

# Review: Low-molecular-weight heparin is more effective than unfractionated heparin for preventing reinfarction in STEMI

Eikelboom JW, Quinlan DJ, Mehta SR, et al. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation*. 2005;112:3855-67. Epub 2005 Dec 12.

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

## QUESTION

In thrombolytic- and aspirin-treated patients with ST-elevation acute myocardial infarction (STEMI), is low-molecular-weight heparin (LMWH) more effective than unfractionated heparin (UFH)?

## METHODS

**Data sources:** MEDLINE and EMBASE/Excerpta Medica (1966 to February 2005), Cochrane Library (issue 1, 2005), conference abstracts from major international cardiology meetings, and bibliographies of relevant studies.

**Study selection and assessment:** Randomized controlled trials (RCTs) that compared intravenous UFH or subcutaneous LMWH with placebo or no heparin, or compared UFH with LMWH, in thrombolytic- and aspirin-treated patients with STEMI. Studies evaluating subcutaneous UFH were excluded. 14 RCTs ( $n = 25\ 280$ ) met the selection criteria. LMWH was compared with UFH (6 RCTs,  $n = 7098$ ) and placebo (4 RCTs,  $n = 16\ 943$ ). UFH was compared with no heparin (4 RCTs,  $n = 1239$ ). Quality assessment was based on concealment, blinding, and follow-up.

**Outcomes:** Mortality, MI, stroke, and bleeding at 7 and 30 days.

## MAIN RESULTS

LMWH led to a lower incidence of MI and a higher incidence of minor bleeding than

UFH (Table). LMWH and UFH groups did not differ for mortality, stroke, and major bleeding. Compared with placebo, the LMWH group had a lower incidence of MI and death, but a higher incidence of major and minor bleeding (Table). LMWH and placebo groups did not differ for stroke. Patients who received UFH had a higher incidence of minor bleeding than the no-heparin group (Table). UFH and no-heparin groups did not differ for mortality, MI, stroke, or major bleeding.

## CONCLUSIONS

In thrombolytic- and aspirin-treated patients with ST-elevation acute myocardial infarction, low-molecular-weight heparin is more effective than unfractionated heparin or placebo for preventing reinfarction. Low-molecular-weight heparin is better than placebo for reducing mortality.

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### Low-molecular-weight heparin (LMWH) vs unfractionated heparin (UFH) or placebo (plac), and UFH vs no heparin in ST-elevation myocardial infarction (MI) at 7 and 30 days\*

Outcomes	Number of trials (n)	Comparisons	Follow-up	Weighted event rates	RRR (95% CI)	NNT (CI)
Mortality	3 (16 842) 3 (16 167)	LMWH vs plac	7 d	7.9% vs 8.7%	9.2% (1.0 to 19)	125 (62 to 1258)
			30 d	9.7% vs 11%	13% (4.5 to 20)	72 (45 to 202)
MI	6 (7093) 5 (5454) 3 (16 842) 3 (16 167)	LMWH vs UFH	7 d	3.0% vs 5.2%	42% (26 to 54)	47 (36 to 75)
			30 d	3.7% vs 5.6%	35% (15 to 49)	52 (37 to 118)
		LMWH vs plac	7 d	1.6% vs 2.2%	28% (10 to 41)	165 (110 to 464)
			30 d	2.1% vs 2.7%	24% (6.8 to 37)	158 (100 to 543)
				<b>RRI (CI)</b>	<b>NNH (CI)</b>	
Major bleeding	3 (16 842)	LMWH vs plac	7 d	1.1% vs 0.4%	168% (82 to 294)	149 (85 to 304)
Minor bleeding	4 (6393) 2 (1272) 3 (1022)	LMWH vs UFH	7 d	23% vs 19%	20% (9.5 to 32)	26 (17 to 55)
			7 d	15% vs 5.2%	190% (100 to 308)	11 (7 to 20)
		UFH vs no heparin	7 d	20% vs 13%	58% (19 to 106)	14 (8 to 43)

\*Abbreviations defined in Glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from odds ratios in article.

## COMMENTARY

The role of adjunctive antithrombotic therapy after fibrinolytic therapy in patients with STEMI has been debated for years. In the review by Eikelboom and colleagues, 4 small trials of intravenous UFH compared with no heparin were underpowered to show benefit. The addition of 4 trials that compared LMWH with placebo, particularly the CREATE trial (1), provides support for adjunctive antithrombotic therapy and LMWH may be preferred in this setting.

The challenge of declaring LMWH as the superior antithrombotic over UFH, bivalirudin, or fondaparinux is confounded by drug, dose, treatment duration, other adjunctive interventions, and study design. Previous studies in acute coronary syndromes showed benefit for enoxaparin, but not nadroparin or dalteparin, when compared with UFH. The dose of UFH has varied across trials. The ExTRACT-TIMI 25 trial (2) used 3 different doses of enoxaparin adjusted for age and renal function. It is important to note that UFH was given for only 2 days in ExTRACT-TIMI 25 (2) and OASIS-6 (3), while enoxaparin was given for 7 days and fondaparinux for 8 days. Therefore, a longer treatment strategy may be more important than the type of antithrombotic. Also, definitions for MI and bleeding vary across trials—there is no accepted standard for comparison—so the net clinical benefit is difficult to define.

There is also a “new playing field.” Clopidogrel decreases MI in patients treated with lytics and aspirin (4), an accomplishment also claimed for the early invasive strategy with revascularization of the infarct artery. Thus, the number of preventable events with improved antithrombotic therapy may be less now than in the trials of this review.

The recently published ExTRACT-TIMI 25 trial (2) reinforces the conclusions of this meta-analysis, showing that enoxaparin was superior to UFH in reducing reinfarction and death but increased minor and major bleeding. However, the major benefit of LMWH over intravenous UFH may be more practical than pharmacological: ease of administration, reliable anticoagulation without the need for therapeutic monitoring, and extended treatment duration.

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## References

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