ANALYSIS AND CLINICAL IMPLICATIONS OF THE SYNERGY TRIAL

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ABSTRACT

The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors) trial is the latest in a series of landmark studies comparing the safety and efficacy of enoxaparin to unfractionated heparin (UFH) in patients with unstable angina and non–ST-segment elevation myocardial infarction. This large, multicenter, open-label study provides important information on the use of anticoagulant therapies in the current clinical setting that promotes earlier and more aggressive interventions and the use of concomitant antiplatelet therapies. This article briefly reviews the history of major clinical trials comparing enoxaparin to UFH, in an attempt to place the rationale and study design of SYNERGY in perspective. The strengths and weaknesses of this study, in addition to the clinical implications for pharmacists and physicians, are discussed. Several factors go into the decision of which anticoagulant therapy to use, and some cardiologists are more comfortable with older, established therapies, such as UFH. Enoxaparin has important advantages over UFH in terms of ease of administration and perhaps cost. However, the bleeding risk in certain patient populations must be considered. Studies, such as SYNERGY, help to illuminate best practices for the pharmacist and clinician to help them make the most appropriate therapy choice in each particular case.

A HISTORY OF ENOXAPARIN VERSUS UNFRACTIONATED HEPARIN

To understand the rationale for and clinical impact of the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors) trial, it is useful to briefly review the evolution of clinical data on enoxaparin versus unfractionated heparin (UFH). Two large clinical trials compared enoxaparin with UFH in the setting of predominantly conservative strategies for management of acute coronary syndrome (ACS): the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events; n = 3171) and the TIMI (Thrombolysis in Myocardial Infarction; n = 3910) 11B trials.1,2 A meta-analysis of the TIMI-IIB and ESSENCE Studies showed significant reductions with enoxaparin versus UFH in the composite endpoint of death or myocardial infarction (MI) by approximately 20% within 48 hours; this treatment benefit with enoxaparin was noted by 48 hours and through all time points through study end (day 30 and day 43, respectively).3 Formal recommendations for enoxaparin in the treatment of unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI) were then included in the updated guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC).4 After these initial positive results, the clinical community remained hesitant to combine enoxaparin with the emerging glycoprotein (GP) IIb/IIIa receptor antagonists. The ACUTE (Antithrombotic Combination Using Tirofiban and Enoxaparin) II trial compared treatment with enoxaparin plus GP IIb/IIIa inhibitor versus UFH plus GP IIb/IIIa inhibitor, resulting in similar outcomes and bleeding risks between the 2 treatments.5 The INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment) study compared enoxaparin plus GP IIb/IIIa inhibitor plus aspirin versus UFH plus GP

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IIb/IIIa inhibitor plus aspirin in 746 high-risk patients with non–ST-segment elevation ACS. In this study, enoxaparin was more effective than UFH in reducing ischemia during the monitoring period and death or MI at 30 days. In addition, noncoronary artery bypass surgery-related bleeding was significantly lower, but minor bleeding was higher, with enoxaparin compared to UFH.6

The use of low-molecular weight heparin (LMWH) in combination with percutaneous coronary intervention (PCI) has become increasingly important given the study results showing the benefit of more aggressive invasive therapy for UA/NSTEMI.7,8 However, physicians were reluctant to use enoxaparin during PCI because of the inability to monitor the level of anticoagulation, incomplete reversibility with protamine, and concerns with sheath management. However, several studies have shown that enoxaparin monotherapy is safe and efficacious in the setting of elective and urgent PCI. The largest study of enoxaparin with PCI, the NICE (National Investigators Collaborating on Enoxaparin)-4 study, was an open-label, multicenter study of 818 patients undergoing elective or urgent PCI. The safety of enoxaparin plus abciximab (a GP IIb/IIIa inhibitor) was assessed relative to historic controls from 2 other trials with abciximab. Cotreatment of enoxaparin plus abciximab resulted in low rates of death or MI and non–bypass-related major bleeding.10 The CRUISE (Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin) trial compared enoxaparin plus GP IIb/IIIa inhibitor with UFH plus GP IIb/IIIa inhibitor in patients undergoing PCI and showed no significant differences between the 2 treatment groups in bleeding risk, vascular complications, or angiographic complications, including in patients receiving closure devices.11

Thus, enoxaparin has emerged as a possible preferred therapy over UFH, in many respects because of its ease of use. Perhaps its greatest attraction is eliminating the need for blood collection and laboratory analysis to determine the level of anticoagulation (as is needed for UFH monitoring). A cost analysis of the ESSENCE study aimed to identify any differences in cost between UFH and enoxaparin treatment. The analysis evaluated total and US-only cohorts of the study population. In the US cohort, enoxaparin offered significant reductions in medical resource use compared with UFH during the first 7 days for angioplasty only, but all measures of medical resource use (diagnostic cardiac catheterization, coronary artery

Table. Economic Analysis of the ESSENCE Study: Hospitalization and Medical Resource Consumption

| Initial resource consumption | US Patients | | Total ESSENCE Cohort | | |
|------------------------------|-------------|-----------------|-----------------|-----------------|
|                              | Heparin | Enoxaparin | P       | Heparin | Enoxaparin | P       |
| Diagnostic cardiac catheterization | 57% | 53% | .33 | 46% | 43% | .08 |
| PTCA | 20% | 15% | .04 | 17% | 13% | .001 |
| CABG | 14% | 12% | .51 | 11% | 11% | .6 |
| ICU LOS (days); mean ± SD | 2.5 ± 3.5 | 2.2 ± 3.0 | .2 | 3.0 ± 3.8 | 2.8 ± 3.4 | .26 |
| Total LOS (days); mean ± SD | 6.2 ± 4.9 | 5.9 ± 4.6 | .37 | 8.5 ± 6.7 | 8.2 ± 6.4 | .28 |

| Cumulative 30-day resource consumption | | |
|----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Diagnostic cardiac catheterization | 63% | 57% | .04 | 51% | 47% | .03 |
| PTCA | 22% | 18% | .08 | 18% | 14% | .003 |
| CABG | 17% | 14% | .15 | 13% | 12% | .42 |
| ICU LOS (days); mean ± SD | 2.8 ± 3.6 | 2.4 ± 3.3 | .05 | 3.2 ± 3.9 | 3.0 ± 3.5 | .16 |
| Total LOS (days); mean ± SD | 7.0 ± 5.2 | 6.5 ± 5.0 | .17 | 9.2 ± 6.9 | 8.9 ± 6.7 | .33 |

All comparisons by intention to treat.

CABG = coronary artery bypass graft; ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events; ICU = intensive care unit; LOS = length of stay; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

Adapted with permission from Mark et al. Circulation. 1998;97:1702-1707.
bypass graft (CABG), intensive care unit length of stay (ICU LOS), and total LOS showed trends in favor of enoxaparin (Table). At 30 days, significant reductions in medical resource use with enoxaparin versus UFH were observed for diagnostic catheterization, angioplasty, and ICU LOS, with trends supporting enoxaparin for the other outcomes. Cost savings with enoxaparin at 7 days were $763 compared to UFH treatment, but the difference was not significant. By day 30, the cost savings were $1172 (P = .04). The study showed complete recapture of incremental acquisition cost of enoxaparin plus cost savings of $763 and $1172 at days 7 and 30, respectively. Some of the reductions in medical resource consumption that were not significant in the US cohort were significant when the total cohort was analyzed (Table). Coronary stenting practices are different in the United States compared to other countries. We use invasive strategies more frequently, thus if the ESSENCE trial had been conducted in the United States alone, the cost advantage with enoxaparin may have been even larger (although hospital stays tend to be shorter in the United States). Estimations in time-saving for nurses were not included in the costs. The authors indicate that those types of costs are difficult to account for, thus only laboratory costs were included for monitoring costs of UFH. Therefore, the biggest effect on time/money savings for nursing resource use may be significantly underestimated.

In accordance with the wealth of data showing positive results with LMWH, a review of trials of enoxaparin versus UFH involving nearly 22,000 patients showed that enoxaparin significantly reduced the composite endpoint of death or MI at 30 days in the intent-to-treat population (ie, those patients who had received at least 1 dose of study treatment), in addition to those patients who had received no prerandomization anticoagulation therapy (in whom the rates of endpoints were significantly lower compared to UFH). The only equivalent results were in death by any cause at 30 days in the intent-to-treat population. In this review, the reduction in composite endpoint of death or MI at 30 days with enoxaparin treatment is driven mostly by preventing MI and not by the effect on death.

Therefore, the results from these and other smaller studies of enoxaparin versus UFH in different clinical settings and management strategies created support for enoxaparin as superior therapy to UFH in patients with UA/NSTEMI. Enoxaparin is easier to administer and monitor, and resource use is less costly. It may also be attractive if long-term therapy is necessary, particularly because the prothrombotic state may persist for several months after the index event of ACS and may be of benefit as a medical bridge to PCI in patients for whom invasive procedures are delayed. However, some reluctance remains among the medical community regarding using enoxaparin, especially the safety of transitioning high-risk patients with UA treated with enoxaparin to catheterization and PCI.

The concept of the SYNERGY study arose from those remaining questions regarding enoxaparin use in light of recent advances in and more aggressive use of invasive therapy and the development of adjunctive drugs, namely GP IIb/IIIa inhibitors.

**The Rationale for Synergy**

SYNERGY is 1 of 2 studies comparing enoxaparin with UFH, which were published very recently. The other study, the A-to-Z trial, was designed to assess the safety and efficacy of enoxaparin or UFH plus a GP IIb/IIIa inhibitor in phase A, then compare early initiation of an intensive statin regimen with delayed initiation of a less intensive statin regimen in patients with ACS. The SYNERGY and A-to-Z trials were designed and conducted to address remaining questions on the balance of the risk versus benefit of enoxaparin in different populations of patients with ACS (ie, low risk vs high risk) and in the current medical practice setting for ACS management. We now benefit from important advances in early invasive management strategies, coronary stent technology, and adjunctive pharmacotherapy (ie, GP IIb/IIIa inhibitors and clopidogrel). Most patients who present with UA/NSTEMI are medically managed for a period of time; they receive some anticoagulant therapy before intervention. In this setting of shorter times to invasive strategies, enoxaparin should also be compared to UFH “upstream” of catheterization.

Despite the clinical data in support of enoxaparin, the AHA/ACC guideline stopped short of unequivocally recommending enoxaparin (or LMWH in general) as a preferred therapy for UA/NSTEMI. For patients undergoing PCI, the recommendation is specifically for UFH in combination with a GP IIb/IIIa inhibitor. This caution on LMWH stems from a lack of large trials of LMWH in these clinical contexts. However, an expert consensus statement reviewed the clinical data that emerged since the guidelines were published to "formu-
late recommendations based on all available data for the use of LMWH, with and without GP IIb/IIIa receptor antagonists, and to provide seamless integration of care during the transition from medical to interventional management. The recommendations indicate LMWH therapy initiation as soon as UA/NSTEMI is identified and dose adjustments, concomitant GP IIb/IIIa receptor antagonists, and supplementation with UFH, depending on the time of catheterization after the last subcutaneous dose of LMWH (Figure 1).19

However, what about the high-risk patients who will be undergoing PCI as an early intervention? The objective of the SYNERGY study was to evaluate the efficacy and safety of enoxaparin versus UFH when administered with established therapy, including GP IIb/IIIa receptor antagonists and aspirin, in patients at high risk who present with UA/NSTEMI and were to be managed with an early invasive strategy. The study design and population (8000 patients enrolled at approximately 500 sites worldwide, which increased to 10 000 patients during enrollment) is described in Figure 2. High-risk patients were identified by 3 factors: older age, positive cardiac biomarkers, and definitive ST-segment changes. The study drug (ie, enoxaparin or UFH) was administered immediately after enrollment and continued until the patient required no further anticoagulation and at least through angiography and PCI, if performed.20

SYNERGY was an open-label study. Although double-blind studies are the preferred design of clinical trials, comparing a subcutaneous with an intravenous therapy presents obvious logistical difficulties. Other studies of treatments for ST-elevation MI were not blinded and had consistent results with other blinded studies, thus the precedent for acceptable use of an open-label design for anticoagulant therapy exists.20-23 However, bias may have been introduced in the physicians’ choices of medical therapies, the decision to perform cardiac catheterization, and physician assessment of endpoints. The alternative argument to those potential biases based on knowledge of the treatment assignment is that the data provide insight

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**Figure 1. Strategies for Transition from Medical Management to Procedural Anticoagulation**

- UA/NSTEMI identified, LMWH therapy begun
- Early invasive strategy
- Early conservative strategy with subsequent indication for emergent catheterization
- Catheterization begun within 8-12 h of last SC dose
- GP IIb/IIIa

**Figure 2. SYNERGY Trial Design**

- **High-risk patients with ACS**
  - Randomize (n = 8000)*
  - IV heparin
  - Enoxaparin

**Patient population**
- 2 of the following:
  - Age >60
  - ST ↑ or ↓
  - CK-MB or troponin

**Planned aggressive/invasive treatment**
- Cardiac catheterization
- Other therapy per AHA/ACC guidelines

**Primary endpoint:** Death or MI at 30 days

*For percutaneous coronary intervention, wait at least 30 to 60 minutes after SC injection, depending on molecular weight of the agent (30 minutes for enoxaparin, 60 minutes for dalteparin).

Insufficient data are available to guide heparinization in patients who have received only 1 dose of SC LMWH.

Fewer data are available on patients treated with SC enoxaparin and no GP IIb/IIIa receptor antagonist undergoing percutaneous coronary intervention.

If the patient had been receiving dalteparin, switch to UFH because there are no available data on transitioning from medical to interventional therapy when the last SC dose of dalteparin was administered 8 to 12 hours before percutaneous coronary intervention.

Consideration can be given to enoxaparin 0.5 mg/kg in those patients not receiving concomitant GP IIb/IIIa receptor antagonist.

ACT = activated clotting time; Enox = enoxaparin; GP = glycoprotein; IV = intravenous; LMWH = low-molecular weight heparin; SC = subcutaneous; UA/NSTEMI = unstable angina and non-ST-segment elevation myocardial infarction; UFH = unfractionated heparin.


into physician preferences for ACS management in high-risk patients.

The primary outcome measure was a composite endpoint of death or nonfatal MI during the first 30 days after randomization. Secondary outcome measures were the combined incidence of all-cause mortality, nonfatal MI, stroke, or recurrent ischemia requiring revascularization and individual components of the composite endpoint at 14 and 30 days after randomization. Other secondary outcomes include the incidence of death or nonfatal MI at 14 days and 6 months after enrollment and mortality at 1 year. The definition of an MI has varied across clinical trials, including criteria such as clinical symptoms, ECG changes, or biomarker elevations (eg, troponin I, troponin T, and creatinine phosphokinase [CK-MB]).

For this study, nonfatal MI as an endpoint is defined based on whether the patient was experiencing an MI at enrollment and on CK-MB or ECG evidence.

The trial was designed to determine if enoxaparin was superior to UFH in this setting. However, the protocol also included a contingency for a noninferiority analysis if enoxaparin was not shown to be superior to UFH. Noninferiority refers to the efficacy of a study drug falling within a predetermined margin of efficacy of the established therapy. In other words, assuming there is a range of efficacy with UFH, enoxaparin is not inferior if its efficacy falls within that range. Noninferiority is a complex statistical concept, but an important one when comparing a new experimental therapy with an established therapy. With the logistical advantages of enoxaparin, it is necessary to show whether it is superior to UFH (the established therapy) or at the very least not inferior.

Concomitant study medications included aspirin, clopidogrel, and GP IIb/IIIa inhibitors, which were determined by physician choice.

A REVIEW OF THE SYNERGY RESULTS

The efficacy results of the SYNERGY study showed that enoxaparin was not superior or inferior to UFH in this patient population. As reported in its publication, the rates of the primary endpoint of all-cause death or nonfatal MI were almost identical between the 2 treatment groups. Nor were there any differences found in rates of ischemic events during PCI. Several subgroup analyses were performed to further compare the effects of enoxaparin to UFH. The differences arose in subcohorts of patients based on prerandomization antithrombin therapy. Approximately 75% of the patients received UFH or LMWH before randomization. In patients that received no prerandomization antithrombin therapy or those patients in whom the prerandomization therapy was the same as the randomized therapy, enoxaparin treatment reduced the relative risk of death or nonfatal MI by 18%.

Switching therapies after randomization and before revascularization resulted in markedly higher adverse events and endpoints. The rate of 30-day death or MI increased by 33%, from 13.9% in patients that did not crossover to 18.5% in those patients who crossed over; blood transfusions in crossover patients also increased from 15.2% to 31.5%.

Enoxaparin-treated patients experienced more bleeding in 1 of 3 endpoints for bleeding. TIMI major bleeding was significantly higher in the enoxaparin group (9.1% vs 7.6%; \( P = .008 \)). In contrast, GUSTO-defined (Global Utilization of Streptokinase and t-PA for Occluded Arteries) bleeding was 2.7% versus 2.2% (\( P = .08 \); enoxaparin vs UFH, respectively) and transfusions were performed in 17% vs 16% of patients (\( P = .16 \); GUSTO bleeding is defined as intracranial hemorrhage/bleeding resulting in hemodynamic compromise). The study results show that the increased bleeding risk is compounded in those patients with prerandomization treatment (75% of the study population) and crossovers (ie, those patients who received UFH or LMWH before PCI). In the study publication, we discuss a series of analyses to eliminate the influence of prerandomization treatment or crossovers, with the result of no excess bleeding with enoxaparin.

The relationship between pretreatment and risk of bleeding has not been established as causal and many other factors can also come into play, such as age, renal function, coronary procedures, and adjunctive therapies. We concluded that enoxaparin is a safe and effective alternative to UFH in high-risk patients, and the observed modest excess risk of bleeding should be balanced with the advantages of convenience with enoxaparin dosing.

SYNERGY STRENGTHS AND WEAKNESSES

The results from the SYNERGY trial enable clinicians to evaluate the safety and efficacy of enoxaparin in high-risk patients with ACS treated with an aggressive early invasive strategy similar to what is currently used in many clinical settings. The large treatment groups in SYNERGY consisted of patients identified using broad
inclusion criteria. The study population was from geographically diverse areas and different clinical practice settings. Similarly, the use of GP IIb/IIIa inhibitors was not mandatory but left to physician discretion. These design strategies were useful because they offered the chance to observe physician choice of medical management strategies during PCI and as frontline therapy, to gain insight into physician preference for these types of drugs, to reduce trial costs, and to evaluate the 2 thrombin inhibitors within the complexities of current clinical practice.

The extent of prerandomization treatment and the number of patients who crossed over to a different therapy after randomization was not expected. In total, 75% of enrollees were started on antithrombin therapy before enrollment and randomization. After randomization and initiation of trial therapy, another 12% of patients assigned to the enoxaparin group received UFH during PCI and 4% vice versa. The role of such postrandomization crossovers (n = 798) in bleeding risk is difficult to assess, yet it remains an important consideration for physicians who are faced with patients already on another antithrombin therapy with which they are not comfortable and are inclined to change. The open-label design, while offering certain attractive advantages, also presented the possibility to affect choice of medical therapies, decision to perform catheterization (ie, physicians not comfortable with enoxaparin during PCI may elect to hold off on the procedure), and assessment of endpoints by knowing treatment assignment.

**CLINICAL IMPLICATIONS OF THE SYNERGY STUDY**

The SYNERGY results, in combination with a systematic overview of clinical studies with enoxaparin in close to 22 000 patients, show that enoxaparin is more effective compared to UFH in preventing the composite endpoint (death or nonfatal MI). This benefit has remained consistent across trials in patients who did not receive antithrombin therapy before randomization, and the bleeding complications through the first 7 days of treatment were similar between enoxaparin and UFH groups. Therefore, enoxaparin should remain a superior first-line agent for UA/NSTEMI, even in high-risk patients.

The SYNERGY results also tell us that antithrombin therapies should not be switched in patients with ACS because this switch appears to be associated with an increased bleeding risk and decreased clinical benefi...
antithrombotic treatment and remaining on it during PCI), enoxaparin offers distinct advantages. It is also effective and safe to transition patients treated with subcutaneous LMWH to the catheterization laboratory for coronary angioplasty. The results from this study suggest that enoxaparin is a useful alternative to UFH in patients undergoing aggressive, early intervention with concomitant antiplatelet therapy. Bleeding risk is determined by myriad factors, all of which should be considered when developing management strategies.

REFERENCES


