Fractionating Heparins and Their Clinical Trial Data—Something for Everyone

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Heparin, a glycosaminoglycan of varying polysaccharide units and molecular weights, has been shown to reduce ischemic events beyond that of aspirin alone in the setting of an acute coronary syndrome (ACS). This benefit translated into a class I indication for unfractionated heparin in the 2000 American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines for non–ST-segment elevation ACS. Unfractionated heparin has several known limitations, however, including a narrow therapeutic window, poorly predictable kinetics, platelet activation, and inability to inhibit clot-bound thrombin.

In comparison, enoxaparin, a low-molecular-weight heparin (LMWH), has a higher anti-factor Xa–anti-factor IIa ratio, thereby reducing some of these limitations. For intermediate and longer-term administration as part of medical therapy, enoxaparin has been considered particularly convenient and cost minimizing because it can be given subcutaneously twice daily without the need for routine monitoring. Based on several LMWH studies, including 2 with enoxaparin (ESSENCE and TIMI-11B) showing a moderate benefit over unfractionated heparin, LMWH and unfractionated heparin have shared the class I indication as alternatives to one another.

An accumulation of evidence and weight of evidence prompted an update to the prior ACC/AHA guidelines within 2 years. The current (2002) guidelines moved the level of evidence for unfractionated heparin and LMWH to the highest rank (level A), and enoxaparin was made possibly preferable (class IIa) to unfractionated heparin. Even with this update and upgrade, more key questions emerged for enoxaparin since simultaneous advancements in the treatment of patients with ACS demonstrated the benefits of platelet glycoprotein (Gp) IIb/IIIa inhibitors and an early invasive strategy in reducing ischemic events. While observational and small open-label studies suggested that the combination of enoxaparin and Gp IIb/IIIa inhibitors with or without an early invasive strategy was not associated with increased bleeding risks when compared with historical controls, data from large-scale randomized clinical trials were lacking. With this in mind, and appreciating interventional cardiologists’ concerns regarding the inability to rapidly monitor or fully reverse the anticoagulant effects of enoxaparin, the ACC/AHA guidelines suggested an alternative approach: the use of LMWH prior to invasive procedures (ie, “upstream”) with a switch to unfractionated heparin for procedural anticoagulation while withholding the dose of enoxaparin prior to the procedure. Soon thereafter, and to assess the contemporary safety and efficacy of enoxaparin relative to unfractionated heparin (or more specifically whether the benefits of upstream enoxaparin over unfractionated heparin would be affected by concomitant Gp IIb/IIIa inhibitors or an early invasive strategy), the “A phase” of the A to Z and SYNERGY trials were forged.

The results of these trials, presented in this issue of JAMA, advance the current understanding and potential future role of enoxaparin in the management of non–ST-segment elevation ACS. From the A phase of the A to Z trial, Blazing and colleagues report the outcome of nearly 4000 patients randomized to receive enoxaparin or unfractionated heparin therapy superimposed on a background of tirofiban and aspirin. They report that the primary end point (a 7-day composite of death, myocardial infarction [MI], or refractory ischemia) occurred in 8.4% of patients assigned to receive enoxaparin vs 9.4% assigned to receive unfractionated heparin (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.71-1.08). The authors conclude that enoxaparin is an effective, noninferior alternative to unfractionated heparin for treatment of ACS.

In the SYNERGY trial, Mahaffey and colleagues bridged upstream and inpatient anticoagulation therapy by randomizing more than 10000 high-risk patients with ACS undergoing an early invasive strategy to receive enoxaparin or unfractionated heparin. They found that the primary end point (a 30-day composite of death or MI) occurred in 14.0% of patients assigned to receive enoxaparin vs 14.5% assigned to receive unfractionated heparin (HR, 0.96; 95% CI, 0.86-1.06). The authors also conclude that enoxaparin was not superior but was noninferior to unfractionated heparin.

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See also pp 45, 55, and 89.
In a third article, Peterson and colleagues\(^9\) report a meta-analysis combining summary data from older studies with these 2 new trials and including nearly 22,000 patients with ACS randomized to receive enoxaparin or unfractionated heparin. The authors report a significant reduction in the 30-day composite of death or MI with enoxaparin in the overall trial populations (odds ratio, 0.91; 95% CI, 0.83-0.99) and particularly among those receiving no prerandomization antithrombin therapy (odds ratio, 0.81, 95% CI, 0.70-0.94). The authors conclude that enoxaparin is superior to unfractionated heparin in preventing the 30-day occurrence of death or MI and is similar to unfractionated heparin with respect to frequency of blood transfusion and major bleeding.

These 2 new trials and the meta-analysis provide plenty of material for opposing viewpoints and interpretations. Indeed, there is something for everyone. Had the “A” portion of A to Z or SYNERGY shown enoxaparin to be superior to unfractionated heparin, as some had expected and many had hoped, commentators would be giving accolades instead of point-counterpoint perspectives. Likewise, a meta-analysis including older and smaller studies would not be needed to defend the benefits of enoxaparin.

On the other hand, these new trials present their own complexities enticing clinicians to fractionate their results. For example, roughly two thirds of patients were already receiving LMWH or unfractionated heparin before being enrolled, such that prerandomization crossover was double that seen in prior trials. In SYNERGY, the largest and most contemporary trial, the hazard ratio for 30-day death or MI with enoxaparin vs unfractionated heparin changes from 0.96 to 0.83 when shifting focus from the overall cohort to the minority of patients who received no prerandomization therapy. However, the odds ratio for TIMI major bleeding with enoxaparin correspondingly changes from 1.17 to 1.45 for these same cohorts. As such, proponents of enoxaparin as a cornerstone of anticoagulant therapy in ACS now have more evidence that this drug is a reasonable alternative to unfractionated heparin even when combined with contemporary strategies including Gp IIb/IIIa inhibitors and an early percutaneous coronary revascularization. For those preferring unfractionated heparin, these studies suggest that enoxaparin provides less benefit than previously observed, perhaps due to a shortened interval of ischemic risk between hospital admission and coronary revascularization. The residual value of enoxaparin may be additionally offset by bleeding in the era of progressively higher-risk patients, polypharmacy anticoagulation, and arteriotomy closure devices during invasive cardiac procedures.

Adding more fuel to the subgroup-analysis controversy, cardiologists switched open-label therapies before coronary revascularization (postrandomization crossover) in nearly 800 patients in the SYNERGY trial. There may be several reasons this happened, but it does suggest that there remains a contingency of interventionalists who are hesitant to use enoxaparin in the cardiac catheterization laboratory. While this group of crossover patients likely has confounding factors precluding certainty in the interpretation of these data, their markedly higher rate of adverse events is striking as compared with those who stayed with their original treatment assignment. The 30-day occurrence of death or MI increased by one third (13.9% to 18.5%), and the percentage of patients receiving blood transfusions more than doubled (15.2% to 31.5%) when late crossover occurred.

Considering the concerns of interventional cardiologists, enoxaparin has some limitations during percutaneous revascularization procedures, particularly among some patients with ACS. Ischemic cardiac events have been noted to occur more frequently among those with particularly low anti-Xa levels. Montalescot et al\(^{10}\) reported underanticoagulation (anti-Xa level <0.5 IU/mL) in 8.1% of 755 consecutive patients with ACS receiving enoxaparin, and the corresponding 30-day occurrence of death or MI was several times higher than for those with adequate anti-Xa levels (19.7% vs 5.8%; P<.001). The distribution of anti-Xa levels ranges 2- to 3-fold in a treated ACS population,\(^{11}\) and detecting the extent of anticoagulation during some coronary interventions is desirable. Yet without monitoring enoxaparin in SYNERGY, no procedural differences in ischemic events were observed between the study groups. Enoxaparin does have a dose-response effect regarding bleeding, and this has been noted in the TIMI-11A\(^{12}\) and ELECT\(^{13}\) studies.

How might cardiologists and other physicians caring for patients with ACS interpret the findings from A to Z and SYNERGY relative to other major trials and in the context of the current ACC/AHA guidelines? Several recent studies, such as ISAR-COOL, FRISC-2, and TACTICS,\(^{14-16}\) have either formed the supporting basis or provided additional evidence for the benefit of early coronary revascularization among high-risk patients with ACS. Each trial randomized patients to an initial conservative vs an early invasive strategy and has shown a relative risk reduction in 30-day death or MI in the invasive group ranging from 33% to 49%. Importantly, the occurrence of adverse events abated soon after the interventional procedure was completed. This has been observed in several studies and suggests that the benefits of potent antithrombotic therapy are most evident prior to and during percutaneous coronary revascularization.

With this in mind, the early benefits seen for reducing adverse events in the ESSENCE and TIMI-11B trials fit well with those of A to Z and SYNERGY. As reported by Antman and colleagues in their meta-analysis of ESSENCE and TIMI-11B,\(^7\) the absolute reduction in death or MI in the first 48 hours of study with enoxaparin was 0.4%. If percutaneous revascularization were to occur at that time or sooner, it is plausible little or no further separation in the event curves would be seen between LMWH and unfractionated heparin treatments. This interpretation may parallel SYNERGY
wherein the absolute reduction in death or MI with enoxaparin was 0.8% and 0.5% at 48 hours and 30 days, respectively. Taking these trials into perspective, enoxaparin and its longer half-life appear superior as an upstream therapy. On the other hand, when the interval of prerevascularization therapy is diminished for high-risk patients with ACS, the interval of potential benefit is minimized as well. Finally, enoxaparin is not inexpensive, and its cost-minimizing impact may also be attenuated in contemporary ACS practice should patients need only 24 hours of therapy before undergoing coronary revascularization.

Both the A to Z and SYNERGY trials provide evidence that enoxaparin remains a reasonable alternative to unfractionated heparin in contemporary ACS treatment. Enoxaparin has several unique benefits and apparently few limitations. From SYNERGY, the numbers needed to treat with enoxaparin to prevent an occurrence of death or MI at 30 days and to produce a TIMI major bleeding event are 184 and 68, respectively. It will be interesting to see if these latest mega-trials affect the use of enoxaparin and the associated guidelines related to non–ST-segment elevation ACS.

REFERENCES