Enoxaparin for 7 days was better than unfractionated heparin for 2 days for reducing death and MI but not bleeding in STEMI

Antman EM, Morrow DA, McCabe CH, et al. **Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction.** N Engl J Med. 2006;354:1477-88.

Clinical impact ratings: Emergency Med ★★★★★★☆ Hospitalists ★★★★★☆☆ Cardiology ★★★★★★☆

QUESTION

In patients with ST-elevation myocardial infarction (STEMI), how does enoxaparin compare with unfractionated heparin (UFH) as adjunctive therapy with fibrinolysis for reducing death or MI?

METHODS

Design: Randomized controlled trial (The Enoxaparin and Thrombolysis Reperfusion for Acute MI Treatment–Thrombolysis in MI [ExTRACT-TIMI] 25 study).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, {data collectors, outcome assessors, and manuscript writers}†.*

Follow-up period: 30 days.

Setting: 674 centers in 48 countries.

Patients: 20 506 patients ≥ 18 years of age (median age 60 y, 77% men, 87% white) who had ≥ 20 minutes of ischemic symptoms at rest within 6 hours before randomization, and ST-segment elevation ≥ 0.1 mV in 2 limb leads, or 0.2 mV in ≥ 2 contiguous precordial leads, or left bundle-branch block. Exclusion criteria included cardiogenic shock, contraindications to fibrinolysis, receipt of low-molecular-weight heparin in the previous 8 hours, and renal insufficiency.

Intervention: Enoxaparin (n = 10 256) or UFH (n = 10 223). The enoxaparin group received placebo UFH plus intravenous (IV) enoxaparin bolus, 30 mg (omitted for patients ≥ 75 y) and 1.0 mg/kg subcutaneously every 12 hours for patients < 75 years; or 0.75 mg/kg every 12 hours for patients ≥ 75 years; or enoxaparin, 1.0 mg/kg per day for creatinine clearance < 30 mL/min, for 8 days or until discharge. The UFH group received placebo enoxaparin plus IV UFH bolus, 60 U/kg body weight, and 12 U/kg per hour infusion for ≥ 48 hours. All patients received fibrinolysis and aspirin.

Outcomes: A composite endpoint of death or nonfatal MI at 30 days. Secondary outcomes included major bleeding and various composite endpoints.

Patient follow-up: 99.9% (20 479 in the intention-to-treat analysis).

MAIN RESULTS

Enoxaparin led to a lower incidence of the primary endpoint and all other composite endpoints than did UFH, but increased major bleeding at 30 days (Table).

CONCLUSIONS

In patients with ST-elevation myocardial infarction, 7 days of enoxaparin was better than 2 days of unfractionated heparin as adjunctive therapy with fibrinolysis for reducing death and nonfatal myocardial infarction. Enoxaparin increased risk for major bleeding.

Source of funding: Sanofi-Aventis.

For correspondence: Dr. E.M. Antman, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. E-mail eantman@rics.bwh.harvard.edu. ■

*See Glossary.

†Information provided by author.

Enoxaparin vs unfractionated heparin (UFH) in patients undergoing fibrinolysis for ST-elevation myocardial infarction at 30 days‡

Outcomes	Enoxaparin	UFH	RRR (95% CI)	NNT (CI)
Death or nonfatal MI	9.9%	12%	17% (10 to 23)	50 (37 to 84)
Death, MI, or urgent revascularization	12%	15%	19% (13 to 25)	37 (28 to 54)
Death, MI, or nonfatal stroke	10%	12%	18% (11 to 24)	46 (34 to 74)
Death, MI, or major bleeding	11%	13%	14% (7.0 to 20)	56 (40 to 112)
Death, MI, or intracranial hemorrhage	10%	12%	17% (10 to 23)	49 (36 to 82)
			RRI (CI)	NNH (CI)
Major bleeding	2.1%	1.4%	53% (23 to 89)	139 (83 to 320)

‡MI = myocardial infarction. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from relative risks in article.

COMMENTARY

How does one make sense of trials where a difference is shown, but it might be due to different drug products, different routes of administration, different anticoagulation effects, and different durations of therapy?

In the ExTRACT-TIMI trial by Antman and colleagues, the only unbiased comparison was at 48 hours, when both groups were receiving treatment. At that time, the slight, albeit nonsignificant, reduction in the primary endpoint (5 per 100) with enoxaparin was counterbalanced with an increase in major bleeding (4 per 100). Thereafter, enoxaparin was associated with prevention of nonfatal MI at the cost of increased major bleeding. However, at 30 days, the net clinical benefit still favored enoxaparin. Ultimately, for every 3 nonfatal MI events prevented, 1 major bleeding episode was caused by enoxaparin. Moreover, more patients with major bleeding died on enoxaparin than on standard UFH.

Data on the degree of anticoagulation (e.g., target partial thromboplastin times or anti-Xa levels) and bleeding risk for patients > 75 years of age would be of interest. Previous studies suggested that usual enoxaparin dosing regimens were associated with increased risk for major bleeding in older patients (1). In the ExTRACT-TIMI trial, the enoxaparin dose was lower in older patients and may confer less benefit. Low anti-Xa levels can also increase 30-day mortality (2).

Is there a role for enoxaparin up to hospital discharge? In the context of net clinical benefit, this strategy has merit. Enoxaparin use should be avoided in patients with renal failure, the morbidly obese, and older patients. In jurisdictions where primary percutaneous coronary intervention is standard, clinicians will probably use heparin with or without glycoprotein IIb/IIIa inhibitors in the cardiac catheterization laboratory.

The OASIS-5 trial by Yusuf and colleagues showed that fondaparinux was as effective as enoxaparin for patients with ACSs without ST-segment elevation, but was associated with lower bleeding risk. In other trials of antithrombotic regimens, clinicians have faced trade-offs between a somewhat greater clinical benefit and an increased risk for major bleeding–a price to pay for preventing additional cardiac events.

It is not surprising that fondaparinux was associated with less bleeding because a "DVT prophylaxis" dose of fondaparinux was compared with a "therapeutic" dose of enoxaparin. The effectiveness data are more surprising. If fondaparinux is as effective as enoxaparin, why is

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Fondaparinux was noninferior to enoxaparin for death, MI, and refractory ischemia but reduced bleeding in angina and non-STEMI

Yusuf S, Mehta SR, Chrolavicius S, et al. **Comparison of fondaparinux and enoxaparin in acute coronary syndromes.** N Engl J Med. 2006;354:1464-76.

Clinical impact ratings: Emergency Med ★★★★★★☆ GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★★☆ Cardiology ★★★★★★☆

QUESTION

In patients with unstable angina or non–ST-segment elevation myocardial infarction (MI), is fondaparinux noninferior to enoxaparin for reducing death, MI, or refractory ischemia and superior for reducing major bleeding?

METHODS

Design: Randomized controlled trial (The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes [OASIS-5] trial).
Allocation: Concealed.*
Blinding: Blinded (clinicians, patients, {outcome assessors}†, and data safety and monitoring committee).*
Follow-up period: Up to 6 months.
Setting: 576 centers in 41 countries.
Patients: 20 078 patients (mean age 67 y, 62% men) who met ≥ 2 of the following criteria: age ≥ 60 years, high troponin or creatine kinase MB isoenzyme levels, or electrocardiographic changes indicating ischemia. Exclusion criteria were recent hemorrhagic stroke, contraindications to low-molecular-weight heparin, indications for anticoagulation for reasons other than the acute coronary syndrome (ACS), and serum creatinine level ≥ 3 mg/dL (265 µmol/L).
Intervention: Fondaparinux, 2.5 mg/d plus, subcutaneous placebo enoxaparin twice daily (n = 10 057); or enoxaparin, 1 mg/kg of body weight twice daily plus subcutaneous placebo fondaparinux once daily (n = 10 021).
Outcomes: A composite endpoint of death, MI, or refractory ischemia and major bleeding at 9 days. Secondary outcomes included individual outcomes at 30 and 180 days.
Patient follow-up: 99.9% (intention-to-treat analysis).

MAIN RESULTS

Fondaparinux was noninferior to enoxaparin for the primary composite endpoint and death or MI was superior for reducing death at 30 and 180 days; and led to a lower incidence of major bleeding (Table).

CONCLUSIONS

In patients with unstable angina or non–ST-segment elevation myocardial infarction, fondaparinux was noninferior to enoxaparin for reducing death, MI, and refractory ischemia. Fondaparinux decreased risk for major bleeding.

Sources of funding: Sanofi-Aventis; Organon; GlaxoSmithKline.

For correspondence: Dr. S. Yusuf, McMaster University, Hamilton, Ontario, Canada. E-mail yusufs@mcmaster.ca.

*See Glossary.
†Information provided by author.

Fondaparinux vs enoxaparin for unstable angina or non–ST-segment elevation myocardial infarction‡

Outcomes	Follow-up	Fondaparinux	Enoxaparin	Difference (95% CI)	
Composite endpoint§	9 d	5.8%	5.7%	–0.06% (–0.72 to 0.56)‖	
	30 d	8.0%	8.6%	0.58% (–0.17 to 1.33)	
	180 d	12%	13%	0.86% (0 to 1.72)	
Death or MI	9 d	4.1%	4.1%	0.04% (–0.52 to 0.57)‖	
	30 d	6.2%	6.8%	0.66% (–0.07 to 1.26)	
	180 d	11%	11%	0.85% (0 to 1.71)	
Death	9 d	1.8%	1.9%	0.09% (–0.31 to 0.42)	
				RRR (CI)	NNT (CI)
	30 d	2.9%	3.5%	17% (2.9 to 29)	170 (100 to 966)
	180 d	5.8%	6.5%	10% (0.005 to 20)	152 (76 to 342 249)
Major bleeding	9 d	2.2%	4.1%	47% (39 to 55)	52 (44 to 64)
	30 d	3.1%	5.0%	37% (27 to 45)	55 (45 to 74)
	180 d	4.3%	5.8%	27% (18 to 35)	65 (50 to 101)

‡MI = myocardial infarction. Other abbreviations defined in Glossary; difference, RRR, NNT, and CI calculated from hazard ratios in article.
§Death, MI, or refractory ischemia.
‖Criteria for noninferiority were met because the upper limit of the CI was < prespecified delta margin of 1.185.

COMMENTARY

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there excess catheter-related thrombus? This is potentially important and suggests that fondaparinux use during coronary intervention needs more study. Alternatively, adjunctive periprocedural heparin may be required, which may increase bleeding risk at the access site.

Could the results be explained by increased bleeding risk with enoxaparin rather than decreased risk with fondaparinux? Perhaps, in part, considering that 61% of patients in the OASIS-5 trial were ≥ 65 years of age. In the ASSENT-3 trial (admittedly in patients treated with thrombolysis), there was an increased bleeding risk for those ≥ 75 years of age (1). As a result, the dose of enoxaparin was lowered for older patients in the ExTRACT-TIMI trial. Simply lowering the dose of enoxaparin to reduce bleeding risk may not be the answer because effectiveness has not been shown at lower doses. Furthermore, the fondaparinux group had a lower risk for major bleeding in patients < 65 years of age. Therefore, while older patients may have a potential disadvantage at the lower enoxaparin dose, this may only partially explain the bleeding difference.

Major bleeding is important. In similar trials, major bleeding was associated with increased mortality. In the OASIS-5 trial, all excess deaths in the enoxaparin group were bleeding related. Although it was not possible to tell from this study whether bleeding caused the increased deaths, data from other studies, including the ExTRACT-TIMI trial, strongly suggest that it does.

Fondaparinux should definitely be used in patients with ACS. The once-daily fixed dose may allow for fewer dosing errors (3), and the lower cost of fondaparinux will be attractive to clinicians and hospital administrators. However, in jurisdictions where a routine aggressive early-intervention approach is used, the potential for catheter-related thrombus may be of sufficient concern that fondaparinux will not be considered. Instead, clinicians will use familiar periprocedural antithrombotic strategies. It is possible that fondaparinux will be used for patients with lower-risk ACS.

David Massel, MD
London Health Sciences Center
London, Ontario, Canada

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