0.35) (Table 3). The rates of minor bleeding were higher in the enoxaparin group than in the placebo group, and the combined rates of all bleeding events were higher in the enoxaparin group (risk ratio, 1.5; 95% CI, 1.1 to 2.1).

The rate of all adverse events was 37.8% in the enoxaparin group (with an event occurring in 1577 of 4171 patients) and 36.9% in the placebo group (with an event occurring in 1528 of 4136 patients). The two groups did not differ significantly with respect to the rate of either serious adverse events (5.8% [243 of 4171 patients] in the enoxaparin group and 5.3% [219 of 4136 patients] in the placebo group) or adverse events leading to death (2.9% [121 of 4171 patients] and 2.9% [119 of 4136 patients] in the two groups, respectively). The rate of adverse events leading to permanent discontinuation of the study drug was higher in the enoxaparin group than in the placebo group (3.6% [151 of 4171 patients] vs. 2.8% [116 of 4136 patients]). There were no cases of heparin-induced thrombocytopenia.



No. of Deaths/ No. at Risk				
Placebo	1/4136	199/3922	291/3813	355/3745
Enoxaparin	2/4171	205/3950	292/3846	348/3785

Figure 2. Death from Any Cause.
The percentage of patients in the intention-to-treat population who died from any cause up to day 90 after randomization is shown.

DISCUSSION

We did not detect a difference in the rate of death from any cause among patients hospitalized for an acute medical illness when a strategy of pharmacologic prophylaxis in addition to the use of elastic stockings with graduated compression was compared with the use of elastic stockings with graduated compression alone. Pharmacologic prophylaxis was not associated with increased rates of major bleeding but was associated with increased rates of total bleeding.

These findings appear to be counterintuitive, given the fact that pharmacologic prophylaxis has been shown to reduce the risk of venous thromboembolism, including asymptomatic deep-vein thrombosis, by at least 45% in hospitalized, acutely ill medical patients.[7-9] It has been assumed that the natural history of deep-vein thrombosis, well established in surgical patients,[18] would be the same in acutely ill medical patients, in whom it has been shown that those with asymptomatic proximal vein thrombi have a higher risk of death than those with distal thrombi.[19] This assumption may be incorrect; perhaps the natural history of deep-vein thrombosis differs between medical and surgical patients.

Although Halkin et al.[20] reported that the rate of death among medical patients was reduced with pharmacologic prophylaxis, other studies have failed to show that result, regardless of whether the studies were evaluating the use of in-hospital prophylaxis[7-9,21-24] or extended, out-of-hospital prophylaxis.[25] The study by Gärdlund was promising because it showed that pharmacologic prophylaxis appeared to delay the early occurrence of fatal pulmonary embolism; however, prophylaxis did not improve the overall clinical outcome by day 60.[22]

Our study may have been underpowered to show a between-group difference in mortality. The rate of death from any cause was lower than expected but was similar in the two study groups at all the time points we assessed (day 14, day 30, and day 90). With an observed mortality of 4.8% rather than the 7% originally anticipated, our study had 77% power to detect a 25% reduction in the rate of death from any cause and 57% power to detect a 20% reduction. The Prophylaxis

Table 3. Bleeding Outcomes during the Treatment Period.

Outcome	Placebo (N=4136)	Enoxaparin (N=4171)	Risk Ratio for Enoxaparin vs. Placebo (95% CI)	P Value
	no. of patients (%)			
Any bleeding*	60 (1.5)	91 (2.2)	1.5 (1.1–2.1)	0.01
Adjudicated major bleeding	11 (0.3)	16 (0.4)	1.4 (0.7–3.1)	0.35
Resulting in death	0	2 (<0.1)		
Requiring transfusion of ≥2 units of red cells or whole blood	6 (0.1)	5 (0.1)		
Resulting in fall in hemoglobin of ≥20 g/liter	8 (0.2)	12 (0.3)		
Requiring surgical intervention	2 (<0.1)	1 (<0.1)		
Retroperitoneal, intracranial, or intraocular	1 (<0.1)	1 (<0.1)		
Other	2 (<0.1)	0		
Minor bleeding				
Any	47 (1.1)	73 (1.8)	1.5 (1.1–2.2)	0.02
Clinically relevant nonmajor	14 (0.3)	18 (0.4)	1.3 (0.6–2.6)	0.49
Unclassified bleeding	4 (0.1)	6 (0.1)	1.5 (0.4–5.3)	0.75

* Included in this category are patients who had at least one bleeding event. Some patients may have had more than one type of bleeding event.

in Medical Patients with Enoxaparin (MEDENOX) study, which established the efficacy of the regimen of 40 mg of enoxaparin daily in acutely ill medical patients, showed a 25% reduction in mortality associated with this pharmacologic regimen.[7] Although a pulmonary embolism is identified on autopsy in 9 to 21% of medical patients,[26-28] in the MEDENOX study, only one death in the placebo group and two in the group receiving 40 mg of enoxaparin were attributed to pulmonary embolism by the end of the follow-up period. This finding suggests that the observed favorable trend in overall survival associated with effective prophylaxis may be due to a reduction not only in deaths related to venous thromboembolism but also in deaths from other causes, most likely cardiovascular events. Indeed, pharmacologic prophylaxis in surgical patients has been shown to reduce, in addition to fatal pulmonary embolism, fatal myocardial infarction and death from other causes.[10,11] Multiple coexisting illnesses and numerous other potential causes of death in medical patients might make fatal pulmonary embolism a less important determinant of mortality in this group than in surgical patients, thus diminishing the ability of pharmacologic prophylaxis to improve the overall clinical outcome. In addition, the reported rate of pulmonary embolism has historically been lower in Asian populations than in Western populations,[29] although contemporary studies indicate that there is little difference in the frequency of deep-vein thrombosis between Asian and Western populations.[30-32]

One possible explanation for our findings is that the use of elastic stockings with graduated compression alone is effective in preventing venous thromboembolism, thus reducing the frequency of fatal pulmonary embolism. Although elastic stockings with graduated compression have been shown to be effective in reducing the risk of deep-vein thrombosis in moderate-risk surgical patients and some medical patient populations,[33,34] the use of stockings did not prevent the occurrence of deep-vein thrombosis in patients recuperating from severe, disabling stroke who were participants in the Clots in Legs or Stocking after Stroke trial (CLOTS; Current Controlled Trials number, ISRCTN28163533).[35] Furthermore, the knee-length stockings used in our study have recently been shown to be less effective than thigh-length stockings for the prevention of deep-vein thrombosis.[36]

The prevention of venous thromboembolism in acutely ill medical patients — for a population in which low-molecular-weight heparins have al-

ready been shown to be effective[7,8] — was not the primary objective of our study. Therefore, we did not screen for asymptomatic deep-vein thrombosis. We observed very low rates of symptomatic venous thromboembolism in both groups. These low rates may be due either to a decreased awareness of the disease in participating countries in which less frequent diagnostic testing for suspected events was offered or to the inclusion in this study of a population that was at lower risk for venous thromboembolism, as compared with other studies. For example, the mean age of the patients in our study was approximately 9 years younger than the mean age of patients in the MEDENOX study, and the mean body-mass index was approximately 2 units lower; the proportion of obese patients was 11% in our study, as compared with 20% in the MEDENOX study. In addition, in our study, as compared with the MEDENOX study, there was a decrease by a factor of almost 10 in the proportion of patients with a history of venous thromboembolism.[7] We did not collect data on mobility status, an important determinant of the risk of venous thromboembolism.[5] The adherence both to the injections and to the use of elastic stockings was excellent in both groups in our study.

In summary, the results of the LIFENOX trial showed that among hospitalized, acutely ill medical patients, the rate of death from any cause did not differ significantly between patients who were randomly assigned to pharmacologic prophylaxis with enoxaparin in addition to elastic stockings with graduated compression and those who were assigned to elastic stockings with graduated compression alone. Pharmacologic thromboprophylaxis continues to have proven benefits in preventing venous thromboembolism, thus reducing the need for the treatment of symptomatic venous thromboembolism with high doses of anticoagulant agents over a prolonged period of time. Furthermore, venous thromboembolism can lead to nonfatal complications such as the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, which are often not treated successfully.

Supported by Sanofi.

Dr. Kakkar reports receiving consulting fees, grant support through his institution, and lecture fees from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, GlaxoSmithKline, Pfizer, and Sanofi; Dr. Cimminiello, receiving consulting fees from Sanofi; Dr. Goldhaber, receiving consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, EKOS, Medscape, Merck, Portola, and Sanofi and grant support through his institution from Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, EKOS, Johnson & Johnson, and Sanofi; Dr. Parakh, receiving consulting fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Novartis, Pfizer, and Sanofi and support for travel, accommodations, or meeting expenses from Bayer, Daiichi Sankyo, and Sanofi; and Dr. Bergmann, receiving consulting fees from AstraZeneca, Association des Pharmaciens de l'Industrie–Communication Globale Santé–Prioritis, Bayer, GlaxoSmithKline, Lilly, Novartis, Pfizer, and Sanofi and grant support through his institution from Agence Nationale de Recherche contre le SIDA, Bayer, GlaxoSmithKline, and Pfizer. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank A. Correges (Altizem) and G. Salette (Sanofi) for performing statistical analyses, R. Spice (Excerpta Medica, funded by Sanofi) for editorial assistance, and Dr. S. Rushton Smith (Thrombosis Research Institute) for writing assistance.

REFERENCES

1. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. Arch Intern Med 1992;152:1660-4.
2. Moreno-Cabral R, Kistner RL, Nordyke RA. Importance of calf vein thrombophlebitis. Surgery 1976;80:735-42.
3. The Surgeon General's call to action to prevent deep venous thrombosis and pulmonary embolism. Washington, DC: Department of Health and Human Services, 2008 (http://www.surgeongeneralgov/topics/deepvein).
4. Oger E, Bressollette L, Nonent M, et al. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. Thromb Haemost 2002;88:592-7.
5. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:Suppl: 381S-453S.
6. Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalized patients: a necropsy review. J Clin Pathol 2004;57:1254-7.
7. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999;341:793-800.
8. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-9.
9. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325-9.
10. Prevention of fatal postoperative pulmonary embolism by low doses of heparin: an international multicentre trial. Lancet 1975;2:45-51.
11. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988;318:1162-73.
12. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146:278-88.
13. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371: 387-94. [Erratum, Lancet 2008;371:1914.]

14. Kakkar AK, Cohen AT, Tapson VF, et al. Venous thromboembolism risk and prophylaxis in the acute care hospital setting (ENDORSE survey): findings in surgical patients. Ann Surg 2010;251:330-8.
15. Bergmann JF, Cohen AT, Tapson VF, et al. Venous thromboembolism risk and prophylaxis in hospitalised medically ill patients: the ENDORSE Global Survey. Thromb Haemost 2010;103:736-48.
16. Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Int Angiol 2006;25:101-61.
17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
18. Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. Lancet 1969;2:230-2.
19. Vaitkus PT, Leizorovicz A, Cohen AT, et al. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. Thromb Haemost 2005;93:76-9.
20. Halkin H, Goldberg J, Modan M, Modan B. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. Ann Intern Med 1982;96:561-5.
21. Dahan R, Houlbert D, Caulin C, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Haemostasis 1986;16:159-64.
22. Gärdlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. Lancet 1996;347:1357-61.
23. Fraisse F, Holzapfel L, Couland JM, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. Am J Respir Crit Care Med 2000;161:1109-14.
24. Mahé I, Bergmann JF, d Azémar P, Vaissie JJ, Caulin C. Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study. Eur J Clin Pharmacol 2005;61:347-51.
25. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med 2010;153:8-18.
26. Karwinski B, Svendsen E. Comparison of clinical and postmortem diagnosis of pulmonary embolism. J Clin Pathol 1989;42:135-9.
27. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest 1995;108:978-81.
28. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med 1989;82:203-5.
29. Hwang WS. The rarity of pulmonary thromboembolism in Asians. Singapore Med J 1968;9:276-9.
30. Leizorovicz A, Turpie AG, Cohen AT, Wong L, Yoo MC, Dans A. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. J Thromb Haemost 2005;3:28-34.
31. Leizorovicz A. Epidemiology of postoperative venous thromboembolism in Asian patients: results of the SMART venography study. Haematologica 2007;92:1194-200.
32. Piovella F, Wang CJ, Lu H, et al. Deep-vein thrombosis rates after major orthopedic surgery in Asia: an epidemiological study based on postoperative screening with centrally adjudicated bilateral venography. J Thromb Haemost 2005;3:2664-70.
33. Sachdeva A, Dalton M, Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2010;7:CD001484.
34. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients: results of meta-analysis. Ann Surg 1988;208:227-40.
35. Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet 2009;373:1958-65.
36. CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. Ann Intern Med 2010;153:553-62.