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Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture

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ABSTRACT

BACKGROUND

Clinical guidelines recommend low-molecular-weight heparin for thromboprophylaxis in patients with fractures, but trials of its effectiveness as compared with aspirin are lacking.

METHODS

In this pragmatic, multicenter, randomized, noninferiority trial, we enrolled patients 18 years of age or older who had a fracture of an extremity (anywhere from hip to midfoot or shoulder to wrist) that had been treated operatively or who had any pelvic or acetabular fracture. Patients were randomly assigned to receive low-molecular-weight heparin (enoxaparin) at a dose of 30 mg twice daily or aspirin at a dose of 81 mg twice daily while they were in the hospital. After hospital discharge, the patients continued to receive thromboprophylaxis according to the clinical protocols of each hospital. The primary outcome was death from any cause at 90 days. Secondary outcomes were nonfatal pulmonary embolism, deep-vein thrombosis, and bleeding complications.

RESULTS

A total of 12,211 patients were randomly assigned to receive aspirin (6101 patients) or low-molecular-weight heparin (6110 patients). Patients had a mean (±SD) age of 44.6±17.8 years, 0.7% had a history of venous thromboembolism, and 2.5% had a history of cancer. Patients received a mean of 8.8±10.6 in-hospital thromboprophylaxis doses and were prescribed a median 21-day supply of thromboprophylaxis at discharge. Death occurred in 47 patients (0.78%) in the aspirin group and in 45 patients (0.73%) in the low-molecular-weight–heparin group (difference, 0.05 percentage points; 96.2% confidence interval, −0.27 to 0.38; P<0.001 for a noninferiority margin of 0.75 percentage points). Deep-vein thrombosis occurred in 2.51% of patients in the aspirin group and 1.71% in the low-molecular-weight–heparin group (difference, 0.80 percentage points; 95% CI, 0.28 to 1.31). The incidence of pulmonary embolism (1.49% in each group), bleeding complications, and other serious adverse events were similar in the two groups.

CONCLUSIONS

In patients with extremity fractures that had been treated operatively or with any pelvic or acetabular fracture, thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin in preventing death and was associated with low incidences of deep-vein thrombosis and pulmonary embolism and low 90-day mortality. (Funded by the Patient-Centered Outcomes Research Institute; PREVENT CLOT ClinicalTrials.gov number, NCT02984384.)

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A Quick Take is available at NEJM.org

Venous thromboembolism is a well-recognized, potentially fatal complication after orthopedic trauma.[1-4] Numerous clinical guidelines recommend thromboprophylaxis therapy to reduce the risk of death and complications associated with venous thromboembolism after traumatic orthopedic injuries.[5-8]

Findings from recent trials and meta-analyses suggest that aspirin may be an effective thromboprophylaxis alternative to low-molecular-weight heparin in patients who have undergone total joint arthroplasty, with a more favorable safety profile.[9-12] However, evidence from head-to-head comparisons among patients with fractures that have been treated operatively is limited.[1,13,14] Patients with fractures have shown a strong preference for aspirin if clinical outcomes are similar among thromboprophylaxis options, given the lower cost of aspirin and its oral administration (as compared with subcutaneous injection of low-molecular-weight heparin).[15,16]

We conducted the Prevention of Clot in Orthopaedic Trauma (PREVENT CLOT) trial to examine the effectiveness and safety of thromboprophylaxis with aspirin as compared with low-molecular-weight heparin in patients with a fracture. This pragmatic, randomized trial was designed from the perspective of a hospital thromboprophylaxis policy and aimed to assess whether aspirin would be noninferior to low-molecular-weight heparin with regard to thromboembolic outcomes in patients with orthopedic trauma.

METHODS

TRIAL DESIGN

We conducted the PREVENT CLOT trial at 21 trauma centers in the United States and Canada. The trial was investigator-initiated, designed by the protocol committee, and planned and conducted in collaboration with patients and other relevant stakeholders. The trial objectives and design have been published previously.[17] The protocol (including the statistical analysis plan) and the Supplementary Appendix (including detailed descriptions of the outcomes) are available with the full text of this article at NEJM.org.

Members of the writing committee performed the analyses and wrote the first draft of the manuscript. All the members of the writing committee made revisions to the draft, agreed to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. There were no agreements between the sponsor and the authors or their institutions concerning the confidentiality of the data.

TRIAL OVERSIGHT

The sponsor had no role in the design or conduct of the trial, collection and analysis of the data, or preparation of the manuscript. The Department of Orthopedics at the University of Maryland School of Medicine and the Major Extremity Trauma Research Consortium Coordinating Center at the Johns Hopkins Bloomberg School of Public Health co-led the trial and oversaw data collection by research staff at the enrolling centers. The trial was approved by the research ethics boards at the coordinating center and at all participating hospitals.

PATIENTS

Patients who were included in the trial were 18 years of age or older and had an extremity fracture that was treated operatively or a fracture of the pelvis or acetabulum that was treated operatively or nonoperatively. We included upper extremity fractures from the shoulder to the wrist and lower extremity fractures from the hip to the midfoot. We excluded fractures of the hand (carpals, metacarpals, and phalanges) and forefoot (metatarsals and phalanges). Key exclusion criteria were presentation to the hospital more than 48 hours after injury or receipt of three or more doses of thromboprophylaxis before providing informed consent for enrollment in the trial. Patients who had a history of a venous thromboembolism diagnosis in the past 6 months, were receiving therapeutic anticoagulation at the time of admission, or had a chronic blood-clotting disorder were excluded. Additional inclusion and exclusion criteria are described in the Supplementary Appendix and the protocol. All the participants provided written informed consent.

RANDOMIZATION AND INTERVENTIONS

Patients were randomly assigned in a 1:1 ratio to receive aspirin or low-molecular-weight heparin for thromboprophylaxis. Randomization was performed with variable block sizes and stratified

according to clinical site with the use of an automated structure embedded into the Research Electronic Data Capture system.[18] Patients and their treating physicians were aware of the trial-group assignments. However, the assigned thromboprophylaxis was concealed for purposes of data monitoring, adjudication, and analysis.

Patients in the low-molecular-weight–heparin group received subcutaneous enoxaparin at a predetermined dose of 30 mg twice daily. Adjusted dose levels were permitted for patients with obesity or renal disease or as the result of other medical indications according to the protocols at each site. Patients in the aspirin group received aspirin at a dose of 81 mg twice daily to balance the probability of adherence to a twice-daily intervention. The duration of thromboprophylaxis could end at hospital discharge or continue on the basis of the clinical protocols of each hospital, given the lack of consensus on the appropriate duration of treatment.[6,8] However, sites were instructed not to vary the indication or duration of thromboprophylaxis on the basis of the group assignment.

Adherence to treatment was monitored daily during the index hospital admission and at the time of discharge from the hospital. Adherence to the protocol was determined by two conditions. First, the patient had to adhere to at least 80% of the assigned in-hospital trial medication doses.[19] This definition allowed doses that were scheduled during the inpatient period to be missed for medical reasons (e.g., medication withheld for surgery). Second, if thromboprophylaxis therapy was prescribed at the time of hospital discharge, it had to be the trial medication that had been randomly assigned to that patient. A patient who met both conditions was considered to have adherence to the protocol.

TRIAL OUTCOMES

The primary outcome was death from any cause at 90 days. The initial primary outcome was death related to pulmonary embolism, with death from any cause as a secondary outcome. The primary outcome was changed to death from any cause in January 2021, before publication of the protocol,[17] finalization of the statistical analysis plan, completion of recruitment, or review of the trial data. The change in primary outcome was made because of concern regarding misclassification and competing risk with the outcome of cause-specific death. We used the LexisNexis Accurint database, including data from the Limited Access Death Master File, to obtain additional mortality information with regard to patients with unknown status at 90 days after randomization.

Secondary efficacy outcomes included cause-specific death, nonfatal pulmonary embolism, and deep-vein thrombosis. A three-person committee whose members were unaware of trial-group assignments adjudicated cause-specific death with a specific focus on death related to pulmonary embolism. Three grades of cause-specific death were used: related to pulmonary embolism, possibly related to pulmonary embolism, and unlikely to be related to pulmonary embolism. Nonfatal pulmonary embolism was also adjudicated by the committee and reported as any, massive, submassive, clinically significant, or asymptomatic and in a segmental or subsegmental location.[20] In addition, deep-vein thrombosis events were subclassified according to the proximal or distal location. The criteria for adjudicating secondary outcomes are described in the Supplementary Appendix. The protocol did not specify screening for pulmonary embolism and deep-vein thrombosis in asymptomatic patients.

Secondary safety outcomes included bleeding events, wound complications, and surgical-site infections. Bleeding events included symptomatic bleeding into a critical area or organ; bleeding that caused a drop in the hemoglobin level of 20 g per liter or more within a 24-hour period and led to a transfusion of two or more units of whole blood or red cells; or bleeding that led to reoperation.[10] Wound complications included wound drainage, hematoma, or seroma of an orthopedic injury that led to subsequent surgery. We defined surgical-site infections using the Centers for Disease Control and Prevention criteria for a deep incisional or organ-space infection leading to surgical treatment.[21]

All the trial outcomes were evaluated within 90 days after randomization and were ascertained by means of an interview with the patient that was performed by the clinical research team during a clinical appointment or by telephone. Additional methods used in patients who ceased clinical follow-up before 90 days or who did not

respond to telephone contact are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample-size calculation used in the trial assumed a baseline incidence of death from any cause in the low-molecular-weight–heparin group of 1.0%.[13,22] On the basis of surveys of patients and surgeons, we established a noninferiority margin for death from any cause of 0.75 percentage points.[15] (Details of the statistical analysis are provided in the Supplementary Appendix and protocol.) We calculated that a sample size of 12,200 patients would provide the trial with 95% power to determine whether aspirin was noninferior to low-molecular-weight heparin with respect to death from any cause. The sample-size calculation accounted for two interim analyses with an O'Brien–Fleming stopping boundary and 7.5% attrition. The interim analyses, with trial-group assignments masked, were performed by a coordinating center analyst and evaluated only by the data and safety monitoring board. No changes resulted from the interim analyses.

We followed the intention-to-treat approach for our primary analysis. The primary outcome was evaluated with the use of treatment-specific Kaplan–Meier estimators, and we assessed noninferiority with the upper boundary of a two-sided 96.2% confidence interval (to account for two interim analyses) and a noninferiority margin of 0.75 percentage points.[23] If the noninferiority criterion was satisfied, we planned to test for superiority.

We assessed all secondary outcomes using cumulative incidence functions that included death from any cause as a competing risk for nonfatal events and cause-specific death as a competing risk for other causes of death. If a patient's final outcome status was missing, the data were censored at the patient's last known clinical encounter. A secondary analysis estimated the treatment effects in the per-protocol population of patients who adhered to at least 80% of their in-hospital doses of medication and who received the randomly assigned trial drug at the time of discharge if thromboprophylaxis was prescribed. We reported risk-difference estimates and 95% confidence intervals for all secondary outcomes but did not perform formal hypothesis testing. We did not stratify treatment estimates according to center to avoid the imposition of additional modeling assumptions that might arise given the number of centers relative to the low event rates. We report treatment-specific 90-day outcome probabilities, as calculated by a Kaplan–Meier estimator for the primary outcome and cumulative-incidence functions for the secondary outcomes. This method was chosen over simple percentages to reflect the differential follow-up in some patients and for consistency with our treatment-effect estimates. We did not adjust the widths of the secondary outcome confidence intervals for multiple comparisons, and therefore the 95% confidence intervals should not be used to infer treatment effects.

We included one prespecified subgroup analysis for death from any cause that explored the effect-modification according to age (<60 years or ≥60 years).[2] All analyses were performed with R Software, version 4.0.2 (R Project for Statistical Computing).

RESULTS

PATIENTS

From April 2017 through August 2021, we obtained written informed consent from 12,211 patients who were randomly assigned to receive aspirin (6101 patients) or low-molecular-weight heparin (6110 patients) for the primary analysis (Fig. S1 and Tables S1 and S2 in the Supplementary Appendix). Patient follow-up was completed in February 2022, with primary outcome data available for 96.8% of the patients.

The majority of the patients were men (62.3%), and the mean (±SD) age was 44.6±17.8 years. The median Injury Severity Score (a standardized measure of the severity of traumatic injuries based on the worst injuries present across a maximum of three different body regions; scores range from 1 to 75, with a higher score indicating more severe injury) was 9 (interquartile range, 4 to 10). The demographic, medical, and surgical characteristics of the patients at baseline were similar in the two groups in both the intention-to-treat and per-protocol populations and were largely representative of the target population (Table 1 and Tables S3 through S5). Orthopedic trauma with or without surgery was the only known risk factor of thromboembolic events in 3328 patients (27.3%). Most patients (69.2%) had received fewer than two doses of low-molecular-weight heparin before consent

was obtained (Table S6). The mean hospital duration was 5.3±5.7 days. At the time of hospital discharge, the injured extremities in 5447 patients (45.4%) were non–weight-bearing, and 4373 patients (36.4%) were allowed to bear full weight on their injured extremities (Tables S7 and S8).

ADHERENCE TO THE ASSIGNED INTERVENTION

The inpatient protocol-adherence criteria were met in 5778 patients (94.7%) in the aspirin group and in 5291 patients (96.9%) in the low-molecular-weight–heparin group. The mean number of inpatient doses of a trial medication was 8.6±10.8 in the aspirin group and 9.1±10.5 in the low-molecular-weight–heparin group. At the time of discharge, 91% the patients were receiving thromboprophylaxis: 93.6% in the aspirin group and 88.8% in the low-molecular-weight–heparin group (Table S9). The median duration of thromboprophylaxis prescribed at discharge was 21 days (interquartile range, 19 to 21) in the aspirin group and 21 days (interquartile range, 14 to 21) in the low-molecular-weight–heparin group. The protocol-adherence criteria at discharge were met by a total of 5760 patients (94.4%) in the aspirin group and 5305 patients (86.6%) in the low-molecular-weight–heparin group. The per-protocol population included 87.4% of the enrolled patients (90.2% of the aspirin group and 84.6% of the low-molecular-weight–heparin group) who met both the inpatient and discharge protocol-adherence criteria.

PRIMARY OUTCOME

During the 90-day follow-up period, death occurred in 47 of 6101 patients (90-day probability, 0.78%) in the aspirin group and 45 of 6110 patients (90-day probability, 0.73%) in the low-molecular-weight–heparin group (difference, 0.05 percentage points; 96.2% confidence interval [CI], −0.27 to 0.38) (Table 2, Fig. 1, and Fig. S2). Aspirin was noninferior to low-molecular-weight heparin ($P<0.001$) but not superior ($P=0.63$) in preventing death from any cause. A per-protocol analysis of the primary outcome produced similar findings (difference, 0.03 percentage points; 96.2% CI, −0.31 to 0.38). Of the 92 patients who died, 79 (85.9%) had been adherent to the protocol and had received a mean of 13.1±12.1 inpatient doses of trial medication. We did not observe a differential treatment effect according to patient age on death from any cause: among patients less than 60 years of age, the difference was 0.02 percentage points (95% CI, −0.21 to 0.25), and among patients at least 60 years of age or older, the difference was 0.16 percentage points (95% CI, −0.94 to 1.25) (Fig. S3).

SECONDARY OUTCOMES

The between-group difference in the 90-day probability that death was related to pulmonary embolism was similar to the difference in probability that death was not related to pulmonary embolism (−0.02 percentage points and −0.03 percentage points, respectively) (Table 2, Figs. S4 and S5, and Table S10). The between-group difference in the 90-day probability that death had possibly been caused by pulmonary embolism (0.08 percentage points) was similar to that of the primary outcome (Table 2 and Fig. S6).

Nonfatal pulmonary embolism occurred in 90 patients (90-day probability, 1.49%) in the aspirin group and in 90 patients (90-day probability, 1.49%) in the low-molecular-weight–heparin group (difference, 0.00 percentage points; 95% CI, −0.43 to 0.43) (Table 2 and Fig. S7). The majority of nonfatal pulmonary embolisms took place within 7 days (interquartile range, 3 to 22) after randomization, and venous thromboembolism surveillance was similar in the two groups (Table S11).

Deep-vein thrombosis occurred in 151 patients (90-day probability, 2.51%) in the aspirin group and in 103 patients (90-day probability, 1.71%) in the low-molecular-weight–heparin group (difference, 0.80 percentage points; 95% CI, 0.28 to 1.31) (Table 2 and Fig. S8). The between-group difference in distal deep-vein thrombosis was 0.58 percentage points (95% CI, 0.20 to 0.96), and the between-group difference in proximal deep-vein thrombosis was 0.25 percentage points (95% CI, −0.12 to 0.62). The median time from randomization to the occurrence of deep-vein thrombosis was 16 days (interquartile range, 7 to 35).

SAFETY OUTCOMES

Bleeding events occurred in 834 patients (90-day probability, 13.72%) in the aspirin group and in 869 patients (90-day probability, 14.27%) in the low-molecular-weight–heparin group (difference, −0.54 percentage points; 95% CI, −1.78 to 0.69) (Table 2, Table S12, and Fig. S9). The median time to a bleeding event was 2 days after ran-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Aspirin (N=6101)	Low-Molecular-Weight Heparin (N=6110)	Total (N=12,211)
Age — yr†	44.5±18.0	44.7±17.6	44.6±17.8
Male sex — no. (%)†	3832 (62.8)	3769 (61.7)	7601 (62.2)
Race or ethnic group — no. (%)‡			
Non-Hispanic White	3821 (62.6)	3897 (63.8)	7718 (63.2)
Non-Hispanic Black	1236 (20.3)	1216 (19.9)	2452 (20.1)
Hispanic	774 (12.7)	736 (12.0)	1510 (12.4)
Other	212 (3.5)	200 (3.3)	412 (3.4)
Median body-mass index (IQR)§	27.1 (23.6–31.8)	27.5 (23.8–32.8)	27.4 (23.7–32.3)
Risk factor — no. (%)			
Previous VTE	43 (0.7)	46 (0.8)	89 (0.7)
Cancer	140 (2.3)	166 (2.7)	306 (2.5)
Diabetes	500 (8.2)	508 (8.3)	1008 (8.3)
Smoking status¶			
Never smoked	3012 (49.4)	2935 (48.0)	5947 (48.7)
Former smoker	986 (16.2)	1031 (16.9)	2017 (16.5)
Current smoker	2099 (34.4)	2139 (35.0)	4238 (34.7)
Receipt of medication before injury — no. (%)			
Aspirin¶	496 (8.1)	476 (7.8)	972 (8.0)
OCP or estrogen‖	112 (1.8)	107 (1.8)	219 (1.8)
Plavix or other antiplatelet¶	55 (0.9)	52 (0.9)	107 (0.9)
Without health insurance — no. (%)**	1355 (22.2)	1288 (21.1)	2643 (21.6)
Injury Severity Score††			
Median (IQR)	9 (4–10)	9 (4–10)	9 (4–10)
Distribution — no. (%)			
<9	2522 (41.3)	2606 (42.7)	5128 (42.0)
9 to 15	2715 (44.5)	2607 (42.7)	5322 (43.6)
>15	833 (13.7)	864 (14.1)	1697 (13.9)
Injury region — no. (%)††			
Lower extremity	5346 (87.6)	5336 (87.3)	10,682 (87.5)
Upper extremity	1655 (27.1)	1688 (27.6)	3343 (27.4)
Abdomen	758 (12.4)	808 (13.2)	1566 (12.8)
Spine	608 (10.0)	655 (10.7)	1263 (10.3)
Thorax	1083 (17.8)	1163 (19.0)	2246 (18.4)
Neck	59 (1.0)	74 (1.2)	133 (1.1)
Face	816 (13.4)	875 (14.3)	1691 (13.8)
Head	778 (12.8)	783 (12.8)	1561 (12.8)
Fracture — no. (%)			
Lower extremity only	4093 (67.1)	4046 (66.2)	8139 (66.7)
Upper extremity only	724 (11.9)	741 (12.1)	1465 (12.0)
Lower and upper extremities	1253 (20.5)	1290 (21.1)	2543 (20.8)

Table 1. (Continued.)

* Plus–minus values are means ±SD. IQR denotes interquartile range, OCP oral contraceptive pill, and VTE venous thromboembolism.
† Data were not available for 1 patient.
‡ Race or ethnic group was reported by the patient or the patient's proxy. Data were not available for 3 patients; an additional 116 patients declined to provide data.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters. Scores were not available for 12 patients.
¶ Data were not available for 9 patients.
‖ Data were not available for 10 patients.
** Data were not available for 7 patients.
†† The Injury Severity Score and injury location data were not available for 64 patients. Totals in the injury region columns do not match the total number of patients because some patients had injuries that involved more than one region. The Injury Severity Score standardizes the severity of traumatic injuries on the basis of the worst injuries present across a maximum of three different body regions; total scores range from 1 to 75, with higher scores indicating more severe injury. The lower extremity includes the hip to the midfoot, and the upper extremity includes the shoulder to the wrist.

domization (interquartile range, 1 to 4) in the aspirin group and 2 days after randomization in the low-molecular-weight–heparin group (interquartile range, 1 to 3). Wound complications occurred in 8 patients (90-day probability, 0.13%) in the aspirin group and in 14 patients (90-day probability, 0.23%) in the low-molecular-weight–heparin group (difference, −0.10 percentage points; 95% CI, −0.25 to 0.05) (Fig. S10). Deep surgical-site infections occurred in 103 patients (90-day probability, 1.73%) in the aspirin group and in 93 patients (90-day probability, 1.55%) in the low-molecular-weight–heparin group (difference, 0.18 percentage points; 95% CI, −0.28 to 0.64) (Fig. S11). The occurrence of other serious adverse events was similar in the two groups (Table S13).

DISCUSSION

We found that thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin for the prevention of death from any cause in patients with a pelvic or acetabular fracture treated with or without surgery or a fracture of the extremities treated operatively. The result of the prespecified per-protocol analysis was consistent with the primary intention-to-treat finding. The finding of noninferiority for aspirin in the prevention of death from any cause was supported by consistent results with regard to the secondary outcomes, including the outcome of death related to pulmonary embolism and the outcome of nonfatal pulmonary embolism. Orthopedic trauma was the only known risk factor for venous thromboembolism for one quarter of the patients. Fewer deep-vein thromboses were noted among patients in the low-molecular-weight–heparin group than among those in the aspirin group (2.51% vs. 1.71%; difference, 0.8 percentage points; 95% CI, 0.28 to 1.31) as well as fewer distal deep-vein thromboses (1.45% vs. 0.86%; difference, 0.58 percentage points; 95% CI, 0.20 to 0.96). In addition, there was no signal of an increased safety risk with aspirin thromboprophylaxis in this patient population or evidence of differential effectiveness on the basis of patient age.

Our results align with those from a previous trial, which suggests that aspirin is as safe and effective as low-molecular-weight heparin in preventing fatal thromboembolism after orthopedic trauma.[13] Our observation with regard to fewer deep-vein thrombosis events in patients who received low-molecular-weight heparin in this trial is consistent with the point estimates of three previous trials that involved patients who had undergone hip or knee arthroplasty.[24-26] However, the differences that were reported in two of the three previous trials were not statistically significant.

We chose death from any cause as the primary outcome for the trial owing to its paramount importance to patients, its designation in a Cochrane review of thromboprophylaxis in trauma patients, and its scientific reliability.[1,15] However, we also acknowledge that protection against nonfatal thromboembolic events bears careful consideration when thromboprophylaxis agents are compared. As such, we included venous thromboembolism and safety outcomes to provide a more complete comparison of the two trial drugs.

Previous thromboprophylaxis trials have used

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Population			Per-Protocol Population		
	Aspirin (N=6101)	Low-Molecular-Weight Heparin (N=6110)	Difference (CI)†	Aspirin (N=5505)	Low-Molecular-Weight Heparin (N=5170)	Difference (CI)†
	no. (% 90-day probability)		*percentage points*	*no. (% 90-day probability)*		*percentage points*
Primary outcome: death from any cause	47 (0.78)	45 (0.73)	0.05 (–0.27 to 0.38)‡	41 (0.75)	38 (0.72)	0.03 (–0.31 to 0.38)
Secondary efficacy outcome§						
Cause-specific death						
Death related to PE	4 (0.07)	5 (0.08)	–0.02 (–0.12 to 0.08)	4 (0.07)	3 (0.06)	0.01 (–0.08 to 0.11)
Death possibly related to PE	18 (0.30)	14 (0.22)	0.08 (–0.10 to 0.27)	14 (0.26)	10 (0.18)	0.08 (–0.10 to 0.26)
Death unlikely to be related to PE	29 (0.49)	31 (0.52)	–0.03 (–0.28 to 0.22)	27 (0.50)	28 (0.55)	–0.05 (–0.33 to 0.23)
PE type						
Any	90 (1.49)	90 (1.49)	0 (–0.43 to 0.43)	50 (0.92)	43 (0.84)	0.08 (–0.17 to 0.54)
Massive	1 (0.02)	3 (0.05)	–0.03 (–0.10 to 0.03)	0 (0.00)	2 (0.04)	–0.04 (–0.09 to 0.02)
Submassive	22 (0.36)	15 (0.25)	0.12 (–0.08 to 0.31)	11 (0.20)	10 (0.20)	0.01 (–0.16 to 0.18)
Clinically significant	61 (1.01)	64 (1.06)	–0.05 (–0.41 to 0.31)	34 (0.62)	26 (0.51)	0.11 (–0.17 to 0.40)
Asymptomatic	3 (0.05)	5 (0.08)	–0.03 (–0.12 to 0.06)	2 (0.04)	2 (0.04)	0 (–0.08 to 0.07)
Segmental	61 (1.01)	59 (0.98)	0.03 (–0.32 to 0.39)	36 (0.66)	26 (0.51)	0.15 (–0.14 to 0.44)
Subsegmental	38 (0.63)	40 (0.66)	–0.03 (–0.32 to 0.25)	23 (0.42)	22 (0.43)	–0.01 (–0.26 to 0.24)
DVT type						
Any	151 (2.51)	103 (1.71)	0.80 (0.28 to 1.31)	109 (2.01)	73 (1.44)	0.57 (0.08 to 1.07)
Proximal	74 (1.23)	59 (0.98)	0.25 (–0.12 to 0.62)	46 (0.85)	41 (0.81)	0.04 (–0.30 to 0.39)
Distal	87 (1.45)	52 (0.86)	0.58 (0.20 to 0.96)	65 (1.20)	36 (0.71)	0.49 (0.12 to 0.86)
Secondary safety outcome						
Bleeding complication	834 (13.72)	869 (14.27)	–0.54 (–1.78 to 0.69)	730 (13.30)	693 (13.44)	–0.14 (–1.43 to 1.16)
Wound complication	8 (0.13)	14 (0.23)	–0.10 (–0.25 to 0.05)	7 (0.13)	10 (0.20)	–0.07 (–0.22 to 0.09)
Infection	103 (1.73)	93 (1.55)	0.18 (–0.28 to 0.64)	100 (1.86)	69 (1.36)	0.50 (0.02 to 0.98)

* Percentages are calculated with the use of treatment-specific 90-day outcome probabilities, as calculated by a Kaplan–Meier estimator for the primary outcome and cumulative-incidence functions for the secondary outcomes, and do not use the group population as the denominator. This method was chosen over simple percentages to reflect the differential follow-up in some patients and for consistency with the treatment-effect estimates. DVT denotes deep-vein thrombosis, and PE pulmonary embolism.

† The confidence intervals are 95% confidence intervals for all the measures except death from any cause, for which 96.2% confidence intervals are shown.

‡ P<0.001 for noninferiority.

§ Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

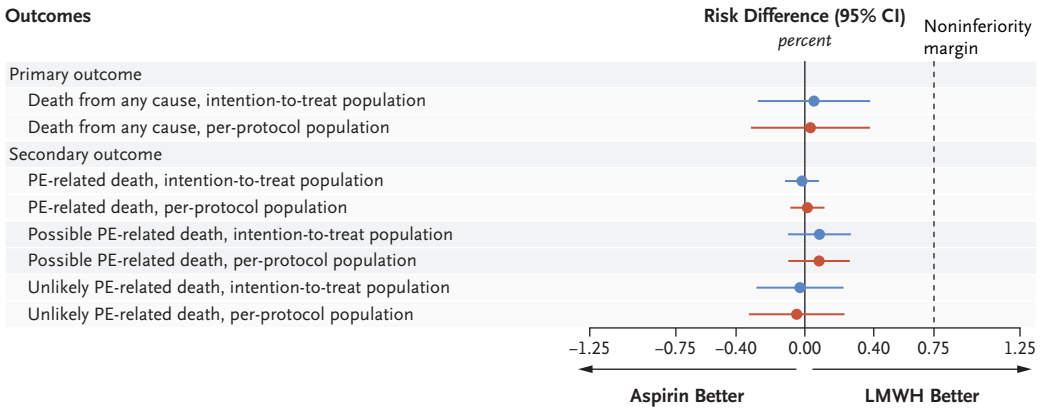

Figure 1. Estimated Difference in Death from Any Cause and Cause-Specific Death in the Intention-to-Treat and Per-Protocol Populations.

The per-protocol population included only patients who were adherent to at least 80% of their in-hospital medication doses and who were prescribed the assigned trial drug at hospital discharge if thromboprophylaxis was recommended. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates. The primary outcome is reported with a 96.2% confidence interval to account for the interim analyses. The secondary outcomes are reported with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. LMWH denotes low-molecular-weight heparin, and PE pulmonary embolism.

a composite outcome of death, pulmonary embolism, or deep-vein thrombosis.[27,28] The size of this trial allowed for the evaluation of each of these outcomes. Health care providers along with patients with traumatic fractures and similar characteristics to those enrolled in this trial can now weigh the noninferiority of aspirin to low-molecular-weight heparin (difference, 0.05 percentage points; 96.2% CI, −0.27 to 0.38) and similar findings of pulmonary embolism in the two groups (difference, 0.00 percentage points; 95% CI, −0.43 to 0.43) against the increased cost and administration by injection of low-molecular-weight heparin and its association with fewer deep-vein thromboses (difference, 0.80 percentage points; 95% CI, 0.28 to 1.31).

This trial has several limitations. First, we anticipated enrollment challenges at the initial hospital admission owing to the critical injuries of the trial population. Therefore, we allowed eligible patients to receive up to two doses of low-molecular-weight heparin as standard care before consent was obtained. Because the half-life of low-molecular-weight heparin is 3 to 4 hours,[29] we suspect that these initial doses were unlikely to have affected the trial findings. Conversely, the longer half-life of aspirin might have provided differential sustained protection in patients who were discharged without thromboprophylaxis. Second, considering the variability in clinical guideline recommendations for the duration of thromboprophylaxis at different institutions and our pragmatic trial design, we did not mandate the duration of thromboprophylaxis therapy. Differences in the duration of thromboprophylaxis therapy after hospital discharge may have influenced the outcomes. However, we did monitor the prescribed duration of thromboprophylaxis, which was similar in the two treatment groups. Third, the trial had an open-label design, so there was a potential for diagnostic suspicion or surveillance bias in our secondary outcomes.[30] However, the risk of this bias was reduced by an objective primary outcome of death from any cause and by the blinded adjudication of death related to pulmonary embolism and of pulmonary embolism events. Also, we observed that a similar proportion of patients in the two groups had undergone screening tests. Finally, the primary outcome was changed from death related to pulmonary embolism to death from any cause after enroll-

ment began but before we published the protocol,[17] finalized the statistical analysis plan or completed enrollment. We completed this change without any knowledge of the trial outcomes.

Despite these limitations, our findings are clinically meaningful. Patients with orthopedic trauma strongly favor aspirin over low-molecular-weight heparin because of the lower costs and less burdensome administration of aspirin.[15,16] In hospitalized patients, oral medications are less often subject to nonadministration than injectable thromboprophylaxis drugs.[31,32] The trial was performed at 21 sites with high follow-up (96.8%) and adherence (87.4%). An adjudication committee whose members were unaware of trial-group assignments reviewed all outcomes of death and pulmonary embolism, which further verified the reliability of our findings.

We found that thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin for the prevention of fatal events in patients with orthopedic trauma and was associated with low frequencies of deep-vein thrombosis, pulmonary embolism, and death from any cause at 90 days. This finding was consistent for outcomes of death related to pulmonary embolism and nonfatal pulmonary embolism. In addition, we found no evidence of additional safety risks associated with aspirin thromboprophylaxis in our trial population.

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

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APPENDIX

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