
The Use of Low-Molecular-Weight Heparins in Acute Coronary Syndromes

EBEM Commentator
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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Magee KD, Sevcik W, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes (Cochrane Review). In: *The Cochrane Library*. Issue 1. Oxford, United Kingdom: Update Software; 2004.

The *Annals'* EBEM editors helped prepare the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To compare the effects of low-molecular-weight heparin with unfractionated heparin for the treatment of patients with acute coronary syndromes.

DATA SOURCES

A broad search of MEDLINE, EMBASE, and CINAHL was conducted, as well as a search of CENTRAL, the controlled clinical trials database of the Cochrane Collaboration. The reviewers searched the bibliographies, contacted trialists, and searched conference proceedings for additional

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published and unpublished studies. Pharmaceutical industry representatives were contacted to determine if unpublished studies that met the inclusion criteria were available. The review is considered updated to November 2002.

STUDY SELECTION

Randomized controlled trials were included if they compared subcutaneous low-molecular-weight heparin to intravenous unfractionated heparin and involved adult patients (>18 years) with acute coronary syndromes (unstable angina or non-ST-segment elevation myocardial infarction) requiring treatment within 72 hours of presentation. For this review, unstable angina was defined as typical chest pain lasting at least 10 minutes within 72 hours of presentation with either historical, electrocardiographic, or angiographic evidence of underlying ischemic heart disease. Non-ST-segment elevation myocardial infarction was defined as chest pain without ST-segment elevation and elevation of cardiac enzymes. The primary outcome was death; however, other secondary outcomes included myocardial infarction, recurrent angina, revascularization, and side effects (major or minor bleeding and thrombocytopenia).

DATA EXTRACTION AND ANALYSES

Two reviewers independently selected articles for inclusion, evaluated methodological quality of the studies and abstracted the data. Continuous variables were reported as weighted mean difference (WMD), and dichotomous variables were reported as relative risk (RR), both with associated 95% confidence intervals (CIs). A fixed effects or random effects model was used, based on the study's heterogeneity.

MAIN RESULTS

From a total of 27 abstracts, 7 articles were included in this review involving 11,092 patients and 4 different low-molecular-weight heparins. Overall, low-molecular-weight heparins did not reduce deaths in patients with acute coronary syndromes compared with unfractionated heparin (RR 1.00, 95% CI 0.69 to 1.44). When the data from all

follow-up periods are combined for myocardial infarction, low-molecular-weight heparin shows a benefit compared with unfractionated heparin (RR 0.83, 95% CI 0.70 to 0.99). Low-molecular-weight heparin showed a trend toward preventing recurrent angina that was not statistically significant in the subacute phase ($n=7,218$) or overall (RR 0.81, 95% CI 0.65 to 1.00; and RR 0.83, 95% CI 0.68 to 1.02, respectively). Patients treated with low-molecular-weight heparin had fewer revascularization procedures compared with those treated with unfractionated heparin (RR 0.88, 95% CI 0.82 to 0.95). The risk of major bleeding was similar between treatment groups (RR 1.00, 95% CI 0.8 to 1.24). Patients receiving low-molecular-weight heparin experienced the same incidence of minor bleeding compared with unfractionated heparin (RR 1.40, 95% CI 0.68 to 2.90). Thrombocytopenia was a rare event, occurring in only 1.5% of patients; however, significantly less thrombocytopenia occurred in patients receiving low-molecular-weight heparin (RR 0.64, 95% CI 0.44 to 0.94).

CONCLUSION

The use of low-molecular-weight heparin instead of unfractionated heparin in unstable angina and non-ST-segment elevation myocardial infarction (acute coronary syndromes) will decrease the risk of recurrent myocardial infarction and recurrent angina, lower the number of revascularization procedures performed, and reduce the incidence of thrombocytopenia. At the same time, the incidence of major or minor bleeding will remain the same.

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COMMENTARY: CLINICAL IMPLICATION

Chest pain is a common cause for presentation to emergency departments (EDs) in North America. Acute coronary syndromes (unstable angina and non-ST-segment elevation myocardial infarction) represent serious diagnostic considerations in patients with chest pain and have a reasonably high mortality. The ED is often the initial point of contact with the health care system for these patients, and many patients are hospitalized for these events. The National Center for Health Statistics reports

1,433,000 hospitalizations for unstable angina or non-ST-segment elevation myocardial infarction in the United States in 1996.¹

Initial assessment usually includes history and physical examination, laboratory investigation, radiography, and ECG. Treatment of acute coronary syndromes is generally aimed at reducing myocardial oxygen demand while maximizing arterial oxygen supply. Anti-ischemic therapy includes the use of oxygen, aspirin, morphine, nitroglycerin, β -blockers, and calcium channel antagonists.² The use of intravenous unfractionated heparin for the acute management of unstable angina/non-ST-segment elevation myocardial infarction was first introduced in 1982.³ It is now a standard approach to therapy in high-risk patients²; however, its use is time-consuming, complicated, and associated with certain adverse events (eg, bleeding, heparin-induced thrombocytopenia), resource implications (eg, frequent monitoring, nursing time, inconvenience to clinicians), and costs (eg, equipment, salaries, monitoring).⁴ The development and marketing of a wide range of low-molecular-weight heparins has been effective in other thrombotic diseases, such as venous thromboembolism,⁵ and holds promise for acute coronary syndromes.

This Cochrane review includes all relevant clinical trials that compare low-molecular-weight heparin to unfractionated heparin in high-risk patients with acute coronary syndromes. The included articles defined "high risk" somewhat differently; however, in summary, these patients had chest pain with one of the following: positive cardiac enzymes, ECG changes, and/or a documented past history of ischemic heart disease. The authors of the review conclude that early treatment with low-molecular-weight heparin offers certain advantages in patients with acute coronary syndromes. For example, although the evidence does not suggest that low-molecular-weight heparins improve mortality from this disease, there are tangible benefits with respect to acute myocardial infarction, recurrent angina, and the need for revascularization procedures. Moreover, the use of this agent is safe and is associated with fewer side effects than the current treatments. Although costs are not addressed in this review, and up-front costs are considerable with low-molecular-weight heparin, the improved outcomes, decreased laboratory testing, and decreased nursing time suggest reduced costs as well.

Unfortunately, many different agents were investigated, making the interpretation of results problematic. Although all low-molecular-weight heparins have a similar mechanism of action and appear to have a class effect, it is not

possible to determine the superiority of one particular agent without head-to-head comparisons. The optimal timing of low-molecular-weight heparin administration also remains unclear. In this review, low-molecular-weight heparin was given within 24 to 72 hours of the onset of symptoms. It is possible that low-molecular-weight heparin may provide greater benefit if administered within the first few hours of symptom onset in the ED. This systematic review did not assess the efficacy or safety of low-molecular-weight heparin in combination with glycoprotein IIb/IIIa inhibitors.

TAKE HOME MESSAGE

Low-molecular-weight heparins perform as well as unfractionated heparin in patients presenting to the ED with acute coronary syndromes. Low-molecular-weight heparin must be reserved for those patients with either non-ST-segment elevation myocardial infarction or high-risk unstable angina. Large, randomized, double-blind, controlled trials are required to determine the optimum timing of therapy and whether one preparation of low-molecular-weight heparin performs better than others.

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EBEM TEACHING POINT

Composite endpoints. Most trials in this review reported composite endpoints. Composite endpoints represent derived outcome measures where individual events (in this case, death, myocardial infarction, recurrent angina, etc) are added to reach a summary event rate. These composite endpoints are often reported in cardiovascular, neurovascular, and arthritis studies. Concerns have been raised that this method of reporting can be misleading because it implies all individual endpoints are influenced equally when, in fact, only the most frequent endpoint (ie, the softest endpoint) contributes most heavily to the composite endpoint.⁶ Conversely, with respect to coronary artery disease in particular, others suggest that intermediate outcomes used in a composite outcome are acceptable when they are clinically meaningful and share the same pathophysiologic basis.⁷ Moreover, composite outcomes that include mortality and important intermediate endpoints

allow for comparisons of new regimens, using much smaller trials than the so-called megatrials.⁸ Irrespective of these arguments, readers should be aware of this controversy and attempt to review data for all primary and secondary endpoints before using composite endpoints to reach their treatment decision.

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