The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 19, 2023 VOL. 388 NO. 3

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

Major Extremity Trauma Research Consortium (METRC)*

Background

- Clinical guidelines recommend low-molecular-weight heparin for thromboprophylaxis in patients with fractures.
- 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.
- However, evidence from head-to-head comparisons among patients with fractures that have been treated operatively is limited.

AIM of the study

- To examine the effectiveness and safety of thromboprophylaxis with aspirin as compared with low-molecular-weight heparin in patients with a fracture.

Methods

- The Prevention of Clot in Orthopaedic Trauma (PREVENT CLOT) trial is a pragmatic, multicenter, randomized, noninferiority trial.
- 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 were included.
- Patients were randomly assigned to receive 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 (I)

- A total of 12,211 patients were randomly assigned to receive aspirin (6101 patients) or enoxaparin (6110 patients).
- The demographic, medical, and surgical characteristics of the patients at baseline were similar in the two groups.
- 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.
- 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.

Results (II)

- Death occurred in 47 patients (0.78%) in the aspirin group and in 45 patients (0.73%) in the enoxaparin group (P<0.001 for a noninferiority).
- Deep-vein thrombosis occurred in 2.51% of patients in the aspirin group and 1.71% in the enoxaparin 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.

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)

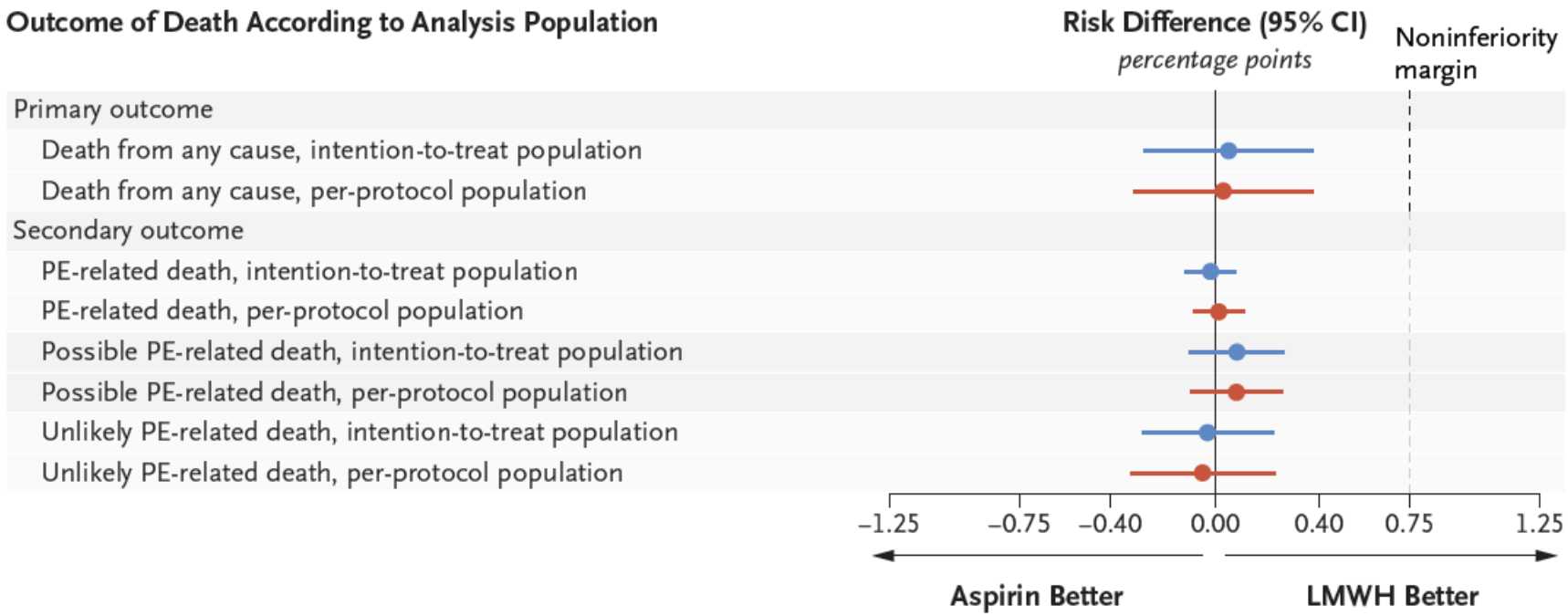

Figure 1. Estimated Difference in Death from Any Cause and Cause-Specific Death in the Intention-to-Treat and Per-Protocol Populations.

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.

Conclusions

- The trial showed that thromboprophylaxis with aspirin was noninferior to enoxaparin 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.
- These findings might determine a reconsideration of current guidelines for the prevention of venous thromboembolism in hospitalized patients, including the option of aspirin in patients with extremity fractures, especially in those with ischemic heart disease and/or a history of coronary revascularization who are already on treatment with single or dual antiplatelet therapy at the time of traumatic injury.
- Whether this strategy for venous thromboprophylaxis might be beneficial to other patient categories needs to be tested in future studies.