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Scientific Update™

Role of Low-Molecular-Weight Heparin in the Contemporary Management of Non-ST-Segment Elevation Acute Coronary Syndromes

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Advances in antithrombotic therapy and improved revascularization techniques have led to reduced morbidity and mortality rates in patients presenting with unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI) acute coronary syndromes (ACS). While unfractionated heparin (UFH) has long been the standard antithrombin agent used to manage these patients, there remain several limitations. Low-molecular-weight heparin (LMWH) possesses a number of pharmacologic and practical advantages over UFH, and one LMWH in particular – enoxaparin – has proven to be superior to UFH in preventing death or cardiac ischemic events in the setting of NSTEMI. However, despite recent revisions to The American College of Cardiology/American Heart Association (ACC/AHA) consensus guidelines, data suggest that LMWH remains relatively underutilized. The integration of LMWH into standard clinical practice that now includes early invasive management strategies and the routine use of glycoprotein (GP) IIb/IIIa receptor antagonists, remains an unresolved issue. This issue of *Cardiology Scientific Update* reviews the role of LMWH in the contemporary management of patients presenting with NSTEMI ACS, including data on its use in conjunction with GP IIb/IIIa antagonists and in the setting of early percutaneous coronary intervention (PCI).

Overview of LMWH

Antithrombin therapy plays an important role in the management of UA/NSTEMI ACS. For many years, UFH has been the standard antithrombin agent used in treating these patients. Of the available antithrombins, LMWH possesses pharmacologic and practical advantages over UFH.[1] LMWHs have greater anti-Xa:anti-IIa activity compared to UFH, resulting in increased proximal inhibition of the coagulation cascade and an enhanced antithrombotic effect. LMWH has a lower incidence of heparin-induced thrombocytopenia and, unlike UFH, does not lead to platelet activation. LMWHs also have more predictable antithrombin activity, a longer half-life, and greater bioavailability than UFH. This allows easier administration of LMWHs as sub-cutaneous injections without the need for routine therapeutic monitoring. These advantages of LMWH over UFH have important therapeutic implications.

Data analysis from the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-2 study estimates that 25%-37% of UA/NSTEMI patients have sub-therapeutic aPTT values up to 72 hours after starting intravenous UFH.[2] Furthermore, subtherapeutic aPTT values (<60 seconds) were strongly associated with recurrent adverse cardiovascular events in that trial (Figure 1). This highlights the importance of maintaining therapeutic levels of antithrombin activity in the management of UA/NSTEMI patients, further emphasizing the potential for the pharmacologic advantages of LMWH to translate into clinical benefits over UFH in these patients.

LMWH versus UFH in the management of NSTEMI ACS

Four large randomized clinical trials have compared LMWH to UFH in patients with NSTEMI ACS (Figure 2).

ESSENCE: The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial,[3] which randomized 3,171 patients to enoxaparin or UFH, demonstrated a significant reduction with enoxaparin in the combined primary endpoint of death, MI, or recurrent angina at 14 days (16.6% vs

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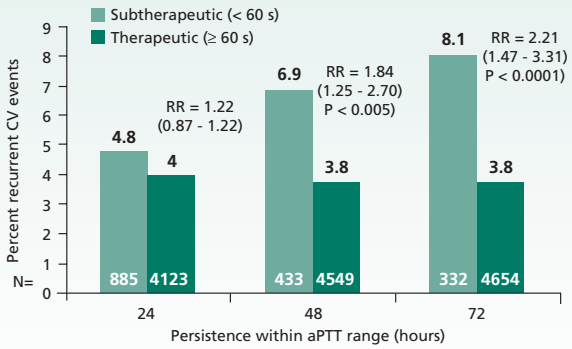
Figure 1: The importance of maintaining therapeutic levels during antithrombotic therapy. Relationship between aPTT values and recurrent adverse cardiovascular events in UA/NSTEMI ACS from the OASIS-2 study

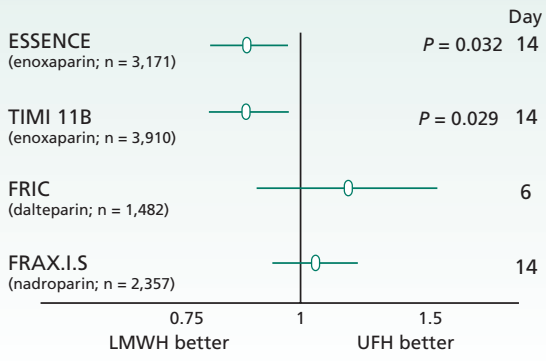


*CV death, MI, refractory angina
s = seconds

19.8%, p=0.019), that persisted at 30 days (19.8% vs 23.3%, p=0.016). There was no significant difference in the rate of major bleeding between the 2 treatment groups. At 1-year follow up, the beneficial effects of enoxaparin over UFH persisted for the combined endpoint (32.0% vs 35.7%, p=0.022).[4]

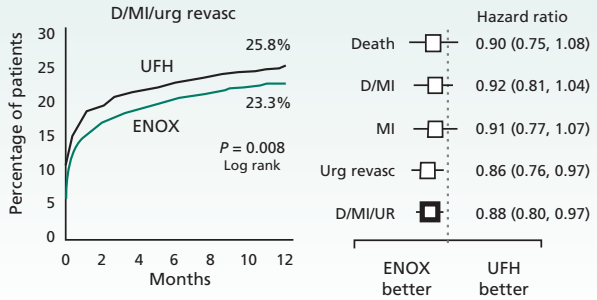
TIMI-IIB: Similarly, the Thrombolysis in Myocardial Infarction (TIMI)-11B trial[5] randomized 3,910 NSTEMI patients to either enoxaparin or UFH. There was a significant reduction in the combined primary endpoint of death, MI, or urgent revascularization at 8 days in the enoxaparin-treated group as compared to the UFH-treated group (12.4% vs 14.5%, p=0.048), without significant differences in the rates of major bleeding. A pre-specified meta-analysis of the data from these 2 trials demonstrated a significant reduction in the combined endpoint of death or MI at day 8 with enoxaparin compared to UFH (4.1% vs 5.3%, p=0.02), which persisted to day 43 (7.1% vs 8.6%, p=0.02).[6] Once again there was no significant difference in the rates of major hemorrhage during acute treatment (1.3% vs 1.1%, p=0.35). This benefit of enoxaparin was durable, with a significant reduction in the

Figure 2: Randomized controlled trials of LMWH in UA/NSTEMI: Effects on triple endpoint of death, MI, recurrent ischemia ± urgent revascularization



LMWH = low molecular weight heparin

Figure 3: TIMI-11B-ESSENCE meta-analysis: Durable treatment effects at 1-year follow-up



UFH = unfractionated heparin
ENOX = enoxaparin

combined risk of death, MI, or urgent revascularization at 1-year follow-up (Figure 3). Importantly, this meta-analysis also showed that the relative benefits of enoxaparin over UFH was proportional to the pretreatment risk as determined by the TIMI risk score (Figure 4).

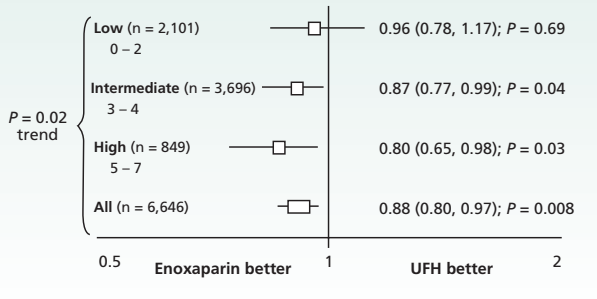
FRIC: Trials comparing LMWHs other than enoxaparin with UFH in NSTEMI patients have yielded inconsistent results (Figure 2). The Fragmin in Unstable Coronary Artery Disease (FRIC) study[7] randomized 1,482 patients to either dalteparin or UFH for 6 days, and then randomized patients to dalteparin or placebo until day 45.

FRAXIS: The Fraxiparine in Ischemic Syndrome (FRAXIS) trial[8] randomized 3,468 patients to receive either nadroparin or UFH. Both studies showed comparable rates of the combined endpoint of death, MI, or recurrent angina during short- and long-term follow-up, with no significant benefit for LMWH over UFH. The reasons for the apparent differences in efficacy between LMWH formulations have not been fully elucidated, however, but they may be due to modest differences in pharmacologic properties.[9]

Adherence to Guidelines for Antithrombotic Therapy in UA/NSTEMI: Global Insights from the GRACE Registry

Task forces from the ACC/AHA[10] and the European Society of Cardiology (ESC)[11] have recently published updated guidelines on the management of patients with UA/NSTEMI that have incorporated newer evidence on LMWH. While both sets of guidelines

Figure 4: TIMI-11B-ESSENCE meta-analysis: Benefit of enoxaparin proportional to pre-treatment risk



acknowledge the pharmacologic and practical advantages of LMWH over UFH, they do not unequivocally endorse the use of LMWH over UFH for antithrombotic therapy. The ACC/AHA guidelines previously placed a class I indication on the use of *either* LMWH or UFH, and a new class IIa indication on the use of enoxaparin *over* UFH if bypass surgery is not planned in the next 24 hours, based primarily upon data from the ESSENCE and TIMI-11B studies. The impact of this change on current clinical practice is unclear.

The GRACE registry is a prospective international registry of over 39,000 hospitalized ACS patients in 94 hospitals across 14 countries.[12] The registry aims to capture a broad diversity of ACS patients in a "real-world," non-clinical trial setting. Approximately 68% of patients enrolled have UA/NSTEMI, and the remainder admitted with ST-segment elevation MI (STEMI). Insights provided from the registry include:

- the risk of death at 6 months is similar for NSTEMI and STEMI patients, and overall event rates are higher in the registry compared to clinical trials
- 20% of patients are re-admitted for ACS during follow-up
- bleeding rates are higher in patients with NSTEMI, and those with major bleeds have higher mortality rates, and
- patients at the highest risk of poor outcomes have the lowest rates of PCI and vice-versa.

Overall, these findings emphasize the significant morbidity and mortality associated with UA/NSTEMI. Therefore, a therapy such LMWH, and enoxaparin in particular, which can reduce rates of death/MI or urgent revascularization without increasing bleeding rates, as compared to the current standard therapy (UFH), may positively impact the management of NSTEMI. Regarding actual LMWH use, the GRACE registry data reveal that it is gradually increasing, particularly in Canada, Europe, Australia, and New Zealand, but less so in the U.S. However, despite recent changes, the current guidelines have not made an overall impact on the use of LMWH in UA/NSTEMI, and it remains relatively underutilized in these high-risk patients. This serves to highlight that, while expert consensus guidelines remain an important aspect of clinical practice, their adherence and incorporation into everyday clinical management of patients remains an unresolved problem.

Recently, the ACC established the Guidelines Applied to Practice (GAP) program to examine acute MI patients. The goals of this demo project included dissecting out the priorities of guidelines and putting them into clinical practice, and creating care tools to emphasize these priorities, and move them to the bedside. The initial GAP program involved nearly 400 cardiologists in 33 hospitals across Michigan, U.S.A. Twelve months after program initiation and changes in the institutions, a positive effect was seen. There was a reduction in in-hospital mortality, with a mild improvement in the use of aspirin, beta-blockers, and statins. Given that the program improved both adherence to guidelines and associated clinical outcomes, the ACC plans to invest in other GAP initiatives.

Thus, despite the convincing results of ESSENCE and TIMI-11B, and the addition of a class IIa indication to updated guidelines, LMWH has not gained widespread acceptance by physicians for the management of patients with UA/NSTEMI ACS. While suboptimal implementation of guidelines is a factor, a number of other factors have likely contributed to the limited use of these agents. There is concern about using LMWH along with GP IIb/IIIa inhibitors, especially since the majority of data on the benefit of GP IIb/IIIa inhibitors was derived from studies with concomitant use of UFH. Another factor is the lack of safety and efficacy data on LMWH use in the setting of early invasive management with coronary angiography and revascularization. The inability to rapidly monitor LMWH during PCI and sheath management remains a concern for physicians. Also, there are inconsistencies in data on the efficacy of LMWH, especially from non-enoxaparin trials, and an absence of a definitive study showing clear benefit on the hard endpoints of death and MI.

Combining LMWH with GP IIb/IIIa inhibitors and with PCI in ACS: Current evidence

LMWH and GP IIb/IIIa Inhibitors

Several registry studies and substudy analyses have evaluated the use of LMWH and GP IIb/IIIa inhibitors in NSTEMI patients. However, since LMWH therapy was instituted in a non-randomized fashion at the discretion of the treating physician, it is difficult to make any firm conclusions on its efficacy and safety in combination with GP IIb/IIIa inhibitors from these trials.

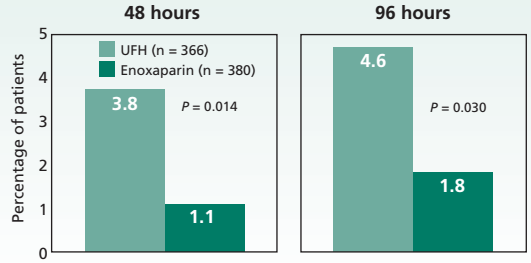
The initial randomized trials of LMWH versus UFH in patients receiving GP IIb/IIIa inhibitors in ACS were small pilot studies with surrogate and safety endpoints.

ACUTE: The Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE)-1 study[13] took 53 NSTEMI ACS patients treated with tirofiban, and randomized them in a double-blind fashion to UFH or enoxaparin. Angiography was postponed for at least 48 hours, with approximately 30% of all patients undergoing PCI. Overall, there were no major bleeding events in either group, with more minor bleeding events noted in the enoxaparin group.

ACUTE-2: In the subsequent ACUTE-2 study,[14] 525 ACS patients were treated with tirofiban and randomized to either enoxaparin 1 mg/kg subcutaneously every 12 hours or standard dose UFH for 24-96 hours. Angiography and PCI were allowed after at least 24 hours, and 8 hours after the last enoxaparin dose. No significant differences were found in the rates of bleeding – including major bleeding – the primary endpoints. The combined outcome of death or MI at 30 days was similar in the 2 treatment groups. There were, however, significant differences in the rates of readmission for UA and refractory ischemia requiring urgent revascularization, favouring enoxaparin. While these earlier studies were not powered to look at clinical endpoints, they did provide valuable data supporting the safety of LMWH when used in combination with GP IIb/IIIa inhibitors, including in the setting of PCI.

INTERACT: The recently published Integrilin and Enoxaparin Randomized assessment of Acute Coronary Syndromes (INTERACT) trial[15] is the largest randomized trial of combined LMWH and GP IIb/IIIa inhibitor to date. A total of 746 patients with NSTEMI ACS received eptifibatide and were randomized to receive, in an open-label fashion, either standard-dose intravenous UFH or enoxaparin 1 mg/kg subcutaneously every 12 hours (for a minimum of 4 total doses). The incidence of non-coronary bypass graft surgery (CABG)-related major bleeding at 96 hours (primary safety outcome) was significantly lower in enoxaparin-treated patients as compared to UFH-treated patients (Figure 5), while minor bleeding was more frequent in the enoxaparin-treated group. Patients treated with enoxaparin were less likely to experience ischemia as detected by continuous ECG monitoring

Figure 5: Primary efficiacy endpoint of the INTERACT trial: Major non-CABG bleeding at 48 and 96 hours



(primary efficacy outcome). Regarding hard clinical endpoints, the pre-specified secondary efficacy outcome of combined death and MI at 30 days was significantly lower in the enoxaparin-treated group compared to the UFH-treated group (Figure 6). This benefit of enoxaparin over UFH was present regardless of management strategy, with significant risk reductions in clinical events in those treated medically and in those undergoing PCI within 96 hours of enrollment.

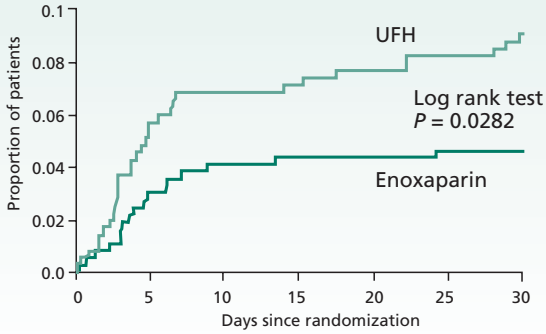
LMWH and PCI

In randomized trials of LMWH versus UFH in ACS, such as ESSENCE and TIMI-11B, LMWH therapy was discontinued before catheterization and the procedures were performed using UFH. More recent observational and registry data suggest that once LMWH has been started, it may be continued safely as a peri-procedural anticoagulant, without necessitating a switch to UFH, even in the setting of ACS.

Collet and colleagues[16] studied 451 patients with UA/NSTEMI treated with enoxaparin for at least 48 hours (> 2 doses). A total of 293 (65%) underwent coronary angiography within 8 hours of their last subcutaneous enoxaparin dose, and 132 (28%) underwent immediate PCI. GP IIb/IIIa inhibitor use in this study was low. No additional LMWH or UFH was given at the time of PCI, and sheaths were removed 10 hours after the last enoxaparain dose, without anticoagulant monitoring. These investigators found that measured anti-Xa activity was high (>0.6 IU/mL) in 97.6% of patients at the time of angiography/PCI and remained stable over the 8-hour period between the last dose of enoxaparin and catheterization. There were no abrupt closures and no requirements for urgent revascularization after PCI. The incidence of major hemorrhage was low at 0.7% overall, and 0.8% in the PCI group. This observational study suggests that patients with ACS receiving enoxaparin within the preceding 8 hours can safely undergo catheterization and PCI without the need for further anticoagulation at the time of PCI.

The National Investigators Collaborating on Enoxaparin (NICE)-3 study[17] looked at 616 NSTEMI patients treated with enoxaparin and a GP IIb/IIIa inhibitor. A total of 292 patients underwent PCI, with additional boluses of intravenous enoxaparin 0.3 mg/kg given at the time of procedure if the last enoxaparin dose was >8 hours prior to PCI. Overall, non-CABG bleeding rates were low (1.9% in all patients, 1.0% in PCI patients). At 30 days, the rate of death or MI was also low at 3.7%.

Figure 6: Pre-specified secondary efficacy endpoint of the INTERACT trial: Death or MI at 30 days



The Pharmacokinetic study of Enoxaparin in Patients undergoing percutaneous Coronary Intervention (PEPCI) trial[18] studied 47 patients undergoing PCI 8-12 hours after the last subcutaneous enoxaparin dose. The study found that in 96% of the patients, predictable anti-Xa activity within the defined therapeutic range (by convention 0.6-1.8 IU/mL) could be achieved by giving a supplemental dose of intravenous enoxaparin 0.3 mg/kg at the start of PCI. However, the optimal anti-Xa levels for ACS patients, particularly those undergoing PCI, are not clearly defined.

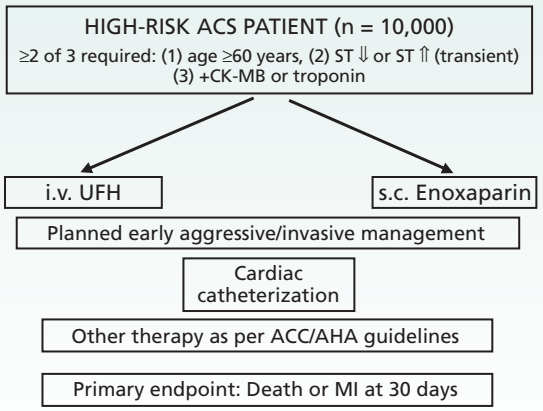
The ELECT trial[19] assessed a point-of-care device that measured enoxaparin effects. This device may be useful for anticoagulant monitoring in special patient populations, such as those with chronic renal insufficiency or extreme obesity.

Thus, current data suggest that LMWH, particularly enoxaparin, is safe when used in conjunction with GP IIb/IIIa inhibitors and, given the results of the INTERACT trial, may be superior to UFH. In addition, data suggest that medical therapy with LMWH can be safely transitioned into the catheterization laboratory, with additional intravenous boluses if it is >8 hours since the last subcutaneous dose. Citing these data, a recent expert consensus has been published[20] that strongly supports the use of LMWH, along with GP IIb/IIIa inhibitors and early catheterization, for UA/NSTEMI patients; it also includes recommendations for specific LMWH therapy algorithms.

Predicting SYNERGY: Insights from the GRACE registry

The Superior Yield of the New strategy of Enoxaprin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) study is a prospective, randomized, open-label, multicentre trial comparing enoxaparin with UFH in high-risk NSTEMI ACS patients. The goal of the study is to compare enoxaparin to UFH in a contemporary management strategy in NSTEMI ACS patients, including the use of early coronary angiography and intervention, and the widespread use of GP IIb/IIIa inhibition. The rationale and design of SYNERGY has been published previously,[21] and the study design is summarized in Figure 7. The study plans to enroll 10,000 patients at 500 study sites worldwide. Enrollment began in January 1, 2000 and is almost complete. Study inclusion and

Figure 7: SYNERGY Study Design



exclusion criteria are listed in Table 1. Patients were required to have at least 2 of the following 3 high-risk markers: age 60 years; ST-segment deviation, either ST-depression or transient ST-elevation; and positive cardiac biomarkers.

An early invasive management strategy will be strongly encouraged, with early cardiac catheterization and revascularization as required. Other therapy will be administered as per ACC/AHA guidelines. The primary endpoint is death and non-fatal MI at 30 days. The primary safety endpoint is major bleeding and stroke. The results of SYNERGY are expected in 2004 and will likely yield important information regarding the use of the LMWH, enoxaparin, in the contemporary management of patients with NSTEMI.

The GRACE registry is an ongoing observational study of hospitalized patients with ACS. It aims to capture a contemporary "real-life" population reflecting the full spectrum of ACS. Thus, using the GRACE registry as a database to select SYNERGY-eligible patients, one can simulate SYNERGY by comparing the efficacy and safety outcomes of these "SYNERGY-eligible" GRACE patients treated with enoxaparin or UFH. In doing so, this exercise may allow some insights into the potential results of SYNERGY, bearing in mind the numerous limitations of this simulation.

Study methods and results

A total of 31,068 ACS patients from the GRACE registry were screened, yielding 18,922 NSTEMI ACS patients. Of these, 3,612 were deemed SYNERGY-eligible. When 235 patients from non-SYNERGY countries were excluded, this left a total of 3,377 NSTEMI ACS patients from countries participating in SYNERGY. Baseline demographic data from these patients were well-matched with patients currently enrolled in SYNERGY (Table 2). Overall, the SYNERGY patients had slightly higher rates of elevated cardiac biomarkers and ST-segment changes, but fewer had a history of a prior MI or congestive heart failure. When medications were compared, there was higher use of GP IIb/IIIa inhibitors (58% vs 28%) and statins (81% vs 57%) in the SYNERGY patients as compared to the GRACE subset patients. Rates of cardiac catheterization were also higher in SYNERGY patients compared to GRACE patients

Table 1: Main SYNERGY inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Age ≥18 years	• Angina from secondary causes
• Ischemic chest pain at rest ≥10 minutes and within 24 hours	• High risk of bleeding
• At least 2 of the following: – Age ≥60 years – ST-segment changes – Elevated biomarkers	• Severe liver disease • Renal failure (Cr clearance ≤30 mL/min)

(94% vs 58%), as were rates of PCI and coronary bypass surgery, reflecting the study mandate. Thus, there were significant differences between the 2 study cohorts.

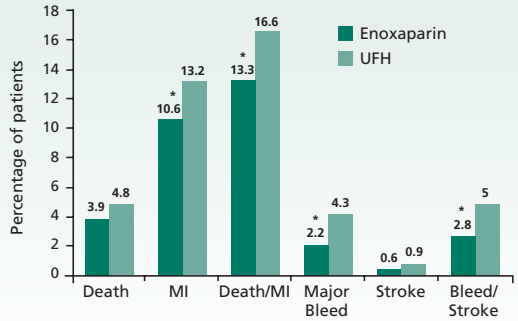
Baseline data for the 3,377 "SYNERGY-eligible" GRACE patients revealed that UFH-treated patients were significantly older, had a higher incidence of elevated biomarkers, and had higher rates of PCI and GP IIb/IIIa inhibitor use compared to enoxaparin-treated patients. Results of SYNERGY efficacy and safety outcomes in this GRACE subset are shown in Figure 8. In this cohort of patients, enoxaparin-treated patients had significantly lower rates of MI, major bleeding, as well as the combinations of death/MI and stroke/major bleed. Thus, if outcome event rates in SYNERGY are comparable to those seen in this simulation, enoxaparin will be more effective than UFH ($p<0.001$) in preventing cardiovascular endpoints, and will be safer than UFH ($p<0.05$) in this population of high-risk ACS patients.

However, the limitations of such a simulation are numerous. Treatment allocation to enoxaparin or UFH was non-randomized, resulting in significant differences in baseline characteristics and management strategies between treatment groups within the GRACE subset, and between the GRACE subset and preliminary data from SYNERGY-enrolled patients. Study endpoints, such as cardiac biomarker measurements for a determination of MI, were not standardized or adjudicated, as they would be in a prospective, randomized clinical trial. In

Table 2: Comparison of baseline characteristics in the SYNERGY and GRACE subset of 'SYNERGY-like' patients

Characteristic	SYNERGY (n=8,757)	GRACE subset (n=3,377)
Age (y)-median[range]	68.0[61-75]	70.7[64.2-77.0]
Female (%)	34.0	34.8
Weight (kg)-median[range]	80[70-92]	77[68-86]
History of diabetes (%)	29	29
History of Hypertension (%)	67	67
Hypercholesterolemia (%)	58	63
CHF (%)	9	13
Prior MI (%)	28	33
Prior PCI or CABG (%)	30	25
ST changes at enrollment (%)	78.8	61
Elevated biomarkers	81.8	77

Figure 8: Results of 'SYNERGY' efficacy and safety endpoints in the subset of 'SYNERGY-like' patients from the GRACE registry



* Significant difference compared to UFH

addition, there is the potential for many other measured and unmeasured confounders. Keeping in mind these substantial limitations, this simulation of the SYNERGY study using the GRACE registry database would suggest that SYNERGY would show superior efficacy and safety of enoxaparin as compared to UFH in high-risk NSTEMI ACS treated in a contemporary fashion, with early angiography and intervention, and a high rate of GP IIb/IIIa inhibitor use.

Conclusions

Despite good evidence for the superiority of LMWH, particularly enoxaparin, over UFH in the treatment of UA/NSTEMI, and appropriate changes to current consensus guidelines, LMWH remains a relatively underutilized therapy. While the ACC recognizes a lack of adherence to guidelines, and have implemented GAP programs to address this, other factors still remain. There remains concern over the lack of evidence for benefit of LMWH in an era of ACS patient management that includes a strategy of early intervention and routine use of GP IIb/IIIa inhibitors. Evidence to date strongly suggests that LMWH is as safe as UFH when used in conjunction with GP IIb/IIIa inhibitors and during PCI, with recent evidence from the INTERACT trial showing a clinical benefit for the combination of enoxaparin and integrilin, along with reduced bleeding rates. Unfortunately, given the limitations of these studies, including modest sample sizes and suboptimal designs, questions will inevitably remain regarding the absolute benefit of LMWH in this patient population.

The ongoing SYNERGY trial will address these questions, in a contemporary setting of routine GP IIb/IIIa inhibitor use and early invasive management. Simulation data presented in this *Cardiology Scientific Update*, while burdened by limitations, suggests that the results of SYNERGY will favour enoxaparin. This, of course, must be confirmed. Thus, the trial results of SYNERGY will more clearly define the expanding role of LMWH in the current management of the UA/NSTEMI patient.

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