Review: Low-molecular-weight heparin is effective and safe in the acute coronary syndromes

Wong GC, Giugliano RP, Antman EM. **Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention.** JAMA. 2003;289:331-42.

QUESTION

In patients with acute coronary syndromes (ACSs), is low-molecular-weight heparin (LMWH) as effective and safe as unfractionated heparin (UFH)?

DATA SOURCES

Studies were identified by searching MEDLINE (1990 to 2002), lists of conference abstracts, and bibliographies of relevant studies; and by contacting experts and pharmaceutical companies.

STUDY SELECTION

Selected studies included randomized controlled trials (RCTs) that compared LMWH with UFH or placebo for ACS (including ST-elevation myocardial infarction [STEMI] and unstable angina/non–ST-elevation myocardial infarction [UA/NSTEMI]).

DATA EXTRACTION

Data were extracted on methods, participant numbers, interventions, and outcomes.

MAIN RESULTS

4 large RCTs compared LMWH with UFH in UA/NSTEMI; 2 of these RCTs (7081 patients) showed that enoxaparin was more effective than UFH at 14 days for the combined endpoint of death, MI, and recurrent ischemia with or without revascularization.

For the initial medical management of UA/NSTEMI, 2 RCTs compared LMWH plus glycoprotein (GP) IIb/IIIa inhibitor with UFH plus GP IIb/IIIa inhibitor and generally showed similar rates of ischemic events at 30 days. The rates of major hemorrhage were low in the LMWH and GP IIb/IIIa groups (range 0.3% to 1.8%) at 96 hours to 30 days.

For STEMI, 10 RCTs compared LMWH with control (UFH or placebo) after fibrinolytic therapy. Mortality at 30 days did not differ in 1 trial (7.1% vs 8.2%). 2 RCTs evaluated the 30-day composite endpoint of death, in-hospital reinfarction, or refractory ischemia. 1 trial found a significant benefit with LMWH (11.4% vs 15.4%, $P < 0.001$), and the other trial found no difference (14.2% vs 17.4%, $P = 0.08$). The rate of death, reinfarction, or rehospitalization at 3 months was reduced with LMWH in 1 RCT (26% vs 36%, $P = 0.04$). Most RCTs showed similar bleeding rates between the LMWH and control groups.

CONCLUSION

In patients with acute coronary syndromes, low-molecular-weight heparin is as safe and effective as unfractionated heparin.

Source of funding: No external funding.

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COMMENTARY

Wong and colleagues provide a systematic review of trials comparing LMWH and UFH in patients with ACS. In patients with UA/NSTEMI, enoxaparin reduced ischemic events more than UFH. Major bleeding was not increased even among those patients proceeding to percutaneous coronary intervention (PCI). Achieving this in practice requires appropriate weight-based dosing, meticulous attention to the timing of PCI, sheath removal relative to the last dose of LMWH, and optimal use of closure devices.

In combination with GP IIb/IIIa inhibitors, patients with UA/NSTEMI have no clear benefit from LMWH compared with UFH but also do not have increased major bleeding. In the PCI setting, administering a GP IIb/IIIa inhibitor to a patient with UA/NSTEMI who has received LMWH does not seem to increase bleeding risk. Thus, among patients with UA/NSTEMI who have no contraindication to antithrombin therapy, LMWH, in particular enoxaparin, is superior to UFH for reducing ischemic events without increasing bleeding. Although a rapid point-of-care assay for enoxaparin has been developed, the accuracy of weight-based dosing and attention to the timing of invasive procedures with regard to supplemental doses of LMWH and sheath removal makes monitoring largely unnecessary.

In patients with STEMI receiving thrombolytic therapy, the use of adjunctive LMWH, compared with UFH, lowers the risk for recurrent ischemic events without increased risk for major bleeding in patients < 75 years of age. In the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial (1), patients > 75 years of age had a greater risk for intracranial hemorrhage if they received enoxaparin than if they received UFH. Ideally, most patients with STEMI would proceed expeditiously to primary coronary intervention. Where this is not feasible, thrombolytic therapy should be given to patients without contraindications. Adjunctive therapy with LMWH seems more beneficial and safe than UFH in patients < 75 years of age.

Enoxaparin is presently the preferred antithrombin agent in patients with UA/NSTEMI. Until additional studies in patients with STEMI or having PCI with adjunctive thienopyridines or GP IIb/IIIa inhibitors are completed, adoption of LMWH in these settings requires careful patient selection based on available data. Even as LMWHs receive ever-broader clinical application in ACS, the direct thrombin inhibitor bivalirudin is being studied in patients with ACS. If the results seen with bivalirudin in PCI are a harbinger for the ACS arena, the next generation of optimal antithrombin therapy may be on the horizon.

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Reference

1. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet. 2001;358:605-13.