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**Low Molecular Weight Heparin is as safe and effective as
Unfractionated Heparin when combined with Glycoprotein IIb/IIIa
inhibitors for the Treatment of Acute Coronary Syndromes**

Pharmaceutical Care Project
Outcomes Literature Evaluation
“Final Paper”

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Safety and Effectiveness of combined Low Molecular Weight Heparin and Glycoprotein IIb/IIIa Antagonists for the Treatment of Acute Coronary Syndromes

Background on Problem or Issue

Acute coronary syndromes (ACS), composed of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), account for more than one million hospitalizations each year. The syndrome is a collective term used to describe any group of symptoms of acute myocardial ischemia (ie, chest pain caused by insufficient blood supply to the heart muscle) that are often caused by atherosclerotic coronary disease. NSTEMI, in particular, has been associated with significantly worse patient outcomes, including higher mortality in the following year. Furthermore, a sizeable percentage of patients presenting with ACS go on to suffer serious sequelae, such as ST-elevation myocardial infarction (STEMI) or reinfarction, urgent or emergent revascularization procedures, CHF, or even death.

STEMI, NSTEMI, and UA are distinct disorders, but they share a common pathophysiologic origin, characterized by disruption or rupture of the fibrous cap of a vulnerable atherosclerotic plaque, exposing substances within the plaque which then activates the coagulation cascade and promotes thrombus formation. The resultant thrombus then occludes the coronary artery and decreases blood flow to the heart muscle downstream from the thrombus. Patients with STEMI typically have complete thrombotic occlusion of a coronary artery, while those with NSTEMI or UA typically have incomplete blockade of the infarct-related vessel. As the clinician's understanding of the vascular biology of ACS has advanced, it has become evident that platelet thrombus formation, not atherosclerotic burden, plays the pivotal role in the pathogenesis of ACS in the vast majority of patients. This activation of the coagulation cascade serves as the basis for the use of antiplatelet and antithrombotic drugs in the management of ACS at the level of the thrombus.

The use of heparin therapy as an adjunct has proven to be beneficial, time and time again, in various clinical studies, in the management of acute coronary syndrome. However, despite extensive use in clinical practice, unfractionated heparin (UFH) continues to have several important limitations. It has an inconsistent anticoagulant effect because the functional complex that UFH forms with plasma antithrombin III (ATIII) is not able to interact with a clot-bound thrombin, which limits the effectiveness of heparin in many clinical situations, such as ACS, where thrombus is already present. In addition, the heparin/ATIII complex has minimal effects on factor Xa, the component responsible for thrombin generation. UFH must be administered by continuous intravenous infusion and has an unpredictable dose-response relationship, largely because of nonspecific binding to plasma proteins and endothelial cells. It needs frequent monitoring because UFH dosing must be titrated to serial aPTT or ACT determinations to optimize its effectiveness. UFH is also susceptible to inactivation by platelet factor 4, produced by activated platelets. In addition, UFH can be associated with a multitude of side effects,

including, significant rates of thrombocytopenia and heparin-induced thrombocytopenia with or without concomitant thrombosis (HIT).

The low-molecular-weight heparin (LMWH) on the other hand exhibits much lower nonspecific binding to plasma proteins and endothelial cells than does UFH, and is less susceptible to degradation by platelet factor 4. Therefore, the LMWH possesses higher bioavailability, a longer elimination half-life, and a much more predictable dose-response relationship than does UFH. These features make subcutaneous administration of LMWH feasible, which greatly improves its ease of use in many clinical settings. At therapeutic doses, LMWH has a minimal effect on the serum aPTT or ACT, making these insensitive measures of LMWH activity, and thereby eliminating that need for laboratory monitoring of activity to optimize dosing. Furthermore, platelet activation after drug discontinuation, or heparin rebound, has not been reported for LMWH as it has for UFH.

With advances in the management of ACS, some issues have emerged regarding the use of LMWH in higher-risk patients, defined by older age, positive cardiac biomarkers and definitive ST-segment changes on presentation. First, because higher-risk patients may be more likely to receive GP IIb/IIIa antagonists, questions arise about the safety (primarily, with regard to bleeding) of the combination. Second, because higher-risk patients are also more likely to be brought to the catheterization laboratory for possible percutaneous coronary intervention (PCI), there are concerns about the feasibility and safety of using LMWH (which unlike UFH is not monitored and adjusted).

These concerns prompted a series of studies aimed at looking at, comparing and addressing questions on the balance of the risk versus benefit issues between the use of the combinations of GP IIb/IIIa and UFH on one hand and GP IIb/IIIa and LMWH on the other, in the management of ACS. The purpose of this paper is to review 6 studies that were conducted to look into the issue.

Premise of treatment (s)

The premise of all these studies is that if it can be proven that LMWH, when combined with the GP IIb/IIIa antagonists in the management of acute coronary syndrome, is equally effective and has equal safety profile as the combination of UFH and the GP IIb/IIIa, why shouldn't clinicians use the LMWH, which does not need to be monitored, and does not have many of the limitations that UFH possesses.

Evaluation of Studies

PARAGON B

The Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome events in a Global Organization Network B (PARAGON B) was a double-blind placebo study of over 5,000 patients who were assigned to receive renal dosing of lamifiban (a GPIIb/IIIa antagonist) with LMWH versus lamifiban with UFH.

The study gave a good general review of the purpose, which was to ascertain if the combination of LMWH with lamifiban was as safe an effective, if not better, as the combination of the antiplatelet with UFH in a contemporary clinical trial of patients with

non ST-segment elevation ACS. The title of the study clearly stated the conclusions to follow and a full list of authors disclosed. It was unclear if any of them was affiliated with the manufacturer of enoxaparin (the LMWH which was used 90% of the time in the study). The use of heparin type was not randomized in about 99.5% of the patients. Subsequently, both the participants and the coordinators were aware of the treatment allocations. In a study that important, I thought the failure to randomize the heparin type presented a source of bias which could have produced varying results in terms of the primary composite endpoints. Also of note, was the fact that different LMWHs were used in the LMWH arm of the study. Selection of patients was very thorough. Adequate measures were taken to alleviate selection bias, by adequately defining the study population, which included patients with an ACS without ST-segment elevation, chest pain of >20 minutes duration with onset within 12 hours, and either electrocardiographic evidence of ischemia or a positive cardiac marker. The exclusion criteria, however, was not listed. Significant outcomes were clearly defined as primary of a 30-day composite of death, myocardial infarction (MI), and severe recurrent ischemia (SRI) requiring urgent revascularization, or secondary end point, which included the composite and its components at 7, 30 and 180 days and death at 1 year. The study could have done a better job of including some economic and quality of life data as secondary endpoints. The outcomes were assessed by a blinded clinical events committee, which to me, helped to reduce some of the external biases. The study listed the test names used, which included the Pearson X2, log-rank X2, Kaplan-Meier curves, and the level of statistical significance was set at $P < 0.05$. It was very important that propensity scores be calculated, and it did, to deal with the fact that the heparin type was not randomized, and to also account for the baseline differences between the 2 heparin groups, where patients in the LMWH arm were more likely to be older, have hypertension, and more often had recent angina, a history of CHF and MI. Although a c-index of only 0.68 was used to calculate the propensity analysis, the study could not fully adjust for the bias of physician choice of heparin type.

It was interesting to note that not every patient was accounted for in full in the demographics, and no explanation was offered for it.

Analysis of this sub-study showed that there was a trend in the reduction of various ischemic complications seen in patients treated with the combination of GP IIb/IIIa inhibition and LMWH, and that the lower rate of clinical events was achieved without an increase in bleeding or stroke complications.

The ACUTE II

The objective of the ACUTE II study was to provide estimates of the frequency of bleeding incidences using the TIMI criteria of bleeding, in patients treated with enoxaparin relative to UFH, each in combination with Tirofiban and ASA. It was a prospective, randomized, double-blind, double-dummy study which enrolled 525 patients who were at risk for ischemic events and had UA/NSTEMI and who could possibly be scheduled for elective PCI. The title of the study was short and did not state the outcomes. From the list of the authors, it could be detected that at least 4 of them were affiliated with the sponsor and manufacturer of the tirofiban used for the study, and one of the investigators was affiliated with the company that provided the enoxaparin,

injecting a potential source of bias that could have affected the findings. The abstract looked like a structured summary and gave a good outline of the study. The introduction provided a good rationale for the study, with the purpose clearly stating the outcomes to be assessed. The primary outcome measure of this trial was completed on the basis of a modified intention-to-treat principle, including only patients who were randomized and received both tirofiban and at least 1 dose of UFH or enoxaparin. Baseline characteristics looked very similar in the 2 groups except for prior and post infarction angina pectoris and prior angioplasty where the LMWH arm looked a bit higher. The Fisher exact test, a X2 test and Wilcoxon rank-sum test were used to make up for the various variables. The conclusion from the trial was that combining tirofiban with enoxaparin appeared to be safe, relative to therapy with tirofiban plus UFH, because the results showed that using the TIMI bleeding criteria, there was no significant difference in major and minor bleeding in the 2 groups. Although not powered as a means of comparing ischemic end points, the study observed that the LMWH group showed a significant reduction in re-hospitalization for unstable angina (7.1% vs 1.6%, $P=0.002$) and in revascularization (4.3% vs 0.6%, $P=0.01$).

In the study, however, there appeared to have been a cross-over, because many patients were already receiving heparin before enrollment and randomization, and this could have resulted in period effects, and further diluting the findings. Also the low bleeding rates observed in the study (3.5% LMWH arm -4.8% UFH arm), relative to the predicted bleeding rates set at 12.5% from a pre-specified power detection, rendered this study underpowered in detecting differences in the observed bleeding rates, because comparison with bleeding events in other studies is difficult and unreliable because of differences in criteria for major bleeding used, and differences in time interval over which the bleeding was assessed.

NICE-3

The National Investigators Collaborating on Enoxaparin-3 (NICE-3) study was a prospective, open-label, nonrandomized, observational study designed to examine the safety and efficacy of a strategy involving the combined use of enoxaparin and a GP IIb/IIIa antagonist in patients with ACS, and to determine the feasibility and safety of bringing patients who had already received subcutaneous enoxaparin to the catheterization laboratory for coronary intervention, without the supplemental use of UFH. The primary endpoint was safety measured by the cumulative incidence at 30-day follow-up of non-CABG-related major bleeding. The study also had secondary safety endpoints of total major bleeding, minor hemorrhage, and need for transfusions. Primary efficacy endpoint was all-cause death, MI and urgent revascularization. All the outcome criteria were clearly defined. The study population was adequately defined and included subjects with unprovoked chest pain lasting >20 minutes within the previous 24 hours, and CAD evidenced by definitive ECG changes, elevations in cardiac biomarkers, or a history of MI, PCI. In the study, all patients received enoxaparin 1mg/kg SQ every 12 hours together with any one of the available GP IIb/IIIa inhibitors. Some patients who had received UFH were also allowed for enrollment, but only after aPTT was < 50 seconds and/or the ACT was < 150 seconds. While some patients received aspirin

162.5mg, others received 325mg. There was introduction of bias into the study during the selection process, because it was observational and was not randomized, nor blinded, and this might have led to overestimation of efficacy. There was no uniformity in the medication administration process. Some patients received different combination and doses of medications from others, and this could have changed the study results. Allowing subjects who had had UFH in the study, looked to me like a crossover study, which might have resulted in period effects, all of which might have affected the study. And in a study whose purpose was to look at an endpoint without the use of UFH, the inclusion of these patients defeated the whole purpose. In the end, the results did not account for the subjects that were given UFH. The study's result of non-CABG major bleed of 1.9% with the use of enoxaparin combined with GP IIb/IIIa and 1.4% when the subjects had to undergo PCI, led the investigators to conclude that the combination was associated with low incidence of bleeding, because it was consistent with the incidence range reported in previous large clinical trials of GP IIb/IIIa antagonists. Notwithstanding, comparisons with bleeding events in other studies is difficult and unreliable because of differences in criteria for major bleeding used, and differences in time intervals over which the bleeding was assessed. Patients contacted by telephone at day 30 to measure a primary endpoint potentially introduced bias into the results, based on patients perception of their symptoms and patients understanding of the questions posed, and could have led to under-reporting of events.

NRMI 3

From the title of the study of the National Registry of Myocardial Infarction 3 (NRMI 3), it was hard to determine the treatment outcomes and population. The abstract did not specify how treatment was selected for the patients, and gave too much detail in the results overview. The introduction briefly laid out reasoning for the study, while clearly stating the purpose.

The NRMI 3 was a voluntary, nationwide, United States Registry that collected uniform, prospective, data on the treatment of patients with AMI, intended to be used to analyze national practice patterns for infarct treatment, and also to assess individual hospital practice patterns and outcome. The objective of the study was to determine the safety and efficacy of LMWH in combination with GP IIb/IIIa receptor antagonists. The study was not blinded, nor was it randomized. During the treatment of the patients in the participating hospitals, it was unclear as to the dosages of study drugs that were used. The introduction of these flaws and limitations in the study could have led to an overestimation of the safety and efficacy of the treatment.

Also, the patients were not followed up after they were discharged from the various hospitals, and so the study could not ascertain if any of the patients died, or sustained any major bleeding, recurrent ischemia or AMI thereafter discharge. The study performed multivariate analyses to adjust for confounding baseline variables like gender and race, but it was not clear if the adjustment could make up for the differences in the variables in the 2 arms. Other tests that were used were the chi-square for dichotomous variables and the Student's t for continuous variables to compare general population and specific subgroups.

Despite the limitations, the study concluded that LMWH can be safely and effectively substituted for UFH in patients with AMI who received GP IIb/IIIa inhibitors, because it did not find any significant difference of the in-hospital rate of major bleeding between the 2 groups, and neither was there any difference in the occurrences of stroke and intracranial hemorrhage. Also similar in the 2 arms were recurrent ischemia, rates of in-hospital mortality and combined endpoint. What the study did not specify, however, was the type of LMWH used, making the assumption that all the available LMWHs are the same in terms of efficacy and adverse effects.

The A-to-Z Trial

The A phase of the Aggrastat to Zocor trial (A-to-Z Trial) was a prospective, international, open-label, randomized, non-inferiority trial that was designed to assess and compare the safety and efficacy of enoxaparin or unfractionated heparin with tirofiban in patients with ACS. This trial was designed and conducted to address some of the remaining questions on the balance of the risk versus benefit of enoxaparin in different populations of patients with ACS (that is, low risk versus high risk) and in the current medical practice setting for ACS management. To estimate the power and non-inferiority margin at the time of study inception in this study, data from the most pertinent related study (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms {PRISM-PLUS}) was used, in which the odds ratio (OR) for death, MI, or refractory ischemia was 0.66 for the combination of tirofiban and UFH compared with UFH alone. Taking the inverse of the upper bound of the 95% confidence interval (CI) yielded the non-inferiority margin of 1.14. The study used an original proposed sample size of 5200 patients which provided 89% power to meet the non-inferiority boundary, specified as follows: enoxaparin was to be considered non-inferior to UFH if the upper 1-sided 95% confidence boundary (2-sided 90% CI for the enoxaparin effect relative to UFH was less than 1.14.

The title of the study was long and did not reflect the purpose of the study. There was a maximum disclosure of the authors all of whom had MD degrees. It is worth mentioning here that majority of the authors had received honoraria and grant support from Merck and Aventis, the sponsors of the study, and manufacturers of the 2 study drugs used. Some did receive consulting fees and research support from these 2 companies. Some of them were employees of Merck and potentially owned stock and/or held stock options in the company.

The abstract of the study was structured with purpose, methods, results and conclusions, and gave reasonable overview of the trial, but did not specify how treatment was selected for each patient. The introduction of the study provided a basis for the study and described a therapeutic dilemma, with the purpose very succinctly stated.

Because the study was not blinded, the investigators had knowledge of the study drug, and since assignment to an early invasive or early conservative strategy was left to the discretion of the investigator, this could have resulted in changes in therapy, that might have impacted on the findings of the study. Also, prior knowledge of the study drug could have introduced selection bias, all of which would have gone on to affect safety and efficacy determinations. The permission to cross over from the enoxaparin to the

UFH arm for invasive procedures did limit a direct comparison of enoxaparin with UFH, and could also have impacted on the study findings.

Patients received different doses of aspirin, and I thought they could have been fixed at equal doses to prevent it from having varying responses on the patients which could have affected the outcome of the trial.

Patients who received clopidogrel were not accounted for in the analysis, and not every participant was accounted for at the final phase of the study. The study was funded and sponsored by Merck and company. It was unclear what interest, if any, this company had in the overall study.

The pertinent results of the study were that among patients specified for an early conservative strategy, the primary composite endpoint of death, MI, or refractory ischemia at 7 days was 8.4% (169/2018 patients) randomized to enoxaparin, compared with 9.4% (184/1952) to the UFH arm, with HR of 0.88; 95% CI, 0.71-1.08. This 1% absolute and 12% relative benefit in favor of enoxaparin compared with UFH for the prevention of the composite end point of death, MI, or refractory ischemia fell well within specified bounds for non-inferiority.

The SYNERGY Trial

The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was designed to define the role of enoxaparin in patients with non-ST-segment elevation ACS at high risk who were to be managed with an early invasive strategy, and to evaluate the efficacy and safety of enoxaparin versus UFH when administered with established therapy including GP IIb/IIIa receptor antagonists and aspirin, in these patient populations.

The title specified the treatment and population without stating any conclusions. Together with the abstract, they appropriately reflected the content of the study. Majority of the authors, including the 2 co-principal investigators had affiliation with Aventis-the sponsor of the study, and maker of enoxaparin, and did receive research funding, grants, speakers honoraria and consulting fees from the company. Some of them served as consultants for the company, and one actually worked for Aventis. It was unclear if their association had any influence on the results and conclusions of the trial. The introduction, however, supplied a background that provided a strong rationale for the trial.

The SYNERGY was a prospective, randomized, open-label, multicenter, international trial that looked into the cause of therapy of patients with non-ST segment elevation ACS and also looked into evaluating the potential superiority of enoxaparin over UFH.

Another potential biases may have been introduced because of the open-label study design. Physician choices of medical therapies such as GP IIb/IIIa receptor inhibitors, the decision to perform cardiac catheterization, and investigator assessment of end points could have been influenced by knowing the treatment. Also potential biases may have been admitted by differential reporting of end point events between treatment groups. Since therapies were switched after randomization and before revascularization, this could also have resulted in higher adverse events and end points. The study population

was from geographically diverse areas and different clinical practice settings, and consisted of large treatment group identified using broad inclusion criteria. The efficacy results of the SYNERGY study showed that enoxaparin was not superior or inferior to UFH in this patient population, and the rates of the primary endpoint of all-cause death or nonfatal MI were almost identical between the 2 treatment groups. Nor were there any differences found in rates of ischemic events during PCI.

Summary of Findings

The efficacy results of all these studies showed that LMWH was not superior or inferior to UFH when combined with GP IIb/IIIa inhibitors in this patient population. The studies showed that the rates of the primary endpoint of all-cause death or nonfatal MI were almost identical between the 2 heparin groups when combined with GP IIb/IIIa antagonist, with the A phase of the A-to-Z trial, the ACUTE II and the PARAGON B giving an edge to LMWH, despite the studies' many limitations. After enumerating the advantages and disadvantages of the 2 heparins, the NRMI 3 findings indicated that LMWH could be safely and effectively substituted for UFH, even though UFH has traditionally been the treatment of choice for patients with ACS.

The NICE-3 study which was not powered to assess efficacy of LMWH, demonstrated that a regimen of enoxaparin plus a GP IIb/IIIa antagonist did not result in excess non-CABG major bleeding in patients with ACS, including those undergoing PCI, and compared favorably to event rates in TACTICS/TIMI 18. The notion that the irreversibility of the activities of LMWH could have some limitations in some patients was dispelled during the studies, especially when renally and patient-weight dosed. This finding was supported by the observation made in the A phase of the A-to-Z trial which reported that enoxaparin is not associated with excess bleeding compared to UFH when a conservative management strategy is employed. And because the primary endpoint of death, MI, or refractory ischemia at 7 days did not produce any statistical difference between the 2 arms, the authors of the A phase of the A-to-Z trial concluded that the result fell well within the pre-specified non-inferiority boundary, so enoxaparin was not inferior to UFH.

The SYNERGY study put the 2 groups at par with each other in terms of safety and efficacy. It cautioned, however, that there could be a modest risk of bleeding with enoxaparin, especially in those patients with pre-randomization treatment (about 75% of its study population) and crossovers.

Clinical Recommendations

The 6 study results, in combination with a systemic overview of clinical studies with LMWH in over thousands of patients show that LMWH is equally effective and safe as UFH, in preventing the composite endpoint death or nonfatal MI. The results from these studies suggest that LMWH is an excellent upstream therapy and is a useful and reasonable alternative to UFH in patients with ACS undergoing aggressive, early

intervention with concomitant antiplatelet therapy. An important lesson from the SYNERGY results is that antithrombin therapies should not be switched in patients with ACS, because switching could be associated with an increased bleeding risk and decreased clinical benefits. It is interesting to note that the relationship between pre-treatment and risk of bleeding has not been established as casual, and that many factors can also come into play, such as age, renal function, coronary procedures, and adjunctive therapies.

Since different LMWHs were used in each of these studies, data regarding the efficacy and safety of one LMWH cannot necessarily be extrapolated to another, because each agent of this class is a distinct entity, in terms of its pharmacokinetic and pharmacodynamic profile.

An economic analysis of enoxaparin versus UFH in several different clinical settings would be extremely helpful for not only physicians but also pharmacists and formulary decision makers to make a fully informed choice of antithrombin therapy.

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