Original Article

High-Risk Non-ST Elevation Acute Coronary Syndrome Outcomes in Patients Treated with Unfractionated Heparin Monitored Using Anti-Xa Concentrations Versus Activated Partial Thromboplastin Time

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Abstract

Background: While the activated partial thromboplastin time (aPTT) is the most widely used assay to monitor unfractionated heparin (UFH), providing a general measure of the extent of anticoagulation, it does not reliably correlate with the blood concentration of heparin or its antithrombotic effect. While cost and availability have limited the widespread use of UFH in hospitals, monitoring UFH with heparin levels has been shown to reduce both the number of monitoring tests and the time to a therapeutic range.

Objectives: To compare outcomes in patients with non-ST elevation acute coronary syndrome (ACS) treated with weight-based UFH monitored with anti-Xa concentrations versus aPTT.

Methods: A retrospective chart review was completed in patients admitted with high-risk ACS and compared to the UFH arm of the SYNERGY trial. The primary outcome included the clinical endpoint of all-cause death or non-fatal myocardial infarction until time of hospital discharge. Safety endpoints evaluated included incidence of stroke and major bleeding.

Results: The primary endpoint occurred in 6.3% of patients in the study cohort compared to 6.5% of patients in the heparin arm of the SYNERGY trial at 48 hours ($P = .006$). Bleeding was reduced in the study cohort with a significant decrease in GUSTO severe bleeding ($P = .007$). Additionally the study cohort had significantly fewer patients with an absolute drop in hemoglobin or hematocrit. Thrombolysis in Myocardial Infarction (TIMI) major and minor bleeding, rate of transfusion, and platelet counts were similar between groups.

Conclusions: Outcomes for high-risk ACS patients receiving heparin monitored by anti-Xa concentrations are noninferior to heparin monitored by aPTT.

Key Words—acute coronary syndrome, heparin, non-ST elevation myocardial infarction

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Intravenous unfractionated heparin (UFH) remains an important Class IA recommendation for the antithrombotic treatment of patients with non-ST elevation acute coronary syndromes (NSTEMI/ACS), regardless of initial invasive or conservative treatment strategy.^{1,2} Pooled analysis has demonstrated a 44% relative risk reduction of death and myocardial infarction (MI) with UFH in combination with aspirin compared to aspirin alone.^{1,3–5} For high-risk NSTEMI/

ACS patients initially treated with an invasive treatment strategy, the use of heparin is supported by the results of the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial. This study demonstrated that enoxaparin was noninferior to weight-based UFH in the primary endpoint of all-cause death or nonfatal MI during the first 30 days after randomization.⁶

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The current heparin dosing recommendations by the American College of Chest Physicians (ACCP) in NSTEMI ACS patients are weight-based, with an initial bolus of 60-70 units per kg and initial infusion of 12-15 units/kg/h. Heparin infusions are titrated via aPTT to a target range of 1.5 to 2.0 times the institutional upper limit of normal, equivalent to anti-Xa concentrations of 0.4 to 0.7 units/mL assessed by anti-factor Xa determinations.¹ These recommendations are based on clinical trials where outcomes were assessed using UFH dosed on an activated partial thromboplastin time (aPTT) standard.

The aPTT is the most widely used assay to monitor UFH, providing a general measure of the extent of anticoagulation. The aPTT, however, does not reliably correlate with the blood concentration of heparin or its antithrombotic effect.⁷⁻¹² Suboptimal anticoagulation in ACS, as measured by aPTT, has been correlated to poor outcomes.^{13,14} Additionally, the aPTT therapeutic range and weight-based dosing nomograms must be adjusted based on the aPTT reagent, resulting in significant effort on the part of the clinician each time an institution's laboratory changes reagent. The anti-factor Xa assay, or anti-Xa concentration, is a test of the specific enzyme activity of heparins.¹⁵ While cost and availability have resulted in the limited use of UFH in hospitals, monitoring UFH with anti-Xa concentrations has been shown to reduce both the number of monitoring tests and the time to a therapeutic range.^{16,17}

Outcome data with UFH monitored with anti-Xa concentrations are limited to early studies of prophylaxis of left ventricular mural thrombi and coronary artery patency post tissue plasminogen activator (tPA) administration.^{18,19} No outcomes associated with heparin therapy have been correlated with heparin dosed using anti-Xa concentration nomograms; as such, recommendations regarding the use of anti-Xa concentrations continue to vary within guidelines and limit the broad application of this methodology to clinical practice.

We conducted a retrospective noninferiority comparison of consecutive high-risk NSTEMI ACS patients treated with weight-based UFH monitored with anti-Xa concentrations compared to the UFH arm of the SYNERGY trial to show that the outcomes of therapy with heparin monitored with anti-Xa concentrations were not different than those monitored with aPTT.

METHODS

A retrospective chart review was conducted between November 2006 and June 2007 on 271 consecutive

patients admitted to Cone Health with high-risk ACS. Patients were included if they were admitted with high-risk ACS, with at least 2 of the following: age 60 years or older, troponin or creatine kinase above our institutional upper limit of normal, or ST-segment changes on electrocardiogram (ECG), in addition to receiving heparin for ACS with a minimum of 1 measured anti-Xa concentration. Patients were excluded if they did not have measured anti-Xa concentrations or experienced ST-segment elevations. This protocol was approved by the Cone Health Institutional Review Board prior to data collection.

Data were collected by extensive evaluation of medical records, with determination of inclusion and endpoint events based upon laboratory evaluation and events noted in the dictated history and physical, discharge summary, and cardiac catheterization report. Data were compared to reported 48-hour outcomes in the UFH arm of the SYNERGY trial, and methodology was similar between both studies.⁶ The primary outcome was the composite clinical endpoint of all-cause death or non-fatal MI up to the time of hospital discharge. Safety endpoints evaluated included incidence of stroke and major bleeding, including severe bleeding as determined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial and major and minor bleeding as determined by Thrombolysis in Myocardial Infarction (TIMI).⁶

In all cases, heparin was initiated after the order of the emergency room or admitting physician with all dosing and management by pharmacy protocol. Treatment with heparin continued until the time of cardiac catheterization or until discontinued by physician order. Intravenous UFH was dosed according to a weight-adjusted nomogram, which included a bolus of 50 to 70 units/kg (up to a maximum of 5,000 units) and initial infusion of 12 to 15 units/kg/h with no maximum rate, as determined by pharmacist assessment of patient-specific factors. Doses were titrated based on 6-hour anti-Xa concentrations to a target anti-Xa concentration of 0.4 to 0.7 units/mL, using *STA-Rotachrom* (Diagnostica Stago, Inc., Parsippany, NJ) Heparin 8 reagent. Heparin was stopped on call to cardiac catheterization and either heparin or bivalirudin was used during percutaneous intervention (PCI) to achieve a goal activated clotting time (ACT) of 250 seconds. Per institutional protocol, sheaths were removed once the ACT was less than 180 seconds.

A noninferiority analysis was performed comparing composite primary endpoint results with the

48-hour outcomes in the UFH arm of the SYNERGY trial. In-hospital bleeding results from the SYNERGY trial were compared to bleeding events in our consecutive patient population. Noninferiority was defined using the primary efficacy measure, and the noninferiority margin was set at a risk difference of 4%.

The original sample size of approximately 300 patients was based on an 80% power to detect a 4% risk difference with a 2-sided alpha of 5%, using utilizing *Stata* data analysis and statistical software version 11 (StataCorp LP, College Station, TX). After data were collected and evaluated on 300 consecutive patients, we found that 29 patients did not meet primary inclusion criteria based on the definition of high-risk ACS and were excluded from the analysis. All outcomes were analyzed using a 2-sided Fisher exact test.

RESULTS

Between November 2006 and June 2007, 271 consecutive patients were admitted to Cone Health with high-risk ACS and were treated with UFH meeting study inclusion criteria and were compared with the UFH arm of the SYNERGY trial (Table 1). Patients were treated with guideline-based concurrent medication, including aspirin, clopidogrel, beta-blockers, statins, and glycoprotein IIb/IIIa inhibitors (Table 2).

The primary endpoint of death or non-fatal MI at hospital discharge occurred in 6.3% (17/271) of patients in the study cohort compared to 6.5% (324/4,985) of patients in the heparin arm of the SYNERGY trial at 48 hours ($P = .006$). Heparin managed by pharmacy protocol based on anti-Xa concentrations met noninferiority criteria.

Bleeding was reduced in the study cohort with a significant decrease in GUSTO severe bleeding (-2.2; 95% CI, -2.6 to -1.8; $P = .007$). Additionally the study cohort had significantly fewer patients with an absolute drop in hemoglobin or hematocrit. TIMI major and minor bleeding, rate of transfusion, and platelet counts were similar between groups (Table 3).

Overall, the study cohort had fewer in-hospital events and procedures (Table 4). Occurrence of ventricular tachycardia or fibrillation was less in the study group, with recurrent ischemia, stroke, and cardiac arrest rates being similar between both cohorts. Patients in the SYNERGY arm had more diagnostic coronary angiography and PCI but a similar number of patients receiving coronary artery bypass graft.

DISCUSSION

The 271 consecutive patients in the study cohort were at high-risk for ACS and were treated with an early invasive treatment strategy. Compared to the heparin arm of the SYNERGY trial, patients in the study cohort were more likely to have prior PCI, congestive heart failure (CHF), or stroke. Medical management was similar between the 2 groups, with more patients in the study cohort receiving aspirin. Patients in the SYNERGY cohort received more glycoprotein IIb/IIIa inhibitors, whereas the study cohort received more bivalirudin.

This pragmatic cohort compared 48-hour outcome data with follow-up data recorded through the day of discharge in a patient population with an average length of stay of 8 days. Thus, the management of heparin with anti-Xa concentrations by pharmacy protocol met the criteria for noninferiority with a significant reduction in bleeding.

Efficacy

Heparin has long been a cornerstone in the treatment of high-risk ACS, receiving a Class 1A level of recommendation in the ACCP guidelines and the American College of Cardiology/American Heart Association (ACC/AHA) non-ST-elevation myocardial infarction (NSTEMI) guidelines, regardless of invasive or conservative treatment strategy.^{1,2} Despite guideline inclusion of anti-Xa concentration ranges for monitoring of UFH therapy, aPTT remains the primary test used to measure the therapeutic effect of heparin. This is driven primarily by the long clinical experience with aPTT and the absence of outcome data with UFH monitored with anti-Xa concentrations. However, conflicting evidence exists in the literature for the efficacy of heparin therapy adjusted by aPTT that is correlated with outcomes. As recently as 1996, Becker et al⁹ published an evaluation of heparin dosing in the TIMI IIB trial, demonstrating that neither aPTT or anti-IIa concentrations within the therapeutic range correlated with advantages in outcome. Suboptimal anticoagulation in ACS as measured by aPTT has been correlated to poor outcomes.⁸ Multiple trials in MI post thrombolysis, ACS, and left ventricular mural thrombus have demonstrated an outcome advantage with heparin at therapeutic concentrations based on aPTT.^{11,13,14,18} As early as 1989, evidence of an outcome advantage in post-MI patients was seen with UFH correlated with anti-Xa concentrations determined by protamine titration in the prevention of left ventricular mural thrombus.¹⁸ More recently, an

Table 1. Baseline characteristics

Characteristics	Study cohort (N = 271)	SYNERGY (N = 4,985)	P
Median age	69 years	68 years	-
Male	59.4	66.2	.03
Race			<.001
Caucasian	80.07	85.2	
African American	16.6	6.5	
Asian	2.58	1.0	
Hispanic	0.75	5.0	
Median weight, kg	83.1	80.0	-
Median HR, bpm	82	71	-
Median SBP, mm Hg	136	130	-
Median DBP, mm Hg	75	72	-
Smoking status			
None	45.0	40.6	.02
Current	28.4	24.6	
Previous	26.6	34.8	
Prior angina	15.9	45.5	<.001
Prior infarction	15.9	27.7	<.001
Prior CABG	19.9	17.1	.25
Prior PCI	26.6	19.3	.005
Prior CHF	22.5	9.2	<.001
Prior stroke	12.5	4.5	<.001
Diabetes	35.4	30.1	.07
Hypertension	71.9	67.8	.16
Hypercholesterolemia	53.9	59.4	.08
PVD	17.3	10.2	.001
Family history of CAD	19.9	45.2	<.001
Baseline PT	14.7	Not reported	-
Baseline INR	1.2	Not reported	-
Age ≥ 60 years and elevated cardiac biomarkers, n (%)	71 (26)	952 (19.7) ^a	.01
Age ≥ 60 years and ECG changes, n (%)	0	767 (15.9) ^a	<.001
Elevated cardiac biomarkers and ECG changes, n (%)	56 (21)	936 (19.4) ^a	.58
Age ≥ 60 years, elevated cardiac biomarkers, and ECG changes, n (%)	144 (53)	2,175 (45) ^a	.01

Note: All values given are %, unless otherwise noted. CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; DBP = diastolic blood pressure; ECG = electrocardiogram; HR = heart rate; INR = international normalized ratio; PCI = percutaneous coronary intervention; PT = prothrombin time; PVD = peripheral vascular disease; SBP = systolic blood pressure; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors.

^aOut of 4,830 patients.

evaluation of 803 consecutive ACS patients treated with enoxaparin demonstrated an association with reduced 30-day mortality above a threshold peak anti-Xa level.¹⁴ To date, no studies have evaluated the outcomes associated with the treatment of high-risk

ACS patients with the concurrent dosing and adjustment of UFH therapy using anti-Xa concentrations.

Despite absent outcome data, both the ACC/AHA NSTEMI and ACCP guidelines recommend weight-based heparin dosing to an aPTT 1.5 to 2.0 times the

Table 2. Concomitant medications during hospitalization

Medication	Study cohort (N = 271)	SYNERGY (N = 4,985)	P
Aspirin	97.8	94.7	.02
Beta-blocker	88.6	85.9	.24
Nitrate	79.3	69.6	.001
Statin	66.1	70	.17
Clopidogrel	60.5	63.3	.37
Diuretic	53.9	33.8	<.001
Glycoprotein IIb/IIIa or bivalirudin	48.3	58.2	.002
ACE-I	46.5	62.2	<.001
Glycoprotein IIb/IIIa	35.8	58.2	<.001
Calcium channel blocker	30.6	19.3	<.001
ARB	14.8	6.6	<.001
Ticlopidine	0.4	3.5	.002

Note: Values given as %. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors.

institutional upper limit of normal based on an anti-Xa concentrations standard of 0.3 to 0.7 units/mL.^{1,2} The value of an anti-Xa concentration-based nomogram is clear when considering the limits of using aPTT.

Circadian variation limits the direct correlation of UFH with clinical effect; reagents and methods also fluctuate, which places strain on concerned clinicians due to variable normal ranges.¹⁸ The

Table 3. In-hospital bleeding as described by GUSTO and TIMI bleeding definitions

Bleeding definitions	Study cohort (anti-Xa monitoring) (N=271)	SYNERGY cohort (aPTT monitoring) (N=4,985)	Percent risk difference (95% CI)	P
	Patients n (%)	Patients n/N (%)		
GUSTO severe bleeding	0 (0)	109/4,983 (2.2)	-2.2 (-2.6 to -1.8)	.007
TIMI major bleeding	17 (6.3)	379/4,984 (7.6)	-1.3 (-4.3 to 1.6)	.48
CABG-related	17 (6.3)	295/4,984 (5.9)	0.4 (-2.6 to 3.3)	.79
Non-CABG-related	0 (0)	87/4,984 (1.8)	-1.7 (-2.1 to -1.4)	.02
TIMI minor bleeding	26 (9.6)	603/4,888 (12.3)	-2.7 (-6.4 to 0.9)	.21
Any transfusion	46 (17)	796/4,985 (16)	1 (-3.6 to 5.6)	.67
At least 5 g/dL drop in Hgb or 15% drop in Hct without overt bleeding	11 (4.1)	611/4,882 (12.5)	-8.4 (-11 to -5.9)	<.001
Lowest platelet count, x 10 ³ /μL			N/A	.83
≥100	259 (95.6)	4424/4,697 (94.2)		
>50 to <100	12 (4.4)	250/4,697 (5.3)		
>20 to ≤50	0 (0)	16/4,697 (0.3)		
≤20	0 (0)	7/4,697 (0.1)		

Note: CABG = coronary artery bypass graft; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial (severe bleeding defined as intracranial hemorrhage or bleeding resulting in hemodynamic compromise); Hct = hematocrit; Hgb = hemoglobin; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMI = Thrombolysis in Myocardial Infarction Trial (major bleeding defined as 5 g/dL hemoglobin decrease, 15% hematocrit decrease, or intracranial bleeding, minor bleeding if associated with genitourinary or gastrointestinal bleeding, and either a decrease in hemoglobin by 4 g/dL or hematocrit by 12%).

Table 4. In-hospital events and procedures

	Study cohort (N = 271)	SYNERGY (N = 4,985)	P
Events			
Recurrent ischemia	2.2	4.3	.12
Stroke	0.74	0.9	>.9
Hemorrhagic	0	<0.1	>.9
Nonhemorrhagic	0.74	0.8	>.9
Cardiac arrest	1.1	2.2	.28
Ventricular tachycardia/fibrillation	0.37	4.9	<.001
Procedures			
Diagnostic coronary angiography	79.7	92	<.001
PCI	35.4	47.4	<.001
CABG	16.2	18	.52

Note: Values given as %. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors.

lack of correlation between aPTT and anti-Xa concentrations also brings into question the external validity of the therapeutic ranges of previous outcome trials. Dosing using anti-Xa concentrations has been demonstrated to achieve therapeutic levels more quickly, with fewer dosage adjustments and lab draws with a stable, reproducible therapeutic range.^{16,17,20,21}

This study demonstrates that a pragmatic cohort managed similarly to the heparin arm of the SYNERGY trial can produce similar outcomes with death and non-fatal MI.

Safety

Our study demonstrated a significant reduction in bleeding compared to the heparin cohort in SYNERGY. Bleeding risk has emerged as a driving factor in agent selection in a high-risk ACS population; however, a universal definition or systematic method to compare bleeding risk between agents is still undetermined.^{6,22-25} In SYNERGY, enoxaparin was demonstrated to have a slightly higher risk of bleeding compared with the heparin arm, but the analysis was controversial due to crossover anticoagulation.⁶ Although no crossover anticoagulation between enoxaparin and heparin occurred in our study population, 12.8% of our population were treated with bivalirudin as the anti-coagulant of choice during PCI after discontinuation of heparin on call to catheterization. Our intensive pharmacy anticoagulation protocol, with continual dose adjustments and attention to patient-specific details, may also have contributed to our reduced bleeding rates, regardless of the utilization of anti-Xa concentrations.

Limitations

Our study has several limitations. The retrospective comparison of single centers results to one arm of a clinical trial does not replace randomized study, but it can provide insight into the modern application of UFH therapy for high-risk patients in the increasingly complex treatment of ACS. Additionally, lack of randomization or matching limits our ability to directly compare our population to the heparin arm in SYNERGY. Our study was completed 5 years after SYNERGY, thus it is also possible to attribute some safety advantages to advances in catheterization technique, including utilization of closure devices. Our study included fewer patients with a history of ACS, which may have been due to the methodology of a retrospective chart review.

Conclusion

Outcomes for high-risk ACS patients receiving heparin monitored by anti-Xa concentrations are non-inferior to heparin monitored by aPTT.

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