Efficacy and Bleeding Complications Among Patients Randomized to Enoxaparin or Unfractionated Heparin for Antithrombin Therapy in Non–ST-Segment Elevation Acute Coronary Syndromes

A Systematic Overview

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Context Antithrombin therapy has become a guidelines-recommended standard of care in the treatment of acute coronary syndromes (ACS), but recent trials comparing use of enoxaparin and unfractionated heparin in ACS have yielded less robust efficacy and safety results than have earlier trials of these antithrombin therapies.

Objective To systematically evaluate the end points of all-cause death and nonfatal myocardial infarction (MI), transfusion, and major bleeding observed in the 6 randomized controlled trials comparing enoxaparin and unfractionated heparin in treatment of ACS.

Data Sources The primary data sets for ESSENCE, A to Z, and SYNERGY were available at the Duke Clinical Research Institute. Baseline characteristics and event frequencies for TIMI 11B, ACUTE II, and INTERACT were provided by the principal investigator of each study.

Study Selection All 6 randomized controlled trials comparing enoxaparin and unfractionated heparin in non–ST-segment elevation ACS were selected for analysis.

Data Extraction Efficacy and safety end points were extracted from the overall trial populations and the subpopulation receiving no antithrombin therapy prior to randomization.

Data Synthesis Systematic evaluation of the outcomes for 21,946 patients was performed using a random-effects empirical Bayes model. No significant difference was found in death at 30 days for enoxaparin vs unfractionated heparin (3.0% vs 3.0%; odds ratio [OR], 1.00; 95% confidence interval [CI], 0.85-1.17). A statistically significant reduction in the combined end point of death or nonfatal MI at 30 days was observed for enoxaparin vs unfractionated heparin in the overall trial populations (10.1% vs 11.0%; OR, 0.91; 95% CI, 0.83-0.99; number needed to treat, 107). A statistically significant reduction in the combined end point of death or MI at 30 days was also observed for enoxaparin in the populations receiving no prerandomization antithrombin therapy (8.0% vs 9.4%; OR, 0.81; 95% CI, 0.70-0.94; number needed to treat, 72). No significant difference was found in blood transfusion (OR, 1.01; 95% CI, 0.89-1.14) or major bleeding (OR, 1.04; 95% CI, 0.83-1.30) at 7 days after randomization in the overall safety population or in the population of patients receiving no prerandomization antithrombin therapy.

Conclusion In a systematic overview of approximately 22,000 patients across the spectrum of ACS, enoxaparin is more effective than unfractionated heparin in preventing the combined end point of death or MI.

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See also pp 45, 55, 101.

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ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) and TIMI 11B (Thrombolysis in Myocardial Infarction 11B), the first large clinical trials comparing unfractionated heparin and enoxaparin in ACS, were conducted in an era of predominately conservative management strategies, and both studies demonstrated a significant reduction in the composite end point of death or myocardial infarction (MI) in patients treated with enoxaparin.7-9 Subsequent studies have been conducted in the context of a more aggressive approach to early revascularization and more frequent use of clopidogrel and glycoprotein (Gp) IIb/IIIa antagonists.3,4,10-14 The 2 most recent trials, A to Z (Aggrastat to Zocor)15 and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIB/IIa Inhibitors),16 found statistically insignificant trends toward reduction of the composite of death and MI with enoxaparin, coupled with trends toward excess bleeding. However, in both trials a larger treatment effect in reduction of ischemic events was found in patients who had not been treated with antithrombin therapy prior to randomization (approximately 25% of the enrolled patients).

The differences in the findings from the ACS trials of enoxaparin and unfractionated heparin have raised questions about the balance of risk and benefit between these antithrombin therapies. To investigate if any consistent differences in effect exist between the use of enoxaparin and unfractionated heparin across time and the evolution of treatment strategies, we performed a systematic overview of the 6 randomized controlled trials comparing these 2 antithrombin therapies in non–ST-segment elevation (NSTE) ACS.

### METHODS

#### Data Acquisition

The study designs of ESSENCE, TIMI 11B, ACUTE II (Antithrombotic Combination Using Tirofiban and Enoxaparin II), INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment), INTERACT, Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment, INTERACT, Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment, and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIB/IIa Inhibitors) have been described in detail.

#### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ESSENCE</th>
<th>TIMI 11B</th>
<th>ACUTE II*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1607</td>
<td>1564</td>
<td>1953</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>65 (56-73)</td>
<td>65 (56-73)</td>
<td>65 (56-73)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>529 (32.9)</td>
<td>530 (33.9)</td>
<td>682 (34.9)</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>78 (68-87)</td>
<td>77 (69-87)</td>
<td>77 (68-86)</td>
</tr>
<tr>
<td>Creatinine, median (IQR), mg/dL</td>
<td>NA</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>360 (22.4)</td>
<td>339 (21.7)</td>
<td>385 (19.7)</td>
</tr>
<tr>
<td>ECG changes, No. (%)</td>
<td>897 (55.8)</td>
<td>895 (57.2)</td>
<td>1611 (82.5)</td>
</tr>
<tr>
<td>Biomarker-positive, No. (%)</td>
<td>NA</td>
<td>NA</td>
<td>738 (37.8)</td>
</tr>
<tr>
<td>Pulse, median (IQR), beats/min</td>
<td>72 (63-82)</td>
<td>72 (62-83)</td>
<td>72 (64-81)</td>
</tr>
<tr>
<td>Blood pressure, median (IQR), mm Hg</td>
<td>140 (122-154)</td>
<td>140 (121-156)</td>
<td>136 (120-150)</td>
</tr>
<tr>
<td>Systolic</td>
<td>80 (70-88)</td>
<td>80 (70-90)</td>
<td>80 (70-85)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70 (61-81)</td>
<td>72 (63-82)</td>
<td>70 (70-90)</td>
</tr>
</tbody>
</table>

Abbreviations: ACUTE II, Antithrombotic Combination Using Tirofiban and Enoxaparin II; A to Z, Aggrastat to Zocor study; ECG, electrocardiographic; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events; INTERACT, Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment; IQR, interquartile range; NA, not available; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIB/IIa Inhibitors; TIMI 11B, Thrombolysis in Myocardial Infarction 11B.

*Values for age, weight, pulse, and blood pressure are mean (SD).
Acute Coronary Syndrome Treatment), A to Z, and SYNERGY have been reported elsewhere. The primary data sets for ESSENCE, A to Z, and SYNERGY were available at the Duke Clinical Research Institute. Baseline characteristics and event frequencies for TIMI 11B, ACUTE II, and INTERACT were provided by the study principal investigators and the data were confirmed by the study sponsors.

**Efficacy End Points and Populations**

The efficacy end points were all-cause death and the combined end point of death or nonfatal MI occurring within 30 days of randomization. In the primary study report for the ESSENCE trial, successful resuscitation of sudden death counted as a death, but for the purposes of our analysis only actual death in ESSENCE was used. Cause of death was not available between the 14- and 30-day end points in ACUTE II; therefore, deaths during this period in ACUTE II were presumed not to be due to MI. The frequency of MI was determined for each study using the study protocol definition. The definitions of MI for ESSENCE, TIMI 11B, ACUTE II, INTERACT, and SYNERGY have been published elsewhere, and the A to Z definition was similar to that used in SYNERGY. Briefly, the definitions of spontaneous MI incorporated a creatinine kinase-MB level of greater than the upper limit of normal (ULN) in ESSENCE, TIMI 11B, and INTERACT, and 2 or more times the ULN in ACUTE II and SYNERGY. All studies incorporated a criterion of 3 or more times the ULN in the diagnosis of MI occurring around the time of percutaneous coronary intervention (PCI) and 5 or more times the ULN in the diagnosis of peri-PCI MI. All studies also incorporated electrocardiographic definitions of MI. All efficacy end points were determined using the intention-to-treat

**Table 2. Use of Medications and Procedures**

<table>
<thead>
<tr>
<th></th>
<th>ESSENCE</th>
<th>TIMI 11B</th>
<th>ACUTE II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin</td>
<td>Unfractionated Heparin</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>No.</td>
<td>1607</td>
<td>1564</td>
<td>1953</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic catheterization</td>
<td>770 (47.9)</td>
<td>812 (51.9)</td>
<td>1029 (52.7)</td>
</tr>
<tr>
<td>PCI</td>
<td>236 (14.7)</td>
<td>292 (18.7)</td>
<td>346 (17.7)</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>198 (12.3)</td>
<td>214 (13.7)</td>
<td>117 (6.0)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1045 (65)</td>
<td>1032 (66)</td>
<td>1625 (83.2)</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>42 (2.6)</td>
<td>38 (2.4)</td>
<td>29 (1.5)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1102 (68.6)</td>
<td>1084 (69.3)</td>
<td>1437 (73.6)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>NA</td>
<td>NA</td>
<td>531 (27.2)</td>
</tr>
<tr>
<td>Statin</td>
<td>NA</td>
<td>NA</td>
<td>502 (25.7)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; NA, not available; PCI, percutaneous coronary intervention. See Table 1 footnote for expansions of trial names.

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population of each trial. Efficacy analyses were performed on the overall intention-to-treat population of the trials and the subgroup in each study that received no antithrombin therapy prior to randomization. The ACUTE II data were excluded from the second analysis because the data on the use of antithrombin therapy prior to randomization were not available for individual patients.

**Safety End Points and Populations**

The safety end points were major bleeding and transfusion. The frequency of major bleeding was determined for each patient who received any assigned study drug at any point following randomization during the study period. Several different safety analyses were performed because the definitions of major bleeding and the data collection were different between trials. Analytic approaches included using the end points occurring through day 7 after randomization and the end points occurring through the end of hospitalization. Two analyses of transfusion and major bleeding occurring through day 7 after randomization were performed. In the first, the overall safety population was analyzed; in the second, the safety population receiving no prerandomization antithrombin was analyzed. ACUTE II and A to Z did not record transfusion and major bleeding occurring through day 7 after randomization and did not assess CABG surgery–related bleeding, and therefore these trials were not included in the 7-day analyses. Three analyses of transfusion and major bleeding occurring through the end of hospitalization were performed. In the first, all the trials were included in the analysis of the overall safety population. In the second, trials that did not assess CABG surgery–related bleeding (ACUTE II and A to Z) were excluded in the analysis of the overall safety population. In the third, trials that did not assess CABG surgery–related bleeding were excluded in the analysis of the no prerandomization therapy safety population.

**Figure 1. Intention-to-Treat Population: Efficacy End Points at 30 Days**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE</td>
<td>39/1607 (2.4)</td>
<td>49/1564 (3.1)</td>
<td>0.77 (0.51-1.18)</td>
<td>0.76 (0.58-1.01)</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>66/1953 (3.4)</td>
<td>71/1957 (3.6)</td>
<td>0.93 (0.66-1.31)</td>
<td>0.97 (0.51-1.83)</td>
</tr>
<tr>
<td>ACUTE II</td>
<td>8/315 (2.5)</td>
<td>4/210 (1.9)</td>
<td>2.29 (0.56-9.43)</td>
<td>0.94 (0.73-1.20)</td>
</tr>
<tr>
<td>INTERACT</td>
<td>9/380 (2.4)</td>
<td>15/366 (4.1)</td>
<td>0.58 (0.26-1.32)</td>
<td>1.04 (0.84-1.30)</td>
</tr>
<tr>
<td>A to Z</td>
<td>47/1853 (2.5)</td>
<td>33/1765 (1.8)</td>
<td>1.36 (0.87-2.13)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>160/4982 (3.2)</td>
<td>153/4983 (3.1)</td>
<td>1.04 (0.84-1.30)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>Overall</td>
<td>329/11100 (3.0)</td>
<td>325/10645 (3.0)</td>
<td>1.00 (0.85-1.17)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE</td>
<td>94/1607 (5.8)</td>
<td>118/1564 (7.5)</td>
<td>0.76 (0.58-1.01)</td>
<td>0.94 (0.73-1.20)</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>145/1953 (7.4)</td>
<td>163/1957 (8.3)</td>
<td>0.88 (0.70-1.11)</td>
<td>0.96 (0.86-1.07)</td>
</tr>
<tr>
<td>ACUTE II</td>
<td>25/315 (7.9)</td>
<td>17/210 (8.1)</td>
<td>0.97 (0.51-1.83)</td>
<td>0.91 (0.83-0.99)</td>
</tr>
<tr>
<td>INTERACT</td>
<td>19/380 (5.0)</td>
<td>33/366 (9.0)</td>
<td>0.54 (0.30-0.96)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>A to Z</td>
<td>137/1852 (7.4)</td>
<td>138/1768 (7.9)</td>
<td>0.94 (0.73-1.20)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>696/4982 (14.0)</td>
<td>722/4982 (14.5)</td>
<td>0.96 (0.86-1.07)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>Overall</td>
<td>1116/16290 (11.0)</td>
<td>1192/10847 (11.0)</td>
<td>0.91 (0.83-0.99)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 6.50, P = .02 \) (panel A); \( \chi^2 = 6.59, P = .25 \) (panel B). Black squares indicate odds ratios (ORs); horizontal lines, 95% confidence intervals (CIs). The size of each square reflects the statistical weight of a trial in calculating the OR, and the relative sizes of the squares are accurate within each plot only. ESSENCE indicates Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events; TIMI 11B, Thrombolysis in Myocardial Infarction 11B; ACUTE II, Antithrombotic Combination Using Toroidian and Enoxaparin II; INTERACT, Integrillin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment; A to Z, Aggrastat to Zocor study; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; UFH, unfractionated heparin.
enoxaparin vs unfractionated heparin for transfusion and TIMI major bleeding occurring within 7 days of randomization and during hospitalization were estimated. While none of the safety analyses were prespecified, the consensus of the investigators was that the 7-day end point best approximated study-related bleeding because it approximated average length of stay and eliminated differences in follow-up time. The results from the trials were combined using a random-effects empirical Bayes model, as described by Hedges and Olkin. Heterogeneity was tested using the standard χ² test. The calculations were carried out using FASTPRO software.

RESULTS

Baseline Characteristics

In total, the 6 trials enrolled 21,946 patients. In comparing baseline characteristics of the trials, later trials allowed troponin as an inclusion criterion and generally included higher-risk patients by design (TABLE 1). Baseline creatinine and vital signs were similar across the trials, though median weights in the more recent trials tended to be higher.

In the more recent trials, angiography, PCI, and CABG surgery were more frequently performed, and evidence-based pharmacotherapy, including aspirin, β-blockers, angiotensin converting enzyme inhibitors, and statins, was more frequently prescribed (TABLE 2). In contrast to ESSENCE and TIMI 11B, which were conducted in an era when Gp IIb/IIIa antagonists and clopidogrel were not available, the high use of Gp IIb/IIIa antagonists was protocol-driven in ACUTE II, INTERACT, and A to Z, and administration of clopidogrel was encouraged in accordance with the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for UA/NSTEMI. In SYNERGY the use of all adjunctive therapies was encouraged according to the ACC/AHA guidelines for UA/NSTEMI, but ultimately was left to the discretion of the treating physician.

TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE</td>
<td>39/1607 (2.4)</td>
<td>0.77 (0.51-1.18)</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>41/1257 (3.3)</td>
<td>0.96 (0.62-1.49)</td>
</tr>
<tr>
<td>INTERACT</td>
<td>4/304 (1.3)</td>
<td>0.37 (0.12-1.12)</td>
</tr>
<tr>
<td>A to Z</td>
<td>18/587 (3.1)</td>
<td>1.64 (0.76-3.52)</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>37/1211 (3.1)</td>
<td>0.85 (0.56-1.32)</td>
</tr>
<tr>
<td>Overall</td>
<td>139/4966 (2.8)</td>
<td>0.88 (0.69-1.11)</td>
</tr>
</tbody>
</table>

TABLE 2. Death at 30 Days

<table>
<thead>
<tr>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>UFH</td>
</tr>
<tr>
<td>ESSENCE</td>
<td>39/1607 (2.4)</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>41/1257 (3.3)</td>
</tr>
<tr>
<td>INTERACT</td>
<td>4/304 (1.3)</td>
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<tr>
<td>A to Z</td>
<td>18/587 (3.1)</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>37/1211 (3.1)</td>
</tr>
<tr>
<td>Overall</td>
<td>139/4966 (2.8)</td>
</tr>
</tbody>
</table>

Figure 2. No Prerandomization Therapy Population: Efficacy End Points at 30 Days

Efficacy Results

In the 30-day end point data of the intention-to-treat populations there was no difference in mortality (3.0% vs 3.0%; OR, 1.00; 95% CI, 0.85-1.17) (FIGURE 1A). In patients treated with enoxaparin, there was a significant reduction in the composite end point of death or MI (10.1% vs 11.0%; OR, 0.91; 95% CI, 0.83-0.99; number needed to treat, 107) (FIGURE 1B). No heterogeneity was observed.

Analysis of the efficacy end points for patients receiving no prerandomization antithrombin therapy demonstrated a decreasing trend in mortality in favor of enoxaparin (FIGURE 2A). A robust and statistically significant reduction in the combined end point of death or MI was observed in patients treated with enoxaparin (8.0% vs 9.4%; OR, 0.81; 95% CI, 0.70-0.94; number needed to treat, 72) (FIGURE 2B).

Safety Results

No significant difference was detected through 7 days after randomization in transfusion or major bleeding in the overall safety population (FIGURE 3A and FIGURE 4A). In the population receiving no prerandomization therapy, no difference was detected in transfusion or major bleeding at 7 days after randomization (FIGURES 3B and 4B).

No significant difference was detected in the analysis of in-hospital blood transfusion (OR, 1.06; 95% CI, 0.95-1.19) or major bleeding (OR, 1.11; 95% CI, 0.81-1.32) in the analysis of the overall safety populations of all the trials. In addition, no significant differences were detected in transfusion or major bleeding in the overall safety population (FIGURE 3A and FIGURE 4A) or among those receiving no prerandomization antithrombin therapy (OR, 0.81; 95% CI, 0.68-0.98).

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difference was detected in analysis of in-hospital transfusion (OR, 1.07; 95% CI, 0.96-1.19) or major bleeding (OR, 1.07; 95% CI, 0.81-1.42) in the overall safety population of trials assessing CABG surgery–related bleeding. A modest but statistically significant increase in major bleeding was detected in the analysis of the no prerandomization therapy population during hospitalization (OR, 1.34; 95% CI, 1.06-1.70), but no difference in blood transfusion was noted (OR, 1.04; 95% CI, 0.85-1.27).

**COMMENT**

Following the demonstration of the superior efficacy and equivalent safety of enoxaparin compared with unfractionated heparin in conservatively treated patients, use of either low-molecular-weight or unfractionated heparin was specifically designated as a Class IA therapy for UA/NSTEMI ACS and enoxaparin as acceptable first-line therapy by the European Society of Cardiology guidelines. However, the management of ACS has evolved considerably in the past decade. Important advances include an early invasive management strategy, improved coronary stent technology, adjunctive pharmacotherapy, and routine use of potent antiplatelet therapy including upstream use of Gp IIb/IIIa antagonists and thienopyridines.

While the primary analyses of the A to Z and SYNERGY trials met pre-specified criteria for noninferiority, neither trial demonstrated a significant difference in the primary end point of death or MI. Compared simply, these findings appear to be inconsistent with the findings of the previous trials and meta-analyses. However, the advances in the standard of care of ACS, the differences in trial design, and the duration of prerandomization therapy all may have obscured a treatment effect. In this systematic over-

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*Figure 3. Safety Analysis: Transfusion Up to 7 Days After Randomization*

**A** Overall Safety Population

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE7</td>
<td>52/1578 (3.3)</td>
<td>0.87 (0.59-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 11B8</td>
<td>13/1938 (0.7)</td>
<td>1.17 (0.53-2.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERACT17</td>
<td>10/380 (2.6)</td>
<td>0.80 (0.35-1.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNERGY18</td>
<td>566/4775 (12.2)</td>
<td>1.03 (0.91-1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>581/8044 (7.2)</td>
<td>1.01 (0.89-1.14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B** No Prerandomization Therapy Safety Population

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE7</td>
<td>52/1578 (3.3)</td>
<td>0.87 (0.59-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 11B8</td>
<td>13/1248 (1.0)</td>
<td>1.79 (0.73-4.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERACT17</td>
<td>6/304 (2.0)</td>
<td>0.66 (0.24-1.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNERGY18</td>
<td>127/7156 (13.0)</td>
<td>0.95 (0.74-1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>208/4186 (5.0)</td>
<td>0.94 (0.77-1.16)</td>
<td></td>
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</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 5.63, P = .13$ (panel A); $\chi^2 = 1.39, P = .71$ (panel B). See Figure 1 legend for expansions of trial names and discussion of sizes of squares. UFH indicates unfractionated heparin.
domination and there was no difference in rates of transfusion. The significant 14.6% relative risk reduction in the composite of death and MI, coupled with the nonsignificant trend toward a reduction in mortality in this subgroup of patients, suggests that the effectiveness of enoxaparin may have been masked by the inclusion of patients receiving prerandomization therapy in A to Z and SYNERGY.15,16

Much has been written about the importance of cross validation when intriguing subgroups are found in a randomized trial.24 In the overall populations of A to Z and SYNERGY, switching antithrombin therapy may have attenuated the benefit and increased the bleeding risk with enoxaparin. Pharmacologically, a switch in therapy could create a gap in therapy and potentially increase the risk of ischemic events, or it could create an overlap of antithrombin effect and potentially increase the risk of bleeding. Taken in isolation, the findings can only be considered hypothesis-generating, but confirmation of the same finding in several independent studies considerably strengthens the result. The consistent treatment benefit of enoxaparin across the trials in the cohort of patients that did not receive antithrombin before randomization corroborates conclusions from previous studies that enoxaparin is superior as first-line therapy.

Limitations

Our analysis has several limitations. Systematic overviews do not replace randomized clinical trials but provide important insights through analyses of the totality of the data. The trial populations are not identical with respect to the baseline characteristics, the duration of study treatment, the time to revascularization, or the use of concomitant medical therapies in the management of UA/NSTEMI ACS. We have attempted to characterize the differences in underlying risk and concomitant therapies, and no heterogeneity in terms of treatment effect was observed. Some imprecision exists in the frequency of events, as the protocols for data collection and definitions of efficacy and safety events varied among the studies. However, the trends in the data are consistent and the definitions are similar and clinically applicable. While the analysis of the no prerandomization antithrombin therapy subgroup was not prespecified in most of the trials, in light of the findings of SYNERGY and A to Z, analysis of this subgroup of patients in other trials is warranted in order to corroborate the findings in these 2 studies. Finally, not having the individual patient data from all the trials precluded more sophisticated statistical analyses.

Conclusions

The data in this systematic overview of approximately 22,000 randomized patients comparing enoxaparin with unfractionated heparin in treatment of UA/NSTEMI ACS demonstrate that, overall, enoxaparin is more effective than unfractionated heparin in preventing the composite of death or nonfatal infarction. Major bleeding and need for transfusions associated with enoxaparin were similar to bleeding and transfusions associated with unfractionated heparin in the overall safety population through 7 days. The substantial and consistent treatment benefit in patients who had not received prior antithrombin therapy indicates that enoxaparin may be superior to unfractionated heparin as a first-line agent in ACS.

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Author Contributions: Dr Mahaffey, as corresponding author, and all coauthors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analyses.


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REFERENCES