Enoxaparin vs Unfractionated Heparin in High-Risk Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Managed With an Intended Early Invasive Strategy
Primary Results of the SYNERGY Randomized Trial

The SYNERGY Trial Investigators[*]

MEDICAL THERAPIES FOR non–ST-segment elevation acute coronary syndromes (ACS) have evolved dramatically over the last decade.[1,2] At the same time, trials in high-risk patients have confirmed the benefit of an early invasive treatment strategy with diagnostic angiography and subsequent revascularization, compared with a conservative approach.[3,4]

Despite the demonstrated superiority of enoxaparin, a low-molecular-weight heparin (LMWH), compared with unfractionated heparin in clinical trials of patients with non–ST-segment elevation ACS receiving medical therapy as their primary treatment strategy, the value of enoxaparin as the principal antithrombin regimen for ACS continues to be debated.[5-12] In part, the fact that enoxaparin is not more broadly used in this patient population may be due to insufficient information about its efficacy and safety when combined with potent antiplatelet therapies in the setting of an early invasive strategy, including a high rate of percutaneous coronary intervention (PCI).

To define the role of enoxaparin in patients with non–ST-segment elevation ACS at high risk for ischemic cardiac complications managed with an early aggressive approach, the Superior Yield of the New Strategy of Enoxaparin, Revas-

Context Enoxaparin has demonstrated advantages over unfractionated heparin in low- to moderate-risk patients with non–ST-segment elevation acute coronary syndromes (ACS) treated with a conservative strategy.

Objectives To compare the outcomes of patients treated with enoxaparin vs unfractionated heparin and to define the role of enoxaparin in patients with non–ST-segment elevation ACS at high risk for ischemic cardiac complications managed with an early invasive approach.

Design, Setting, and Participants The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was a prospective, randomized, open-label, multicenter, international trial conducted between August 2001 and December 2003. A total of 10027 high-risk patients with non–ST-segment elevation ACS to be treated with an intended early invasive strategy were recruited.

Interventions Subcutaneous enoxaparin (n=4993) or intravenous unfractionated heparin (n=4985) was to be administered immediately after enrollment and continued until the patient required no further anticoagulation, as judged by the treating physician.

Main Outcome Measures The primary efficacy outcome was the composite clinical end point of all-cause death or nonfatal myocardial infarction during the first 30 days after randomization. The primary safety outcome was major bleeding or stroke.

Results The primary end point occurred in 14.0% (696/4993) of patients assigned to enoxaparin and 14.5% (722/4985) of patients assigned to unfractionated heparin (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.86-1.06). No differences in ischemic events during percutaneous coronary intervention (PCI) were observed between enoxaparin and unfractionated heparin groups, respectively, including similar rates of abrupt closure (31/2321 [1.3%] vs 40/2364 [1.7%]), threatened abrupt closure (25/2321 [1.1%] vs 24/2363 [1.0%]), unsuccessful PCI (81/2281 [3.6%] vs 79/2328 [3.4%]), or emergency coronary artery bypass graft surgery (6/2323 [0.3%] vs 8/2363 [0.3%]). More bleeding was observed with enoxaparin, with a statistically significant increase in TIMI (Thrombolysis in Myocardial Infarction) major bleeding (9.1% vs 7.6%, $P=.008$) but nonsignificant excess in GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Arteries) severe bleeding (2.7% vs 2.2%, $P=.08$) and transfusions (17.0% vs 16.0%, $P=.16$).

Conclusions Enoxaparin was not superior to unfractionated heparin but was non-inferior for the treatment of high-risk patients with non–ST-segment elevation ACS. Enoxaparin is a safe and effective alternative to unfractionated heparin and the advantages of convenience should be balanced with the modest excess of major bleeding.

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*Authors are members of the Executive and Steering committees of the SYNERGY Trial. Authors and other group members and financial disclosures are listed at the end of this article.

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Figure 1. Patient Flow Through the Trial
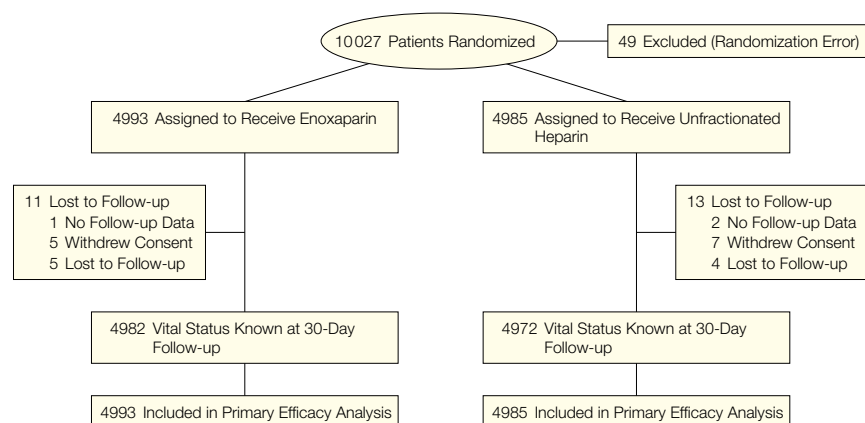
Per protocol, 30-day follow-up was defined as at least 27 days after enrollment.

cularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was conducted.

METHODS
Study Design and Trial Organization

SYNERGY was a prospective, randomized, open-label, multicenter, international trial. The rationale and study design of the trial have been previously published.[13] The randomization scheme was by site with a random block size for each site. SYNERGY was designed to evaluate the efficacy and safety of enoxaparin vs unfractionated heparin when administered with established guidelines-based therapy, including glycoprotein (Gp) IIb/IIIa inhibitors, aspirin, and clopidogrel in high-risk patients who presented with non–ST-segment elevation ACS and were to be managed with an intended early invasive treatment strategy.

Patient Population, Recruitment, and Follow-up

Eligible patients had ischemic symptoms lasting at least 10 minutes occurring within 24 hours before enrollment and at least 2 of the following: age 60 years or older, troponin or creatine kinase elevation above the upper limit of normal, or ST-segment changes on electrocardiogram (ECG).[13] Patients were to be excluded if they had known or sus-

pected pregnancy, contraindications to unfractionated heparin or LMWH, recent (<48 hours) or planned spinal or epidural anesthesia or puncture, PCI or thrombolytic therapy within the preceding 24 hours, increased risk for bleeding complications due to recent stroke or surgery, elevated international normalized ratio (>1.5), past or present bleeding disorder, or creatinine clearance less than 30 mL/min. All patients provided written informed consent. The protocol was approved by the institutional review board or ethics committee at each participating center.

Clinical events, procedures, adverse events, and concomitant medications were documented during the baseline hospitalization and for patients with rehospitalization during the first 30 days after enrollment. All patients were to be contacted 180 days after enrollment for collection of data about key cardiac events and at 1 year to determine survival status.

Primary and Secondary End Points

The primary efficacy outcome was the composite clinical end point of all-cause death or nonfatal myocardial infarction (MI) during the first 30 days after randomization. Key secondary outcome measures included the incidence of death or nonfatal MI at 14 days; the combined incidence of all-cause mortality, nonfatal MI, stroke, or recurrent

ischemia requiring revascularization; and individual components of this composite at 14 and 30 days after enrollment. The primary safety end point was the incidence of major bleeding or stroke. All suspected incidents of MI and stroke were adjudicated by a clinical events committee that was blinded to treatment assignment.

Enoxaparin and Unfractionated Heparin Dosing

Enoxaparin or unfractionated heparin was given immediately after enrollment according to the patient's randomly assigned treatment. Treatment continued until the patient required no further anticoagulation per the treating physician and at least through angiography and revascularization, if performed. Intravenous unfractionated heparin was given according to a weight-adjusted nomogram (bolus of 60 U/kg [maximum of 5000 U] and initial infusion of 12 U/kg per hour [maximum of 1000 U/h initially]) with a goal activated partial thromboplastin time of 1.5 to 2.0 times the institutional upper limit of normal or 50 to 70 seconds.[1] Enoxaparin was given subcutaneously at a dose of 1 mg/kg every 12 hours.

Patients could be enrolled even if they had already received LMWH or unfractionated heparin by the treating physician before randomization; the randomized assignment was independent of any prior antithrombin treatment. Detailed recommendations for dosing of enoxaparin and unfractionated heparin in patients with prior antithrombin treatment, as well as for all patients during PCI, for sheath removal, and prior to coronary artery bypass graft (CABG) surgery were provided to all investigators and coordinators.

For patients randomly assigned to receive enoxaparin, catheterization could be performed anytime after dosing and the sheath removed at least 6 to 8 hours after the last enoxaparin dose. During PCI, if the last enoxaparin dose was given less than 8 hours before balloon inflation, no additional enoxaparin was to be given. If the last enoxaparin dose was given 8 or more hours before bal-

loon inflation, 0.3 mg/kg of enoxaparin was to be given intravenously before proceeding with PCI. If no intravenous enoxaparin was used during PCI, the sheath could be removed at least 6 to 8 hours after the last enoxaparin dose, and if it was used, the sheath could be removed at least 4 to 6 hours after the intravenous enoxaparin dose. Percutaneous closure devices could be used based on institutional standard practice.

For patients assigned to receive unfractionated heparin, catheterization was performed while the patient was receiving unfractionated heparin, and the sheath could be removed when the activated clotting time (ACT) was less than 150 to 180 seconds. During PCI the unfractionated heparin infusion was stopped. Additional intravenous unfractionated heparin was given to achieve an ACT of 250 seconds (lower if Gp IIb/IIIa inhibitors were used) or an ACT based on the individual site standards.

For elective bypass surgery procedures, enoxaparin was to be discontinued at least 8 hours and unfractionated heparin at least 6 hours before surgery. For emergency procedures, enoxaparin or unfractionated heparin was stopped and the patients were taken to surgery regardless of the timing of the last dose.

Concomitant Medications and Cardiac Catheterization

All patients received aspirin at enrollment and daily thereafter at a dose of 162 to 325 mg. Patients with an allergy or contraindication to aspirin received clopidogrel (75 mg) at enrollment, and then 75 mg/d. Other agents were recommended per published guidelines, which were emphasized during site training.[1,2] Glycoprotein IIb/IIIa inhibitor use was encouraged but not mandated. All other medications were administered at the physician's discretion.

Data and Safety Monitoring

The study was monitored by an independent data and safety monitoring board. Prespecified interim analyses and formal stopping rules were established for both efficacy and futility.

End Point Definitions

The definitions for MI, bleeding, and stroke used in the trial have been previously published.[13] The definitions for MI and bleeding also appear in the accompanying systematic overview.[14]

Sample Size Justification and Adjustment

The original sample size of approximately 8000 patients was based on an expected 30-day control group event rate of 15%, with 90% power to detect

Table 1. Baseline Characteristics

	Enoxaparin (n = 4993)	Unfractionated Heparin (n = 4985)
Age, median (IQR), y	68.0 (61.0-75.0)	68.0 (61.0-75.0)
Female sex, No./total (%)	1696/4992 (34.0)	1684/4985 (33.8)
Region, No./total (%)		
Australia/New Zealand	206/4993 (4.1)	207/4985 (4.2)
Europe	908/4993 (18.2)	907/4985 (18.2)
North America	3637/4993 (72.8)	3632/4985 (72.9)
South America	242/4993 (4.9)	239/4985 (4.8)
Race, No./total (%)		
White	4298/4992 (86.1)	4248/4985 (85.2)
Black	309/4992 (6.2)	326/4985 (6.5)
Asian	59/4992 (1.2)	51/4985 (1.0)
Hispanic	236/4992 (4.7)	250/4985 (5.0)
American Indian	18/4992 (0.4)	29/4985 (0.6)
Pacific Islander	15/4992 (0.3)	14/4985 (0.3)
Other	57/4992 (1.1)	67/4985 (1.3)
Clinical variables, median (IQR)		
Weight, kg	80.0 (70.0-91.0)	80.0 (70.0-91.0)
Heart rate, beats/min	71.0 (62.0-81.0)	71.0 (62.0-81.0)
Blood pressure, mm Hg		
Systolic	130.0 (116.0-147.0)	130.0 (117.0-148.0)
Diastolic	72.0 (63.0-81.0)	72.0 (62.0-81.0)
Medical history and risk factors, No./total (%)*		
Killip class		
I	4192/4806 (87.2)	4225/4814 (87.8)
II	488/4806 (10.2)	474/4814 (9.9)
III	103/4806 (2.1)	91/4814 (1.9)
IV	23/4806 (0.5)	24/4814 (0.5)
Hypertension	3411/4992 (68.3)	3378/4985 (67.8)
Diabetes mellitus	1424/4992 (28.5)	1502/4985 (30.1)
Prior angina	2287/4991 (45.8)	2269/4985 (45.5)
Prior infarction	1420/4977 (28.5)	1374/4969 (27.7)
Prior CABG surgery	805/4991 (16.1)	853/4980 (17.1)
Prior PCI	1044/4991 (20.9)	964/4984 (19.3)
Prior congestive heart failure	463/4991 (9.3)	458/4985 (9.2)
Prior stroke	269/4992 (5.4)	225/4985 (4.5)
History of peripheral vascular disease	478/4990 (9.6)	506/4984 (10.2)
Smoking status		
None	2056/4990 (41.2)	2020/4981 (40.6)
Current	1178/4990 (23.6)	1226/4981 (24.6)
Previous	1756/4990 (35.2)	1735/4981 (34.8)
Hypercholesterolemia	2889/4956 (58.3)	2947/4961 (59.4)
Family history of CAD	2301/4964 (46.4)	2235/4944 (45.2)
Time from symptom onset to enrollment, median (IQR), h	14.7 (8.5-20.8)	14.6 (8.5-20.6)
Time from hospital admission to enrollment, median (IQR), h	9.9 (3.9-18.0)	10.0 (3.9-17.9)

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention.
*All data were obtained from the patient's medical record on admission for the episode that resulted in trial enrollment.

a clinically meaningful relative reduction of 17% with a 2-sided type I error rate of 5%. Interim analyses of aggregate event rates were planned with an option to increase the sample size if anticipated event rates were not observed. After approximately 4000 patients had been recruited, the sample size was adjusted to 10 000 patients for 3 reasons. First, the aggregated event rate was 13.5% (below the anticipated 13.75%), so 217 additional patients were added. Second, the first 49 patients in one country were all assigned the same therapy due to a programming error in an automatic randomization system, and the decision was made to replace those patients in the primary efficacy analyses although they

were followed up for safety assessments. Third, because the study drug assignment was open label, treating physicians used nonassigned antithrombin strategies either intentionally or inadvertently. The impact of postrandomization crossover was estimated; since there was a potential for dilution of the ability to detect treatment differences due to these crossover treatment situations, the sample size was increased by 1734 patients. No patients were excluded from the primary analyses because of postrandomization crossover treatment.

Statistical Analyses

Categorical variables are summarized as percentages and continuous variables as

medians with interquartile ranges. The primary efficacy analysis was the time to first event in the 2 treatment groups based on an intention-to-treat strategy (all randomized patients, as randomized) with adjudicated MI results using the stratified log-rank test. The 49 patients not randomly assigned were excluded from this analysis.

The SYNERGY protocol prespecified that if enoxaparin was not demonstrated to be superior to unfractionated heparin, a noninferiority analysis was to be performed. Using SAS PHREG procedure (version 8.2; SAS Institute Inc, Cary, NC), a 95% confidence interval (CI) (adjusted for interim analyses; final $P = .045$) for the hazard ratio for the primary end point with enoxaparin vs unfractionated heparin was constructed. The upper boundary for the noninferiority claim was set at <1.1. This boundary was determined by consensus among the trial steering committee based on an end point of death or nonfatal MI and extensive data already available on enoxaparin and unfractionated heparin in similar patient populations. Under the closed-testing procedure with sequential testing of the superiority and inferiority analyses, the overall 2-sided type I error rate was maintained at 5%.

The primary safety outcomes were major bleeding and stroke. Per-protocol bleeding was to be assessed by both the TIMI (Thrombolysis in Myocardial Infarction) and GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Arteries) criteria during the baseline hospitalization.[13] Transfusions were also collected as part of the safety assessment.

To assess the impact of prerandomization antithrombin therapy and postrandomization crossovers between enoxaparin and unfractionated heparin after enrollment, a series of prespecified analyses were performed. Analyses on groups defined by postrandomization events such as crossovers are recognized to be potentially biased and exploratory in nature. First, subgroups were constructed based on prerandomization anticoagulation

Table 2. Inclusion Criteria*

	No. (%)	
	Enoxaparin (n = 4828)	Unfractionated Heparin (n = 4830)
Age ≥60 y and elevated cardiac biomarkers	996 (20.6)	952 (19.7)
Age ≥60 y and ECG changes	768 (15.9)	767 (15.9)
Elevated cardiac biomarkers and ECG changes	925 (19.2)	936 (19.4)
Age ≥60 y, elevated cardiac biomarkers, and ECG changes	2139 (44.3)	2175 (45.0)

Abbreviation: ECG, electrocardiographic.
*As explained in the "Methods" section. Data missing for some patients.

Table 3. In-Hospital Events and Procedures Through 30 Days

	Enoxaparin (n = 4993)	Unfractionated Heparin (n = 4985)
Events		
Recurrent ischemia*	198 (4.0)	212 (4.3)
Stroke*	48 (1.0)	44 (0.9)
Hemorrhagic	4 (<0.1)	2 (<0.1)
Nonhemorrhagic	44 (0.9)	40 (0.8)
Uncertain etiology	0 (<0.1)	2 (<0.1)
Cardiogenic shock, No. (%)	98 (2.0)	112 (2.3)
Congestive heart failure, No. (%)	401 (8.0)	392 (7.9)
Cardiac arrest, No. (%)	98 (2.0)	109 (2.2)
Ventricular tachycardia/fibrillation, No. (%)	241 (4.8)	246 (4.9)
Atrial fibrillation/flutter, No. (%)	431 (8.6)	383 (7.7)
Procedures		
Diagnostic coronary angiography, No. (%)	4600 (92.1)	4588 (92.0)
Time to angiography, median (IQR), h†	21.7 (6.3-43.6)	21.5 (6.3-42.6)
PCI, No. (%)	2323 (46.5)	2364 (47.4)
Time to PCI, median (IQR), h†	22.7 (6.4-48.8)	22.5 (6.3-48.1)
CABG, No./total (%)	965/4991 (19.3)	899/4982 (18.0)
Time to CABG, median (IQR), h†	91.4 (44.3-166.7)	89.1 (44.7-165.5)

Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
*Reported as hazard rates.
†Time from randomization.

(none, enoxaparin only, unfractionated heparin only, or both). Second, an analysis including only patients who received no prerandomization antithrombin therapy or were randomly assigned to the same antithrombin that they received before randomization was performed. This group represents patients without changes in antithrombin therapy before enrollment or as part of the study drug assignment. Cox proportional hazards modeling was used to examine whether prerandomization antithrombin treatment had an impact on the estimate of the treatment effect, and hazard ratios and CIs were created for each subgroup. Then, an analysis was performed in which all patients were included in the analysis based on the assigned therapy until they received the opposite treatment, at which time they were censored. Finally, a time-dependent covariate model was constructed in which events were attributed to each drug only during the time it was administered. For each of these models, the Cox proportional hazards assumption was confirmed and statistical significance was set at $P<.05$.

RESULTS

Between August 2001 and December 2003, 10027 patients were enrolled from 12 different countries and 467 investigative centers. The primary intention-to-treat analyses included 4993 patients assigned to receive enoxaparin and 4985 patients assigned to receive unfractionated heparin (FIGURE 1). Baseline characteristics were similar between treatment groups (TABLE 1). Eligibility criteria were similar across study drug assignment, with nearly half of patients enrolled due to age, ECG changes, and elevated biomarkers (TABLE 2).

In-hospital cardiovascular events and coronary procedures through 30 days are shown in TABLE 3. Overall, 92% (9188/9978) of patients underwent coronary angiography. Percutaneous revascularization procedures were performed in 47% (4687/9978) of patients and surgical revascularization in 19% (1864/9973) of patients. Median time from randomization to angiography was 22 hours

(interquartile range, 6-43 hours). Patients were treated aggressively with recommended medications including aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors, statins, and Gp IIb/IIIa antagonists (TABLE 4). The use of procedures and concomitant medications was similar in the treatment groups.

The primary end point of death or nonfatal MI by 30 days occurred in 14.0% (696/4993) of patients assigned to enoxaparin and 14.5% (722/

4985) of patients assigned to unfractionated heparin (hazard ratio, 0.96; 95% CI, 0.86-1.06). Enoxaparin was not superior to unfractionated heparin but fulfilled the noninferiority criteria (TABLE 5 and FIGURE 2).

The primary end point in subgroups defined by prerandomization characteristics is shown in FIGURE 3. No differences in ischemic events reported by the physician during PCI were observed between enoxaparin and unfractionated heparin, including similar rates of abrupt

Table 4. Concomitant Medications During Hospitalization

	No./Total (%)	
	Enoxaparin (n = 4993)	Unfractionated Heparin (n = 4985)
Aspirin	4751/4993 (95.2)	4723/4985 (94.7)
β-Blocker	4312/4993 (86.4)	4283/4985 (85.9)
ACE inhibitor	3185/4993 (63.8)	3100/4985 (62.2)
Lipid lowering		
Statin	3453/4993 (69.2)	3490/4985 (70.0)
Other	193/4993 (3.9)	206/4985 (4.1)
Ticlopidine	175/4993 (3.5)	175/4985 (3.5)
Clopidogrel	3119/4993 (62.5)	3154/4985 (63.3)
Antihypertensive		
Angiotensin receptor blocker	276/4993 (5.5)	327/4985 (6.6)
Diuretic	1691/4993 (33.9)	1685/4985 (33.8)
Calcium channel blocker	1006/4993 (20.2)	960/4985 (19.3)
Nitrates	3492/4993 (69.9)	3468/4985 (69.6)
Glycoprotein IIb/IIIa inhibitor		
Any	2819/4992 (56.5)	2898/4982 (58.2)
Preenrollment	1030/2800 (36.8)	1020/2884 (35.4)
Postenrollment	911/2800 (32.5)	956/2884 (33.2)
Before/after catheterization or PCI	859/2800 (30.7)	908/2884 (31.5)

Abbreviations: ACE, angiotensin-converting enzyme; PCI, percutaneous coronary intervention.

**Table 5.** Primary Outcomes at 30 Days as Well as 14 Days and 48 Hours

	No. (%)			
	Enoxaparin (n = 4993)	Unfractionated Heparin (n = 4985)	Hazard Ratio (95% CI)	P Value
30 Days*				
Death or MI	696 (14.0)	722 (14.5)	0.96 (0.86-1.06)	.40
Death	160 (3.2)	153 (3.1)	1.04 (0.84-1.30)	.71
MI	580 (11.7)	627 (12.7)	0.92 (0.82-1.03)	.14
14 Days*				
Death or MI	639 (12.8)	668 (13.4)	0.95 (0.86-1.06)	.38
Death	120 (2.4)	118 (2.4)	1.01 (0.79-1.31)	.91
MI	554 (11.2)	586 (11.8)	0.94 (0.84-1.05)	.28
48 Hours†				
Death or MI	284/4992 (5.7)	323/4983 (6.5)	. . .	.10
Death	21/4992 (0.4)	26/4983 (0.52)	. . .	.46
MI	268/4993 (5.4)	301/4985 (6.0)	. . .	.15

Abbreviations: CI, confidence interval; MI, myocardial infarction; ellipses, not calculated per protocol.
*Reported as hazard rates.
†Observed frequencies reported as No./total (%).

Figure 2. Kaplan-Meier Analysis of Primary End Point
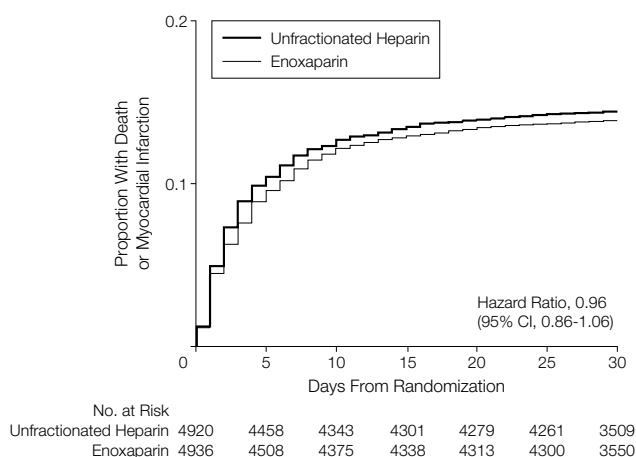
Kaplan-Meier curves showing proportion of patients in each treatment group who experienced death or myocardial infarction to 30 days of follow-up. CI indicates confidence interval.

closure (31/2321 [1.3%] vs 40/2364 [1.7%]), threatened abrupt closure (25/2321 [1.1%] vs 24/2363 [1.0%]), unsuccessful PCI (81/2281 [3.6%] vs 79/2328 [3.4%]), or emergency CABG surgery (6/2323 [0.3%] vs 8/2363 [0.3%]), respectively.

Bleeding was modestly increased in patients assigned to enoxaparin, with a statistically nonsignificant excess in GUSTO severe events, although TIMI major bleeding was significantly higher in patients treated with enoxaparin. The majority of the absolute bleeding excess resulted from CABG-related events and no significant differences in transfusion, intracranial hemorrhage, or thrombocytopenia were observed (**TABLE 6**).

In SYNERGY, patients could be enrolled after antithrombin therapy was already initiated as part of routine care. In total, 75% (7538/9978) of patients already received unfractionated heparin or LMWH prior to randomization. In addition, 12% (593/4993) of patients assigned to enoxaparin received unfractionated heparin and 4% (205/4985) of patients assigned to unfractionated heparin received enoxaparin after randomization (crossovers). Clinical outcomes and bleeding by groups defined by prerandomization and postrandomization therapies are shown in **TABLE 7**.

Across a series of comprehensive analyses, when an effort was made to remove the confounding influence of prerandomization antithrombin therapy or postrandomization crossovers, enoxaparin appeared to have a relative advantage with no excess of bleeding. Using censored techniques, enoxaparin was associated with a reduced hazard for 30-day death or nonfatal MI (0.82; 95% CI, 0.07-0.94) and a similar TIMI major bleeding hazard (1.06; 95% CI, 0.76-1.49). The time-dependent covariate analyses showed a trend toward lower hazard of 30-day death or nonfatal MI (0.93; 95% CI, 0.84-1.03) and TIMI major bleeding (0.95; 95% CI, 0.83-1.09) with enoxaparin.

COMMENT

The SYNERGY trial enrolled a high-risk patient population treated with an early invasive treatment strategy. Compared with earlier trials of patients with non–ST-segment elevation ACS (PURSUIT, PRISM-Plus, GUSTO IV, ESSENCE, TIMI 11B), patients in SYNERGY were older, managed more aggressively with routine coronary angiography, PCI, and CABG surgery, and treated with potent antiplatelet agents.[6,8,15-17] In this setting, treatment with enoxaparin was not superior to but was an effective alternative to unfrac-

tionated heparin. Enoxaparin met the prespecified criteria for noninferiority with a modest increase in the risk of major bleeding.

Efficacy

Enoxaparin has been extensively evaluated in patients with ACS over the past 10 years. Efficacy for enoxaparin compared with unfractionated heparin in the conservative management of patients with non–ST-segment elevation ACS has been clearly demonstrated with 18% to 20% reductions in death or nonfatal MI.[5-7] In the SYNERGY population, a less robust beneficial treatment effect of enoxaparin was observed. Whether this attenuated benefit was because of more aggressive use of other evidence-based therapies, including Gp IIb/IIIa inhibition, clopidogrel, and revascularization procedures, or prerandomization antithrombin treatment and postrandomization crossovers is a complex issue. Importantly, with more than 90% of patients undergoing coronary angiography and 47% undergoing PCI, no increase in periprocedural ischemic complications was observed, including thrombus formation, abrupt closure, stroke, or need for urgent CABG surgery.

A systematic overview of more than 20000 patients with non–ST-segment elevation ACS from the 6 major trials comparing enoxaparin and unfractionated heparin has been performed to put SYNERGY in perspective with the totality of evidence.[14] In aggregate, enoxaparin was associated with a statistically significant reduction in death or nonfatal MI at 14 days, which was maintained through 30 days (odds ratio, 0.91; 95% CI, 0.83-0.99). The results are consistent across the 6 trials that included patients with varying degrees of risk and with evolving concomitant therapies and treatment strategies.

Safety

Overall, patients assigned to enoxaparin had more bleeding. However, no increase in clinically significant bleeding occurred, including intracranial hemorrhage, bleeding associated with he-

modynamic compromise, or need for transfusions. Multiple measures of bleeding have been used in clinical trials, including the GUSTO and TIMI scales and need for transfusions, with continued debate about the strengths and weaknesses of each assessment tool. Additional investigation of bleeding risk is needed because complex relationships exist among many factors including age, renal function, 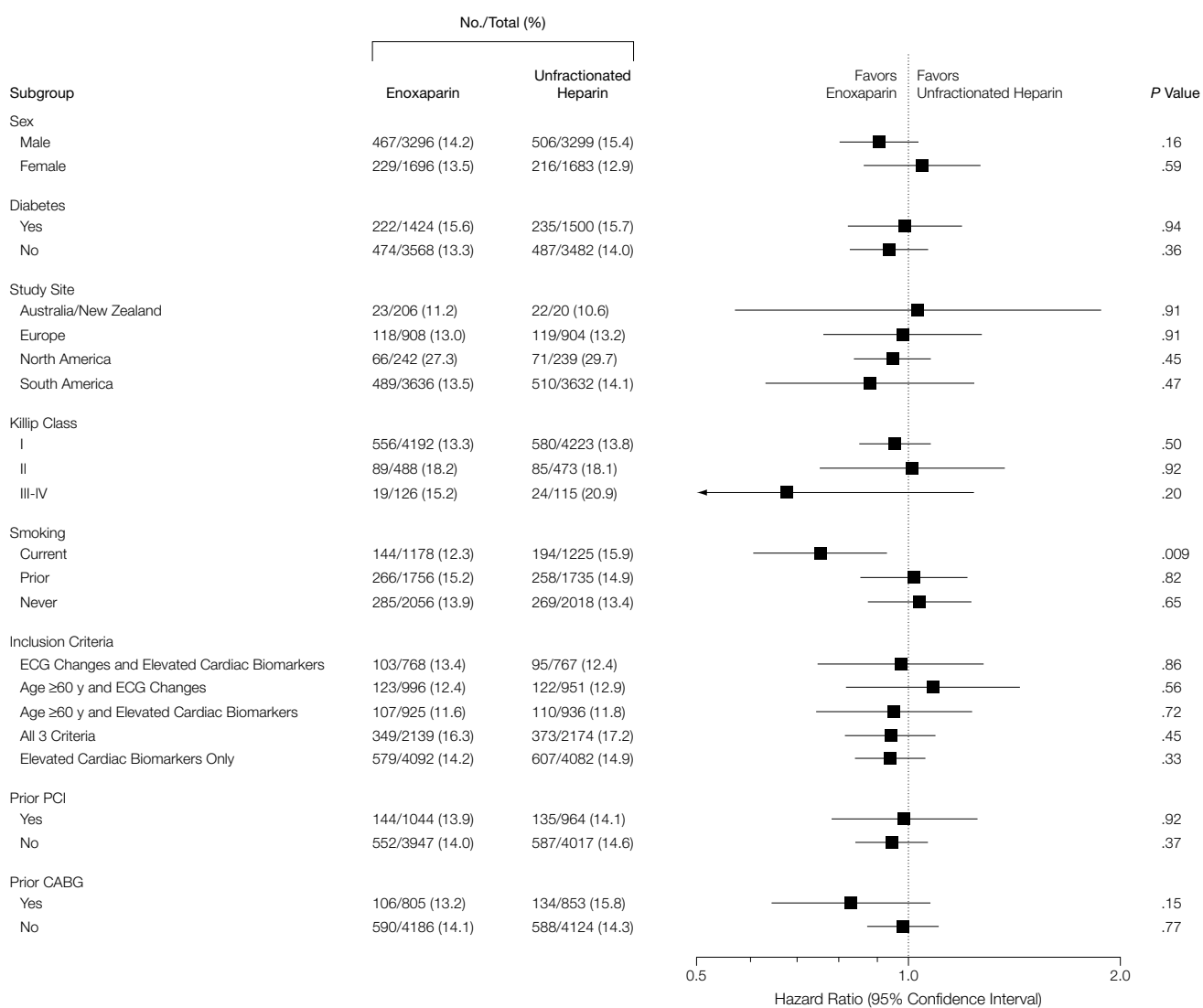coronary procedures, adjunctive therapies, and postrandomization crossover therapy. In the systematic overview, no significant excess was observed of 7-day non-CABG TIMI major bleeding (odds ratio, 1.04; 95% CI, 0.83-1.30) or transfusion (odds ratio, 1.01; 95% CI, 0.89-1.14).[14]

Pretreatment Antithrombin Therapy and Postrandomization Crossovers

The impact of the postrandomization crossovers is unknown and it was not anticipated that 75% of patients would have been started with antithrombin therapy prior to enrollment in SYNERGY. The increase in sample size midway through the trial was based on a speculative estimate of this impact. In TIMI IIB[18] only 35% of patients had antithrombin pretreatment but in the more recent A to Z trial, this practice occurred in nearly two thirds of patients.[19] It appears that prerandomization antithrombotic therapy and post-

Figure 3. Hazard Ratios by Primary Subgroups

Subgroup	No./Total (%)		Favors Enoxaparin / Favors Unfractionated Heparin	P Value
	Enoxaparin	Unfractionated Heparin		
Sex				
Male	467/3296 (14.2)	506/3299 (15.4)		.16
Female	229/1696 (13.5)	216/1683 (12.9)		.59
Diabetes				
Yes	222/1424 (15.6)	235/1500 (15.7)		.94
No	474/3568 (13.3)	487/3482 (14.0)		.36
Study Site				
Australia/New Zealand	23/206 (11.2)	22/20 (10.6)		.91
Europe	118/908 (13.0)	119/904 (13.2)		.91
North America	66/242 (27.3)	71/239 (29.7)		.45
South America	489/3636 (13.5)	510/3632 (14.1)		.47
Killip Class				
I	556/4192 (13.3)	580/4223 (13.8)		.50
II	89/488 (18.2)	85/473 (18.1)		.92
III-IV	19/126 (15.2)	24/115 (20.9)		.20
Smoking				
Current	144/1178 (12.3)	194/1225 (15.9)		.009
Prior	266/1756 (15.2)	258/1735 (14.9)		.82
Never	285/2056 (13.9)	269/2018 (13.4)		.65
Inclusion Criteria				
ECG Changes and Elevated Cardiac Biomarkers	103/768 (13.4)	95/767 (12.4)		.86
Age ≥60 y and ECG Changes	123/996 (12.4)	122/951 (12.9)		.56
Age ≥60 y and Elevated Cardiac Biomarkers	107/925 (11.6)	110/936 (11.8)		.72
All 3 Criteria	349/2139 (16.3)	373/2174 (17.2)		.45
Elevated Cardiac Biomarkers Only	579/4092 (14.2)	607/4082 (14.9)		.33
Prior PCI				
Yes	144/1044 (13.9)	135/964 (14.1)		.92
No	552/3947 (14.0)	587/4017 (14.6)		.37
Prior CABG				
Yes	106/805 (13.2)	134/853 (15.8)		.15
No	590/4186 (14.1)	588/4124 (14.3)		.77

Hazard Ratio (95% Confidence Interval) — axis: 0.5, 1.0, 2.0

Hazard ratio plots for death or myocardial infarction by 30 days according to treatment group. Data markers indicate hazard ratio for enoxaparin vs unfractionated heparin; lines indicate extent of 95% confidence intervals. ECG indicates electrocardiographic; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft. The inclusion criteria (age, ECG findings, and biomarkers) are described in the "Methods" section.

Table 6. In-Hospital Bleeding*

	No./Total (%)		P Value
	Enoxaparin	Unfractionated Heparin	
GUSTO severe	136/4993 (2.7)	109/4983 (2.2)	.08
TIMI major†	453/4993 (9.1)	379/4984 (7.6)	.008
CABG-related	338/4993 (6.8)	295/4984 (5.9)	.08
Non–CABG-related	119/4993 (2.4)	87/4984 (1.8)	.03
TIMI minor	611/4885 (12.5)	603/4888 (12.3)	.80
Decrease in hemoglobin and/or hematocrit‡	743/4874 (15.2)	611/4882 (12.5)	<.001
Any transfusion	850/4993 (17.0)	796/4985 (16.0)	.16
Lowest platelet count, ×10³/µL			
≥100	4393/4675 (94.0)	4424/4697 (94.2)	
>50 to <100	250/4675 (5.3)	250/4697 (5.3)	.67
>20 to ≤50	22/4675 (0.5)	16/4697 (0.3)	
≤20	10/4675 (0.2)	7/4697 (0.1)	

Abbreviations: CABG, coronary artery bypass graft; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Arteries; TIMI, Thrombolysis in Myocardial Infarction.
*GUSTO severe bleeding was defined as intracranial hemorrhage or if bleeding results in hemodynamic compromise. TIMI major bleeding was defined as at least a 5-g/dL decrease in hemoglobin, at least a 15% decrease in hematocrit, or intracranial bleeding. TIMI minor bleeding was noted if it was associated with gastrointestinal or genitourinary bleeding, with an absolute decrease in hemoglobin of 4 g/dL or more, or decrease in hematocrit of at least 12%.
†Associated with clinical bleed.[13]
‡At least a 5-g/dL decrease in hemoglobin or at least a 15% decrease in hematocrit not associated with an overt bleeding event.[13]

Table 7. Safety and Efficacy Outcomes by Pretreatment Antithrombin Therapy and Postrandomization Crossovers

	Enoxaparin	Unfractionated Heparin	Hazard Ratio (95% CI)
Prerandomization Antithrombin Therapy			
No prerandomization antithrombin therapy, No.	1212	1228	
Death or MI at 30 days, No. (%)	152 (12.6)	181 (14.8)	0.84 (0.68-1.05)
Any transfusion, No. (%)	205 (16.9)	212 (17.3)	
Prerandomization enoxaparin only, No.	2186	2108	
Death or MI at 30 days, No. (%)	298 (13.6)	276 (13.1)	1.04 (0.88-1.23)
Any transfusion, No. (%)	369 (16.9)	309 (14.7)	
Prerandomization unfractionated heparin only, No.	1428	1512	
Death or MI at 30 days, No. (%)	216 (15.2)	252 (16.7)	0.89 (0.74-1.08)
Any transfusion, No. (%)	253 (17.7)	253 (16.7)	
Both agents, No.	167	137	
Death or MI at 30 days, No. (%)	30 (18.1)	13 (9.5)	2.0 (1.03-3.90)
Any transfusion, No. (%)	23 (13.8)	22 (16.1)	
No Prerandomization Antithrombin Therapy or Postrandomization Therapy Same as Prerandomization Therapy			
No.	3398	2740	
Death or MI at 30 days, No. (%)	450 (13.3)	433 (15.9)	0.82 (0.72-0.94)
Any transfusion, No. (%)	574 (16.9)	465 (17.0)	
Postrandomization Crossovers*			
No crossover			
No.	4400	4780	
Death or MI at 30 days, No. (%)	593 (13.5)	677 (14.2)	
Crossover			
No.	593	205	
Death or MI at 30 days, No. (%)	103 (17.4)	45 (22.0)	
Any transfusion, No. (%)			
No crossover	671 (15.3)	724 (15.1)	
Crossover	179 (30.2)	72 (35.1)	

Abbreviations: CI, confidence interval; MI, myocardial infarction.
*For enoxaparin, crossover/no crossover hazard ratio (95% CI) is 0.95 (0.85-1.06). For unfractionated heparin, no crossover/crossover hazard ratio (95% CI) is 0.76 (0.53-1.09).

randomization crossover had an important impact on the trial results.

However, interpretation of these findings deserves careful evaluation because of the complexity of the analyses and the potential for confounding. The indefinable biases among practitioners about prerandomization treatment and decisions about postrandomization crossover of antithrombin agent use in the setting of a trial that was not blinded to the investigators further complicates the interpretation. In patients without prerandomization antithrombin therapy, enoxaparin was associated with a 16% relative risk reduction in death and nonfatal MI at 30 days that is consistent with reductions seen in prior trials. In patients without prerandomization antithrombin therapy or in whom prerandomization antithrombin therapy was the same as the randomly assigned therapy, enoxaparin resulted in a statistically significant 18% relative reduction in death or nonfatal MI. Bleeding outcomes in these 2 groups of patients were not increased, and censored analyses and time-dependent covariate analyses confirmed both the efficacy and lack of increased clinically significant bleeding risk. The clinical benefit seen in SYNERGY patients without antithrombin therapy prior to randomization was confirmed in the nearly 9000 patients from the systematic overview,[14] which reported a 12% relative risk reduction in mortality (0.89; 95% CI, 0.70-1.11) and a statistically significant 18% relative risk reduction in death or nonfatal MI (0.82; 95% CI, 0.73-0.95).

Analyses of the impact of postrandomization crossover are more complicated because it is an event that occurs after randomization and is further confounded by the knowledge of the treatment assignment.[20] Overall, it appears that changing antithrombin therapy during the treatment course is not associated with any treatment benefit and is associated with an increased risk of bleeding. Still, caution must be used in interpreting these complex models, since causality and association cannot be definitively delineated.

Limitations

Potential biases from the open-label trial design include physician choices of medical therapies or interventions by knowledge of the treatment assignment and reporting of clinical outcomes. Investigators were encouraged in the protocol, at investigator meetings, and in trial newsletters to adhere to the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for the management of patients with ACS regardless of assigned study drug. The similar use of coronary procedures and medical therapies in both treatment groups supports our conclusion that investigators were not biased in medical decisions. All analyses were based on a strict intention-to-treat principle, all-cause mortality was included in the primary efficacy composite, and a clinical events committee systematically adjudicated all MI events without knowledge of the treatment assignment.

Clinical and Research Implications

The results of pragmatic clinical trials have been heralded as the foundation for changing practice guidelines and clinical care.[21] The design of the SYNERGY trial, with broad inclusion of high-risk patients in geographically diverse areas and across different clinical practice settings, along with definitive end points and an active comparator, strengthen the importance of these results. In high-risk patients with an intended early invasive treatment strategy, enoxaparin and unfractionated heparin are safe and effective alternatives as the antithrombin regimen. Enoxaparin has the advantages of convenience (fixed dosing without need for monitoring or intravenous infusion) and a trend toward a lower rate of nonfatal MI with a modest excess of bleeding. As a first-line agent in the absence of changing antithrombin therapy during treatment, enoxaparin appears to be superior without an increased bleeding risk. Changing antithrombin agents in the midst of an episode of ACS may be hazardous, with an increase in bleed-

ing and less clinical benefit. Clinical investigators developing trials to evaluate new antithrombotic regimens in ACS should consider carefully the potential impact of prerandomization therapy and influence of postrandomization crossovers of therapies on trial conduct and results.

CONCLUSION

In high-risk patients with ACS treated with an early invasive strategy with frequent use of antithrombin therapy prior to enrollment and postrandomization crossovers, enoxaparin is not inferior to unfractionated heparin. Enoxaparin carries a modest increase in bleeding and is likely superior when started as initial first-line therapy without changing to alternative agents.

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