Unfractionated Heparin in Cardiology: Redefining the Standard of Practice

Thomas L. Rihn, Pharm.D., José Díez, M.D., FACC, FSCAI, and the Heparin Consensus Group

Acute coronary syndromes (ACS) consist of unstable angina (UA), non–ST-segment myocardial infarction (NSTEMI) and ST-segment myocardial infarction (STEMI). Timely intervention with effective, predictable antithrombin therapy is critically important in the early management of these conditions. Platelet aggregation is also an important component of thrombus formation in arterial thrombosis. Historically, unfractionated heparin (UFH) has been combined with aspirin to suppress thrombin propagation and fibrin formation; however, its effectiveness has been questioned in this setting. Unlike newer anticoagulant alternatives, UFH paradoxically stimulates platelet aggregation, which may further promote clot formation. In addition, obtaining a valid therapeutic activated partial thromboplastin time (aPTT) in cardiology patients is a major challenge, and dosing is complex. Due to substantial variation in reagents and instruments, target aPTT ranges for UFH in ACS clinical trials cannot be extrapolated to individual institutions. Further, the risk of ischemic events is greater shortly after abrupt discontinuation of UFH compared with alternative agents with longer half-lives and less stimulation of platelet aggregation. Key UA-NSTEMI clinical trials have demonstrated that UFH is inferior to newer agents, such as the low-molecular-weight heparins (LMWHs). Consistent with this evidence, the most recent practice guidelines of the American College of Cardiology and the American Heart Association in UA-NSTEMI identify the LMWH enoxaparin as the agent of choice. In patients with STEMI receiving the fibrinolytic tenecteplase as reperfusion therapy, enoxaparin has also been superior to UFH in combination. In percutaneous procedures, newer indirect (enoxaparin) and direct (bivalirudin) antithrombins have demonstrated safety and efficacy. There is little doubt that as we move forward in optimizing adjunctive anticoagulation in the cardiology setting, UFH will largely be replaced by better antithrombin agents.

Key Words: unfractionated heparin, activated partial thromboplastin time, antithrombin agents, anticoagulation, acute coronary syndromes, low-molecular-weight heparin.

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From the School of Pharmacy, Duquesne University, Pittsburgh, and University Pharmacotherapy Associates, LLC, Monroeville, Pennsylvania (Dr. Rihn); and Catheterization Laboratories, Tulane University Health Sciences Center, New Orleans, Louisiana (Dr. Díez).

Address reprint requests to Thomas L. Rihn, Pharm.D., University Pharmacotherapy Associates, LLC, 4105 Monroeville Boulevard, Monroeville, PA 15146; e-mail: trihn@UPA-LLC.com.

The use of intravenous unfractionated heparin (UFH) for acute management of unstable angina and non–ST-segment elevation myocardial infarction (UA-NSTEMI) was introduced in the early 1980s. Subsequently, the benefits of adding UFH to aspirin were adequately demonstrated, and the combination was widely used in clinical practice. More recently, newer agents have been

adopted in practice because of more favorable pharmacologic profiles, more predictable anticoagulant response, and superior clinical evidence.

To adequately assess contemporary anticoagulant therapy in cardiology practice today, the pharmacologic nuances, laboratory monitoring, scope and depth of clinical evidence, practice guidelines, and pertinent limitations and issues must be evaluated.

Pharmacologic Differentiation: Impact on Surrogate Markers

Unfractionated heparin has the undesirable property of releasing von Willebrand's factor (vWf) from the blood vessel wall.[1] In contrast, low-molecular-weight heparins (LMWHs) may be associated with suppression of vWf, depending on the specific agent. One research group tested the hypothesis that different anticoagulants may produce different effects on platelets and release of vWf in patients with unstable angina.[1] A rise in vWf generally is associated with increased platelet aggregation and negative ischemic outcomes. The study assessed the effect of UFH, enoxaparin, dalteparin, and pegylated hirudin on short-term vWf release. The four different anticoagulants did not provide the same level of protection from vWf release, which was significantly lower with enoxaparin than with UFH or dalteparin. This differentiation is particularly important in the treatment of arterial thrombosis, such as acute coronary syndromes (ACS), in which platelets and platelet aggregation play a central role in the pathogenesis of the disease.

The inhibition of both fibrin formation and platelet aggregation is a desirable attribute for any anticoagulant. However, UFH paradoxically stimulates platelet aggregation as a result of elevated vWf levels and through its interaction or binding with platelet factor 4. These undesirable pharmacologic effects may have important prognostic implications and, in part, may explain different clinical outcomes in UFH versus other comparators observed in comparative clinical trials.

Challenges of Monitoring UFH

Because the anticoagulant response to UFH varies among patients, it is standard practice to adjust the dosage and monitor its effect using the activated partial thromboplastin time (aPTT). In the past, clinicians felt secure in thinking that a strong relationship existed between the effect of UFH on the aPTT and its clinical effectiveness. However, recent evidence has questioned the strength of such a relationship for the following reasons:

- Initial findings supporting a strong relationship between the effect of UFH on aPTT and clinical efficacy were based on retrospective subgroup analysis and were subject to bias.[2]
- No direct relationship between aPTT and efficacy was observed in the substudy analysis of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I study in patients with acute myocardial infarction who were treated with fibrinolytic therapy followed by UFH.[3]
- Even if aPTT results were predictive of clinical efficacy, the predictive value of the test would be greatly limited because commercial aPTT reagents vary considerably in responsiveness to UFH.[4]
- Therapeutic ranges 1.5–2.5 times the control value are subtherapeutic for most modern aPTT reagents. Differences in coagulometer instrumentation are also important.

Although standardization and validation of aPTT values can be achieved by calibration against plasma UFH concentration (0.2–0.4 U/ml based on protamine titration or 0.3–0.7 U/ml based on antifactor Xa chromogenic assay), this is beyond the scope of clinical laboratories in many health systems. Nevertheless, site-specific validation of the aPTT is required to ensure therapeutic dosing of UFH and optimal outcomes in acutely ill cardiology patients.

Despite its limitations, the aPTT remains the most widely used method for monitoring UFH therapy. Activated clotting time (ACT), a test performed on whole-blood samples at the point of care, is used most often in the cardiac catheterization laboratory or in cardiovascular surgery to monitor the effects of high-dose UFH when the aPTT is not suitable.

In contrast to UFH, because of their preferential effect on factor Xa, LMWHs are best monitored using antifactor Xa activity. However, because of their predictable anticoagulant response, antifactor Xa levels are not routinely used in clinical practice. They are generally monitored only when LMWHs are administered in high-risk populations, such as obese patients and those with significant renal impairment.

Clinical Evidence with UFH

The clinical evidence with UFH in cardiology patients, and more specifically those with ACS, can be divided into two main sections: UA-NSTEMI, requiring medical stabilization with or without a glycoprotein IIb-IIIa receptor blocker (GPB); and STEMI, requiring medical stabilization with or without fibrinolytic therapy. An exhaustive discussion of the clinical evidence in each of these areas is beyond the scope of this article, but Figure 1 highlights key clinical trials of UFH in patients with UA-NSTEMI.

UA-NSTEMI

Several randomized, placebo-controlled trials that evaluated UFH for short-term stabilization of UA-NSTEMI have been particularly important in shaping anticoagulant practice.[5–8] When given alone, UFH has been effective in preventing myocardial infarction and recurrent angina.[6–8] Results of a meta-analysis of six small trials suggest that when combined with aspirin, UFH reduces short-term rates of cardiovascular death and myocardial infarction by approximately 30% compared with aspirin alone.[9] Considering the actual risk reduction and confidence intervals, however, the benefit was of borderline significance.[10]

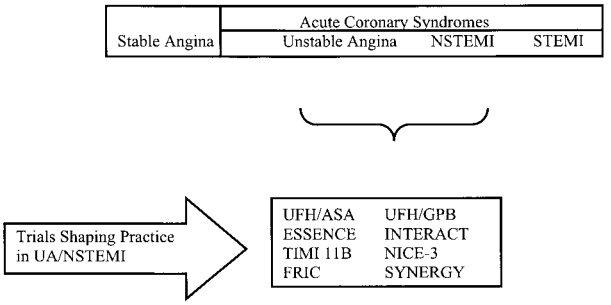

Figure 1. Key trials of unfractionated heparin (UFH) in patients with unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI). STEMI = ST-segment elevation myocardial infarction; UFH/ASA = meta-analysis of six trials of unfractionated heparin with aspirin; ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events; TIMI = Thrombolysis in Myocardial Infarction; FRIC = Fragmin in Unstable Coronary Artery Disease; UFH/GPB = pooled analysis of six trials of unfractionated heparin combined with glycoprotein IIb-IIIa receptor blocker; INTERACT = Integrilin and Enoxaparin Randomized Assessment of Acute Coronary syndrome Treatment; NICE = National Investigators Collaborating on Enoxaparin; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb-IIIa inhibitors.

UFH versus LMWH in Medical Stabilization

A number of randomized controlled clinical trials comparing UFH with LMWH have been conducted. In the Fragmin in Unstable Coronary Artery Disease (FRIC) trial, which compared UFH with dalteparin in patients with UA-NSTEMI, the efficacy and safety of UFH and dalteparin were equivalent.[11] The Thrombolysis in Myocardial Infarction (TIMI) 11B trial and the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trial provide the best comparative efficacy data for the use of UFH versus LMWH in the treatment of UA-NSTEMI.[12, 13] Both of these trials compared UFH with enoxaparin. The primary composite end points were death, myocardial infarction, and urgent revascularization in the TIMI 11B trial; and death, myocardial infarction, and recurrent angina in the ESSENCE trial.

The ESSENCE trial demonstrated a significant reduction in the composite end point at 14 days, 30 days, and 1 year for enoxaparin compared with UFH. In the short-term phase of the TIMI 11B trial, a significant reduction was observed in the composite end point at 14 days compared with UFH. In the long-term phase (43 days of enoxaparin treatment), the composite end point again was reduced significantly compared with UFH. A meta-analysis of the ESSENCE and TIMI 11B trial results (involving 7081 patients) demonstrated the superiority of enoxaparin over UFH.[14]

The benefit was actually greater in the meta-analysis than in the two individual studies. The end point of death in each patient with myocardial infarction was significantly lower with enoxaparin versus UFH. Thus, both of these comparative trials showed that enoxaparin was superior to UFH in the treatment of UA-NSTEMI.

Differences in study design, end points, and treatment regimens prevent a direct comparison of results from these studies of UFH versus LMWH.

With the recognition that platelet activation and aggregation were important contributors to thrombus formation in patients with UA-NSTEMI, it was hypothesized that more potent platelet inhibition through the use of GPBs could further prevent acute ischemic events. In the setting of medical stabilization, UFH in combination with tirofiban in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable

Signs and Symptoms (PRISM PLUS) trial[15] and eptifibatide in the Eptifibatide in the Unstable Angina Receptor Suppression Using Integrilin Trial (PURSUIT)[16] significantly reduced ischemic events at 30 days.

UFH versus LMWH in Percutaneous Procedures

Since the introduction of angioplasty in 1977, UFH has been the standard agent for therapeutic anticoagulation during percutaneous procedures. Close monitoring of UFH during such procedures is mandatory to achieve a balance between efficacy and safety. There is a strong association between subtherapeutic dosing of UFH and thrombotic events during surgical revascularization and percutaneous procedures.[17, 18] The ACT can be evaluated using point-of-care systems, making it more suitable for monitoring during revascularization. The ACT has been inversely related to the likelihood of abrupt vessel closure.[19] However, high ACT levels also are associated with increased bleeding risk, and ischemic events still occur in 6–8% of patients.[20, 21]

A pooled analysis of six randomized clinical trials evaluated ischemic and bleeding events according to the minimum and maximum ACT levels with UFH.[22] A nonlinear decrease was observed in the 7-day composite of death, myocardial infarction, and revascularization with increasing ACT levels. The lowest bleeding risk corresponded to an ACT level of 300–350 seconds in patients not receiving GPBs. In those receiving GPBs, bleeding events increased in patients with ACT values above 300 seconds. Therefore, an ACT of approximately 200 seconds is recommended when UFH is combined with abciximab, and up to 300 seconds with the small-molecule GPBs (e.g., tirofiban and eptifibatide).

The benefit of UFH in combination with GPBs in patients with percutaneous coronary intervention (PCI), with a stent, has been demonstrated. The Evaluation of Platelet IIb-IIIa Inhibitor for Stenting (EPISTENT) trial in patients receiving both abciximab and UFH demonstrated a 50% reduction in ischemic events at 30 days.[23] In contrast, the Enhanced Suppression of the Platelet IIb-IIIa Receptor with Integrilin Therapy (ESPRIT) trial demonstrated a 35% reduction in ischemic events in patients receiving eptifibatide with UFH.[24]

UFH versus LMWH Combined with a GPB

Although UFH plus a GPB has been the combination of choice in patients with PCI, numerous limitations have been associated with the use of UFH. Because GPBs play an important role in the treatment of high-risk patients with ACS, several recent trials compared the use and safety of combining GPBs with UFH versus LMWH.

The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial evaluated 746 high-risk patients with UA-NSTEMI who were treated with the GPB eptifibatide.[25] Patients then were randomized to receive either subcutaneous enoxaparin or intravenous UFH. The primary end point was major bleeding at 96 hours. Secondary efficacy end points were also assessed.

The trial confirmed the difficulty of establishing early therapeutic aPTTs with UFH. Other key findings with UFH were increased major bleeding at 96 hours (enoxaparin 0.6% vs UFH 4.6%, p=0.03), more ischemic episodes (enoxaparin 14.3% vs UFH 25.4%, p=0.0002), and more 30-day deaths and myocardial infarctions (enoxaparin 5% vs UFH 9%, p=0.03). Thus, the results indicated that UFH was less effective and safe than an LMWH combined with a GPB for medical stabilization.

Considering that enoxaparin had been superior to UFH for medical stabilization of patients with UA-NSTEMI and had been preliminarily safe and effective combined with GPBs, the National Investigators Collaborating on Enoxaparin (NICE)-3 trial assessed the use of enoxaparin alone and in combination with a GPB in patients with UA-NSTEMI.[26] The objectives of the study were to assess the safety profile (primarily major bleeding) of enoxaparin and a GPB (abciximab, eptifibatide, or tirofiban) in patients with ACS, and to assess the feasibility and safety of bringing patients to the catheterization laboratory with combination therapy (with no UFH therapy).

A total of 661 patients with UA-NSTEMI were randomized to receive enoxaparin alone or enoxaparin plus a GPB. The primary end point was major bleeding not related to a coronary artery bypass graft (CABG) during hospitalization. Secondary end points were clinical efficacy as the composite end point of death, myocardial infarction, or ischemia-driven target vessel revascularization and minor bleeding. If patients were taken to the catheterization laboratory, combination therapy was continued and UFH was not administered. If they were taken to the laboratory within 8 hours of the last dose of enoxaparin, no additional enoxaparin was given. If more than 8 hours had elapsed

since the last dose of subcutaneous enoxaparin, a dose of intravenous enoxaparin 0.3 mg/kg was given.

Important findings of the NICE-3 study were the following:

- Combining enoxaparin with a GPB did not result in excess major bleeding.
- Patients receiving combination therapy safely underwent PCI.
- Clinical outcomes were comparable to those noted in previous GPB-UFH studies.
- It did not appear necessary to administer UFH in patients with UA-NSTEMI undergoing PCI who were treated with subcutaneous enoxaparin and a GPB.

The recent Aggrastat to Zocor (A to Z) trial showed that in patients with ACS receiving aspirin and tirofiban, the random allocation to enoxaparin versus UFH was associated with a trend toward reduction in the composite of death, myocardial infarction, or refractory ischemia at 7 days with enoxaparin treatment (enoxaparin 8.4% vs UFH 9.4%).[27]

The TIMI 11B, ESSENCE, INTERACT, NICE, and A to Z trials served as an important foundation for real-world investigations, such as the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb-IIIa inhibitors (SYNERGY) trial.[28] Since most patients with UA-NSTEMI undergo early PCI today, the SYNERGY trial evaluated the issue of UFH versus LMWH for treatment initially and during early invasive management. The trial was a prospective, randomized, open-label study evaluating the efficacy and safety of enoxaparin versus UFH in high-risk patients with non–ST-elevation ACS who were treated with an early invasive strategy. A total of 10,027 patients were randomly assigned to either subcutaneous enoxaparin 1 mg/kg every 12 hours or a bolus of intravenous UFH 60 U/kg, then 12 U/kg/hour (Figure 2).

Median patient age was 68 years; 34% of the patients were women. Among patients receiving enoxaparin, catheterization could be performed at any time after the last dose. No additional enoxaparin was given if PCI was performed less than 8 hours since the last subcutaneous dose, but a dose of intravenous enoxaparin 0.3 mg/kg was given if PCI was performed 8–12 hours after the last dose. The SYNERGY trial, conducted at 467 investigative sites in the United States, Canada, Europe, and South America, is the largest trial ever conducted in patients with UA-NSTEMI. Eligible patients met at least two of the following inclusion criteria: age 60 years or older, increasing (transient) or decreasing ST segment, or elevated levels of creatine kinase–MB isoenzyme or troponin. The primary end point of the trial was a composite of death or myocardial infarction at 30 days.

Significant crossover was observed between enoxaparin and UFH during the study; therefore, the enrollment target was extended from 8000 to 10,000 patients. Again, the SYNERGY trial was pivotal because it assessed real-world use of subcutaneous enoxaparin in early transition to PCI without additional anticoagulation with UFH. Results indicated that enoxaparin was not superior to UFH but met prespecified criteria for noninferiority. Thus, it was at least as effective as UFH in reducing the incidence of death or myocardial infarction at 30 days in the treatment of high-risk patients with non–ST-elevation ACS undergoing an early invasive strategy (enoxaparin group 14.0%, UFH group 14.5%, p=NS). There also was no difference in death alone, myocardial infarction alone, or stroke rates.

In both groups, 92% of patients were taken to the catheterization laboratory during their baseline hospitalization (median time approximately 21.5 hrs after randomization). Average time to PCI was 23 hours (range 6–49 hrs) in the enoxaparin group versus 22 hours (range 6–48 hrs) in the UFH group; 56% of the enoxaparin group and 58% of the UFH group were also given a GPB.

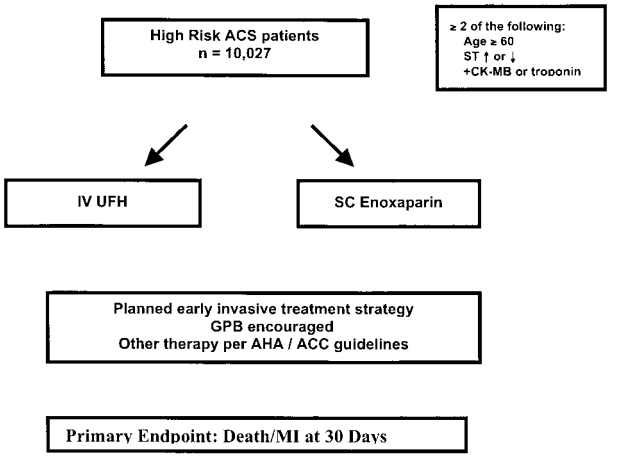

Figure 2. Design of the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb-IIIa inhibitors) trial. ACS = acute coronary syndromes; CK-MB = creatine kinase–MB isoenzyme; GPB = glycoprotein IIb-IIIa receptor blocker; AHA = American Heart Association; ACC = American College of Cardiology.

One of the original concerns about administering enoxaparin in the catheterization laboratory and during PCI procedures was whether the time needed to reach therapeutic anticoagulation would be sufficient when patients were catheterized early. The SYNERGY trial demonstrated no difference in abrupt closures, unsuccessful PCI procedures, or percentage of patients requiring emergency CABG.

Safety in the SYNERGY trial was assessed by GUSTO and TIMI major bleeding criteria, rate of transfusions, and rate of intracranial hemorrhage and bleeding causing hemodynamic instability (Table 1).[28] The frequency of GUSTO severe bleeding was 2.9% with enoxaparin vs. 2.4% for UFH (p=NS). The frequency according to the TIMI non–CABG-related major bleeding criteria was 2.4% for enoxaparin versus 1.7% for UFH (p=0.025), a statistically significant difference. Also, no difference was observed in the frequency of blood transfusions or intracranial hemorrhage. Overall rate of bleeding was confounded by extensive switching of anticoagulant therapy. Rates of severe (GUSTO criteria) and major (TIMI criteria) bleeding and of death or myocardial infarction were higher in patients whose treatment changed from UFH to enoxaparin or vice versa than in those given only one drug.

Of note, outcomes were superior in patients receiving enoxaparin versus UFH throughout the course of therapy. A prespecified secondary analysis of 5637 patients enrolled in the SYNERGY trial showed that those who began receiving treatment with enoxaparin versus UFH before randomization and continued receiving it throughout the course of therapy had an 18% relative risk reduction in the frequency of death and myocardial infarction at 30 days (enoxaparin 12.8% vs UFH 15.6%, p=0.0029). In addition, there was no statistically significant difference in non-CABG GUSTO severe or non-CABG TIMI major bleeding between UFH and enoxaparin in these patients. Non-CABG GUSTO severe bleeding occurred in 2.0% of patients receiving UFH versus 2.7% of patients receiving enoxaparin (p=NS), and non-CABG TIMI major bleeding occurred in 1.8% of patients receiving UFH versus 2.2% of patients receiving enoxaparin (p=NS). To put this in proper perspective, in patients treated with consistent enoxaparin therapy, the number needed to treat with enoxaparin to observe one additional non-CABG TIMI major bleed versus UFH is estimated to be 250 patients. These findings indicate that switching anticoagulant agents during an episode of ACS, including the time spent in the catheterization laboratory, provided no clinical benefit and potentially increased bleeding complications.

Table 1. Bleeding Events Reported in the SYNERGY Trial Based on Criteria from Other Trials

Bleeding Events	Enoxaparin Group (n=4993)	UFH Group (n=4985)	p Value
Severe bleed[a]	2.9	2.4	0.107
RBC transfusion	17.0	16.0	0.155
Major bleed[b]	9.1	7.6	0.008
CABG-related	6.8	5.9	0.081
Non-CABG related	2.4	1.7	0.0025
ICH	< 0.1	< 0.1	NS

SYNERGY = Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb-IIIa inhibitors; UFH = unfractionated heparin; RBC = red blood cell; CABG = coronary artery bypass graft; ICH = intracranial hemorrhage.
Data are percentages of patients.
From reference 28.
[a]As defined in the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) study criteria.
[b]As defined in the TIMI (Thrombolysis in Myocardial Infarction) study criteria.

Extensive data have demonstrated enoxaparin's superiority in the management of ACS, its effectiveness in early invasive patient management, and its convenience of use. Thus, many practitioners now consider enoxaparin the anticoagulant of choice across the ACS continuum.

Practice Guidelines

As evidence evolves, practice guidelines evolve. The American College of Cardiology and American Heart Association (ACC-AHA) 2002 practice guidelines for the management of patients with UA-NSTEMI contained some significant changes relating to anticoagulation therapy.[29] In general, anticoagulation with subcutaneous LMWH or UFH should be added to antiplatelet therapy with aspirin and/or clopidogrel. The level of evidence is A (the highest level), and this is a class I guideline, indicating that the intervention is both useful and effective. The second part of the anticoagulation guideline represents the most important change. Enoxaparin is now recommended as the anticoagulant of choice for such patients, as a class IIa guideline with an A level of evidence. This indicates that the weight of recent evidence favors enhanced efficacy with enoxaparin versus UFH.

A small-molecule GPB (tirofiban or eptifibatide)

Table 2. Treatment Arms in the ASSENT-3 Trial

	Agents Administered		
Study Arm	Fibrolytic	GPB	Anticoagulant
1	Full-dose tenecteplase	—	Standard-dose UFH
2	Half-dose tenecteplase	Abciximab	Low-dose UFH
3	Full-dose tenecteplase	—	Enoxaparin

ASSENT = Assessment of the Study and Efficacy of a New Thrombolytic Regimen; GPB = glycoprotein IIb-IIIa receptor blocker; UFH = unfractionated heparin.
From reference 38.

should be administered in addition to aspirin and LMWH or UFH in patients with continuous ischemia or high-risk features (level A), and to patients for whom catheterization and PCI are planned (level B). Ample evidence supports the safety and efficacy of the combination of UFH and GPBs (both small molecules and the monoclonal antibody abciximab) in the PCI setting. The use of treatment with LMWHs and direct thrombin inhibitors in percutaneous procedures will likely be addressed in future practice guidelines.

STEMI

An overview of randomized clinical trials performed before the fibrinolytic era reported a 17% reduction in mortality and a 22% reduction in reinfarction with UFH therapy.[30] The control groups in these STEMI trials were not given aspirin.

Although in the past it was generally accepted that UFH was effective after coronary fibrinolysis, the results of more recent studies do not fully support this view. The combination of UFH and aspirin was compared with aspirin 325 mg/day alone in the sixth European Cooperative Study Group (ECSG-6) trial.[31] Patency at a mean of 81 hours was 80% in the UFH group and 75% in the aspirin comparison group. Two large trials, the International Study Group[32] and the International Study of Infarct Survival (ISIS-3)[33] assessed the value of adjunctive UFH in patients receiving fibrinolytic therapy and aspirin. In both trials, patients were given subcutaneous UFH 12,500 U every 12 hours.

The International Study Group trial (20,891 patients) reported no difference in mortality between groups, whereas the risk of major bleeding was significantly increased in the UFH group. The ISIS-3 study (41,299 patients) reported no difference in the vascular mortality rate or in-hospital rates of reinfarction between groups. Major bleeding requiring transfusion was more frequent in the UFH group. Thus, in both studies, moderate doses of UFH produced marginal benefits at the cost of increased bleeding.

The issue of whether intravenous UFH would prove more effective and at least as safe as the subcutaneous regimen used in the ISIS-3 study was addressed in the GUSTO-I trial.[34] In this trial, intravenous UFH was not superior to subcutaneous UFH in patients receiving streptokinase in terms of efficacy or safety. Because streptokinase significantly depleted fibrinogen stores and increased the levels of fibrinogen degradation products, and thus bleeding risk, use of UFH was not subsequently recommended in conjunction with streptokinase.

Data regarding the role of UFH in patients treated with tissue plasminogen activator are somewhat limited. A pooled analysis of six randomized trials revealed only a trend toward reduced in-hospital mortality with UFH treatment, but a significantly higher rate of hemorrhagic complications.[35, 36]

The ACC-AHA guidelines for the management of patients with STEMI suggest adjusting the intensity of UFH based on the fibrinolytic agent used and the presence or absence of risk factors for systemic embolism.[37] Unfractionated heparin is a class IIa recommendation for patients undergoing reperfusion with agents such as alteplase, tenecteplase, or reteplase. Of note, the guidelines are 5 years old and have not incorporated the evidence from recent antithrombotic combination trials in STEMI.

Combination Therapy: UFH versus LMWH

The fundamental (two-part) question in assessing various antithrombotic combinations in STEMI is, can the speed, durability, and completeness of pharmacologic reperfusion be enhanced in STEMI, and can fibrinolytic outcomes be further improved through addition of LMWHs (instead of UFH) and/or GPBs?

Table 3. Primary End Points in the ASSENT-3 Trial

Primary End Point	Enoxaparin Group	Abciximab + Low-Dose UFH Group	Standard-Dose UFH Group	p Value
Efficacy				
30-day mortality, in-hospital reinfarction, or refractory ischemia	11.4	11.1	15.4	0.0002 (UFH vs enoxaparin) <0.0001 (UFH vs abciximab)
Efficacy and safety				
30-day mortality, in-hospital reinfarction or refractory ischemia, in-hospital ICH, or other major bleeding events	13.7	14.2	17.0	0.0037 (UFH vs enoxaparin) 0.01416 (UFH vs abciximab)

ASSENT = Assessment of the Study and Efficacy of a New Thrombolytic Regimen; UFH = unfractionated heparin; ICH = intracranial hemorrhage.
Data are percentages of patients.
From reference 38.

Table 4. Individual End Points in the ASSENT-3 Trial

End Point	Enoxaparin Group	Abciximab + Low-Dose UFH Group	Standard-Dose UFH Group	p Value
30-Day mortality	5.4	6.6	6.0	0.25
In-hospital reinfarction	2.7	2.2	4.2	0.0009
In-hospital refractory ischemia	4.5	3.2	6.5	<0.0001
In-hospital ICH	0.9	0.9	0.9	0.98
Other major bleeding events	3.0	4.3	2.2	0.0005

ASSENT = Assessment of the Study and Efficacy of a New Thrombolytic Regimen; UFH = unfractionated heparin; ICH = intracranial hemorrhage.
Data are percentages of patients.
From reference 38.

Evidence regarding the use of antithrombotic combinations in patients with STEMI has been reported. The Assessment of the Study and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial, a phase III study, evaluated novel antithrombotic combinations in patients with STEMI.[38] The specific fibrinolytic, GPB, and anticoagulants that were combined in each arm of ASSENT-3 are shown in Table 2.

The results of the ASSENT-3 trial are summarized in Tables 3 and 4. The full-dose tenecteplase-enoxaparin arm and the half-dose tenecteplase–abciximab–low-dose UFH arm were superior to the full-dose tenecteplase–standard-dose UFH arm in reducing the composite end point of death, myocardial infarction, or refractory ischemia at 30 days. In terms of major bleeding, full-dose tenecteplase-enoxaparin was not statistically different from full-dose tenecteplase–standard-dose UFH. Compared with high-dose tenecteplase–abciximab–low-dose UFH, both full-dose tenecteplase–standard-dose UFH and full-dose tenecteplase–enoxaparin were associated with a significantly lower rate of major bleeding.

The more recently reported ASSENT-3 PLUS trial involved prehospital administration of similar antithrombotic combinations.[39] In this trial, full-dose tenecteplase-enoxaparin decreased reinfarction rates compared with full-dose tenecteplase-UFH. The rate of intracranial hemorrhage was similar for full-dose tenecteplase-enoxaparin and full-dose tenecteplase-UFH in patients younger than 75 years. However, in patients aged 75 years or older, intracranial hemorrhage was more frequent in the full-dose tenecteplase-enoxaparin group, suggesting that the enoxaparin dosage should be reduced in elderly patients. In the continuing Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Trial (ExTRACT–TIMI 25) in patients with STEMI, enoxaparin dosage is being reduced in patients aged 75 years or older by eliminating the 30-mg bolus dose and

decreasing the subcutaneous dosage to 0.75 mg/kg every 12 hours.

Conclusion: Redefining the Standard of Practice

In defining an anticoagulant standard of practice in high-risk cardiology patients, it is essential to assess key clinical evidence carefully as well as important limitations and issues associated with the use of UFH versus other agents. Some of the limitations and issues associated with UFH include the following:

- Complex pharmacokinetics and dosing
- Stimulation of platelet aggregation
- Requirement for constant monitoring
- Uniform reliability and validity of aPTT a major issue
- Difficulty in maintaining therapeutic anticoagulation
- Confusion regarding use and validity of dosing nomograms
- Rebound ischemia after discontinuation in patients with ACS
- ACC-AHA guidelines recommend alternative therapy for UA-NSTEMI
- Many potential drug-related problems
- Significant total health cost

The complex pharmacologic profile and dose-dependent pharmacokinetics of UFH make it difficult to determine an effective dosage rapidly for patients with ACS. The challenge of individually validating a true therapeutic aPTT range and achieving early therapeutic aPTT values is a major issue. A myriad of dosing nomograms further compounds UFH dosing.

In contrast, the pharmacologic profile and dose-independent pharmacokinetics of LMWHs allow for a predictable anticoagulant effect. In addition, they do not require monitoring except in certain high-risk populations. Paradoxically, UFH stimulates platelet aggregation, which may play a role in rebound ischemia on discontinuation of the drug. The LMWHs have longer half-lives, do not stimulate platelet aggregation significantly, and have less potential to produce rebound reactions. Consensus guidelines are evidence based and have integrated the superiority evidence of agents such as enoxaparin into practice recommendations. In addition, UFH is associated with an increased risk of drug-related problems, such as heparin-induced thrombocytopenia and medication errors. Finally, although drug acquisition cost is low, other health costs associated with UFH therapy in patients with ACS have reportedly been higher than with agents such as LMWHs.

These important limitations and issues suggest that a more predictable antithrombin agent should be considered for treatment. However, the search for optimal antithrombin therapy in cardiology patients is not limited to LMWHs. Continuing research will further define the role of pentasaccharides, direct antifactor Xa agents, and direct thrombin inhibitors in this setting. The recommendations of the Heparin Consensus Group on the use of injectable anticoagulants in cardiology are provided in Appendix 1.

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Appendix 1. Recommendations on the Use of Injectable Anticoagulants in Cardiology

1. Because it is a major challenge to obtain a valid therapeutic aPTT with UFH in cardiology patients, and dosing is complex, more predictable anticoagulation would be desirable.
2. Due to substantial variation in reagents and instruments, target aPTT ranges for UFH in ACS trials should not be extrapolated to individual institutions.
3. The greater risk of ischemic events shortly after abrupt discontinuation of UFH therapy compared with other alternatives with longer half-lives and less stimulation of platelet aggregation must be considered.
4. According to the most recent ACC-AHA practice guidelines for treatment of patients with UA-NSTEMI, enoxaparin has been superior to UFH and is recommended as the agent of choice.
5. In patients with STEMI receiving the fibrinolytic tenecteplase as reperfusion therapy, enoxaparin should be considered superior to UFH.
6. In percutaneous procedures, newer indirect (enoxaparin) and direct (bivalirudin) antithrombins have demonstrated safety and efficacy, which should be reflected in practice guidelines.
7. If overall health costs are considered together with safety, efficacy, and convenience, UFH represents an inferior approach, and newer anticoagulants should be used in contemporary practice.