The Use of Antithrombotics for Acute Coronary Syndromes in the Emergency Department: Considerations and Impact

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Evidence-based guidelines for the management of acute coronary syndromes (ACS) identify a central role for unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). A recent study has suggested that interchanging between UFH and LMWH during the course of treatment may be associated with a worse outcome than continued therapy with either form of heparin. Because this has important implications for physicians in the emergency room, this review examines the current evidence for the efficacy and safety of heparins in ACS. In patients with acute myocardial infarction, several studies have shown that LMWHs represent an effective alternative to UFH as an adjunct to thrombolytic therapy and are not associated with an increased risk of major bleeding. In patients with unstable angina or non–ST-segment elevation myocardial infarction, the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events) and TIMI 11B (Thrombolysis in Myocardial Infarction 11B) trials have shown that the LMWH enoxaparin significantly reduces the risk of cardiovascular events, compared with UFH, whereas other trials have shown that the combination of enoxaparin and a glycoprotein IIb/IIIa antagonist is not associated with an excess risk of bleeding. Recently, newer agents such as fondaparinux and bivalirudin have shown equivalent efficacy to the heparins with less bleeding and appear clinically attractive. Care paths for the use of antithrombotic therapy in patients with ACS are presented based on current US management guidelines and available clinical evidence.

Current evidence-based guidelines published by the American College of Cardiology and the American Heart Association (ACC/AHA) include a central role for antithrombotic therapy with heparins in the management of patients with acute coronary syndromes (ACS).[1,2] The guidelines for the management of acute myocardial infarction (MI) give a class I recommendation (a recommendation based on multiple randomized trials or meta-analyses) that either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) should be used in patients at high risk of systemic embolic events, and a class IIa recommendation (some conflicting evidence, but benefits are considered to outweigh risks) for the use of such treatment for at least 48 hours in all patients without contraindications who do not receive thrombolytic therapy.[1] Similarly, guidelines for the management of unstable angina (UA) or non–ST-segment elevation MI (NSTEMI) give a class I recommendation for the use of UFH or LMWH in addition to antiplatelet therapy in such patients, and in addition to aspirin and a glycoprotein (GP) IIb/IIIa inhibitor in patients undergoing percutaneous coronary intervention (PCI).[2] The latter guidelines also include a class IIa recommendation that the LMWH enoxaparin is preferable to UFH in such patients, unless coronary artery bypass graft (CABG) surgery is planned within 24 hours.[2]

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These recommendations reflect the findings of well-designed randomized trials of heparin use in patients with ACS during the last decade, which have clearly shown that such treatment can reduce the mortality and morbidity associated with ACS. An interesting finding, however, has arisen in the recent SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial,[3] which compared the outcome of treatment using enoxaparin with UFH in patients with UA or NSTEMI who were scheduled to undergo early invasive therapy. The protocol specified that patients could be enrolled even if they had already received UFH or LMWH before randomization, and 75% of enrolled patients did receive such treatment. Among these patients, there was some evidence that those who received both UFH and LMWH (ie, those who were randomized to receive UFH after previously receiving LMWH, or vice versa) had a worse outcome than those who received either drug alone (Table 1). In particular, the number of patients requiring blood transfusions was approximately twice as high among patients who received both drugs compared with those who received only one (Table 1). This finding may have important implications for emergency room physicians, who often represent the first point of contact with the health care system and are the first prescribers for patients with ACS. The primary message of this study was that changing anticoagulant in the middle of an episode of ACS is not advisable.

In this article, published randomized trials that have compared anticoagulants in patients with ACS are reviewed to assist physicians in the emergency room in making informed treatment decisions about the choice of anticoagulant to use in such patients.

Safety and Efficacy of Anticoagulants in Patients with ACS

Numerous studies have compared UFH and LMWHs in the treatment of patients with ACS, including those with acute MI (Table 2),[4-11] and those with UA or NSTEMI (Table 3).[12-27] In this review, major clinical trials are discussed in detail with additional reference to other randomized studies. Most studies have focused upon the use of enoxaparin, but dalteparin, nadroparin, and tinzaparin have also been evaluated.

Table 1. Outcome Among Patients in the SYNERGY Trial who Received Prerandomization Treatment with Either Enoxaparin or UFH and were Subsequently Randomized to Receive Either the Same or the Alternative Therapy[3]

	Enoxaparin	UFH
No crossover		
Patients (n)	4400	4780
Death/MI at 30 d (n [%])	593 (13.5)	677 (14.2)
Crossover		
Patients (n)	593	205
Death/MI at 30 d (n [%])	103 (17.4)	45 (22.0)
Any transfusion (n [%])		
No crossover	671 (15.3)	724 (15.1)
Crossover	179 (30.2)	72 (35.1)

For enoxaparin, the crossover–no crossover hazard ratio, with 95% CI, was 0.95 (0.85-1.06); for UFH, the hazard ratio was 0.76 (95% CI, 0.53-1.09).

Patients with Acute MI

Three major trials, ASSENT-3 (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3),[4] ASSENT-3 PLUS (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 PLUS),[5] and ExTRACT-TIMI 25 (The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment, Thrombolysis in Myocardial Infarction-Study 25),[6] have investigated the use of LMWHs as an adjunct to thrombolytic therapy in patients with acute MI (Table 2). The use of LMWH vs UFH in patients with acute MI has also been compared in several other studies including HART II (second trial of Heparin and Aspirin Reperfusion Therapy),[7] ASSENT-PLUS (Assessment of the Safety and Efficacy of a New Thrombolytic Agent),[8] ENTIRE-TIMI 23 (Enoxaparin and TNK-tPA With or Without GP IIb/IIIa Inhibitor as Reperfusion Strategy in ST Elevation MI—Thrombolysis in Myocardial Infarction 23),[9] and TETAMI (Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction in Patients Ineligible for Reperfusion).[10]

The ASSENT-3 trial enrolled 6095 patients and compared the efficacy and safety of enoxaparin, abciximab, and UFH in patients receiving tenecteplase.[4] Enoxaparin was associated with a significant reduction in the incidence of 30-day death, in-hospital MI, or refractory ischemia compared with UFH (11.4% vs 15.4%; $P < .001$; relative risk, 0.74; 95% confidence interval [CI], 0.63-0.87). Importantly, the reduced risk of