RESEARCH LETTERS

Low-Molecular-Weight Heparin as an Adjunct to Thrombolysis in ST Elevation Myocardial Infarction

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)–Thrombolysis in Myocardial Infarction (TIMI)-25 study[1] demonstrated that the administration of enoxaparin sodium, 30 mg intravenously, followed by subcutaneous injections of 1 mg/kg twice daily (dose modified in patients 75 years or older), compared with intravenous unfractionated heparin (UFH), 60 U/kg bolus (maximum 4000 U), followed by 12 U/kg/h (initial maximum, 1000 U/h, and subsequently adjusted to maintain an activated partial thromboplastin time of 1.5-2.0 times the control value), reduced the risk of nonfatal reinfarction in patients with ST elevation myocardial infarction (STEMI) treated with thrombolysis. Because the ExTRACT-TIMI 25 study seems likely to be the last large trial evaluating the efficacy and safety of low-molecular-weight heparin (LMWH) in patients with STEMI, we added the results of this pivotal 20 000 patient trial to our meta-analysis published in 2005.[2] Our updated literature search identified 1 additional study by Wang and colleagues[3] published in 2006 involving 186 patients with STEMI who were randomized to receive parnaparin sodium or UFH; this study was also added to our meta-analysis.

Including the ExTRACT-TIMI 25 study and the study by Wang and colleagues,[3] 8 trials involving a combined total of 27 758 patients have compared LMWH with UFH in patients with STEMI. During hospitalization or at 7 days, LMWH compared with UFH reduced reinfarction by almost one-half (2.1% vs 3.9%) (odds ratio [OR] 0.53; 95% confidence interval [CI], 0.46-0.61) (number needed to treat [NNT], 56) (**Table**). The rates of death were not significantly different in the 2 treatment groups (5.3% vs 5.8%) (OR, 0.92; 95% CI, 0.83-1.02), but LMWH compared with UFH significantly increased major bleeding events (2.2% vs 1.6%) (OR, 1.39; 95% CI, 1.17-1.66) (number needed to harm [NNH], 167) and minor bleeding events (7.2% vs 5.8%) (OR, 1.31; 95% CI, 1.18-1.45) (NNH, 71). The benefit of LMWH in reducing reinfarction remained evident at 30 days, and estimates for other outcomes were similar at 7 and 30 days. Stroke rates were identical in the 2 randomized treatment groups at 30 days.

The inclusion of data from the ExTRACT-TIMI 25 study[1] and the study by Wang et al[3] in our meta-analysis substantially increased the number of outcome events (number of reinfarctions increased from 253 events to 1043 events; death, from 412 events to 1911 events; and major bleeding events, from 206 events to 520 events), thereby greatly improving the precision of the estimates of effect size. A reduced risk of reinfarction became evident after the first trial in 2001, when 4078 patients had been randomized and 144 reinfarctions had occurred (**Figure**). Cumulative data from subsequent trials resulted in a narrowing of the 95% CI, but the point estimates remained similar. A statistically significant increase in the risk of major bleeding with LMWH compared with UFH was not evident until after the publication of the results of the ExTRACT-TIMI 25 study in 2006. There was a nonsignificant 8% lower risk of death observed with LMWH compared with UFH during hospitalization or at days 7 (P=.10) and 30 (P=.08) (Table).

All of the estimates obtained from our updated analysis are similar to our original meta-analysis, approximating a one-half reduction in reinfarction during hospitalization or at day 7 and a one-third reduction in reinfarction through day 30. There was no significant heterogeneity among the trials for any of the outcomes examined, and the data from this meta-analysis represent the best esti-

Table. Patient Outcomes for Patients Comparing LMWH With UFH

Outcome	Total No.	LMWH, No./Total No. (%)	UFH, No./Total No. (%)	Odds Ratio (95% CI)[a]
During hospitalization or at 7 d				
Reinfarction	27 758	296/13 940 (2.1)	540/13 818 (3.9)	0.53 (0.46-0.61)
Death	27 758	740/13 940 (5.3)	799/13 818 (5.8)	0.92 (0.83-1.02)
Stroke	27 758	160/13 943 (1.1)	136/13 815 (1.0)	1.17 (0.93-1.47)
Intracranial bleeding	27 606	122/13 863 (0.9)	98/13 743 (0.7)	1.23 (0.95-1.61)
Major bleeding	27 606	303/13 863 (2.2)	217/13 743 (1.6)	1.39 (1.17-1.66)
Minor bleeding	26 906	978/13 514 (7.2)	778/13 392 (5.8)	1.31 (1.18-1.45)
At 30 d				
Reinfarction	26 119	422/13 122 (3.2)	621/12 997 (4.8)	0.66 (0.58-0.75)
Death	27 758	921/13 940 (6.6)	990/13 818 (7.2)	0.92 (0.84-1.01)
Stroke	25 453	154/12 880 (1.2)	150/12 753 (1.2)	1.02 (0.81-1.28)

Abbreviations: CI, confidence interval; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.
[a] No statistical significant heterogeneity for any outcome.

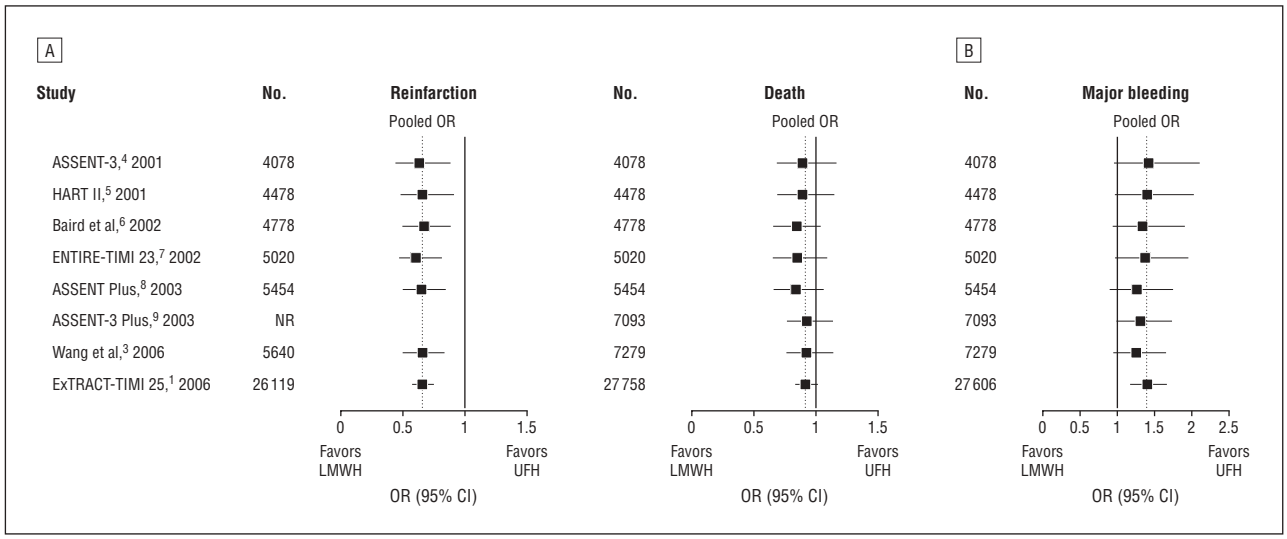

Figure. Cumulative meta-analysis of randomized trials comparing LMWH with UFH showing reinfarction and death at 30 days (A) and major bleeding during hospitalization or at 7 days (B). ASSENT indicates Assessment of the Safety and Efficacy of a New Thrombolytic Regimen; CI, confidence interval; ENTIRE-TIMI 23, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy–Thrombolysis in Myocardial Infarction 23; ExTRACT-TIMI 25, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction; HART II, Second Trial of Heparin and Aspirin Reperfusion Therapy; LMWH, low-molecular-weight heparin; OR, odds ratio; and UFH, unfractionated heparin.

mates of the efficacy and safety of LMWH compared with UFH in patients with STEMI treated with thrombolysis.

Daniel J. Quinlan, MBBS
John W. Eikelboom, MBBS, MSc, FRACP

Correspondence: Dr Quinlan, Department of Radiology, King's College Hospital, Denmark Hill, London SE5 9RS, England (dan.quinlan@consultoberon.com).

Author Contributions: *Study concept and design:* Quinlan and Eikelboom. *Acquisition of data:* Quinlan and Eikelboom. *Analysis and interpretation of data:* Quinlan and Eikelboom. *Drafting of the manuscript:* Quinlan and Eikelboom. *Critical revision of the manuscript for important intellectual content:* Quinlan and Eikelboom. *Statistical analysis:* Quinlan and Eikelboom. *Administrative, technical, and material support:* Quinlan and Eikelboom. *Study supervision:* Quinlan and Eikelboom.
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1. Antman EM, Morrow DA, McCabe CH, et al; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354(14):1477-1488.
2. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. 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(25):3855-3867.
3. Wang XK, Zhang Y, Yang CM, Wang Y, Liu GY. Use of unfractionated heparin and a low-molecular-weight heparin following thrombolytic therapy for acute ST-segment elevation myocardial infarction. *Clin Drug Investig*. 2006; 26(6):341-349.
4. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358(9282): 605-613.
5. Ross AM, Molhoek P, Lundergan C, et al; HART II Investigators. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: Second Trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation*. 2001;104(6):648-652.
6. Baird SH, Menown IBA, McBride SJ, Trouton TG, Wilson C. Randomized comparison of enoxaparin with unfractionated heparin following fibrinolytic therapy for acute myocardial infarction. *Eur Heart J*. 2002;23(8):627-632.
7. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE–Thrombolysis in Myocardial Infarction (TIMI) 23 trial. *Circulation*. 2002;105(14):1642-1649.
8. Wallentin L, Bergstrand L, Dellborg M, et al; ASSENT PLUS Investigators. Low molecular weight heparin (dalteparin) compared to unfractionated heparin as an adjunct to rt-PA (alteplase) for improvement of coronary artery patency in acute myocardial infarction: the ASSENT Plus study. *Eur Heart J*. 2003; 24:897-908.
9. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation*. 2003;108(2): 135-142.

Patient- and Physician-Oriented Web Sites and Drug Surveillance: Bisphosphonates and Severe Bone, Joint, and Muscle Pain

Postmarketing surveillance and the determination of the real-world safety profile of prescription drugs is arguably flawed. Recent identification of significant adverse effects associated with newly approved prescription drugs support the sometimes-held view that a new system needs to be introduced. The present voluntary system has not provided a sufficient early warning system, and some have called for active systems that probe for potential adverse effects of approved prescription drugs.[1] Patient-oriented Web sites may provide an opportunity to identify potential adverse effects early in a drug's postmarket history.

In 2005, Wysowski and Chang[2] published a letter regarding a series of case reports submitted to the Food and Drug Administration (FDA) on severe bone, joint, and muscle pain associated with the use of alendronate so-