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Anticoagulation in the Management of ST-Segment Elevation Myocardial Infarction

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Abstract

Patients with ST-segment elevation myocardial infarction (STEMI) require immediate reperfusion therapy in order to salvage ischemic myocardial tissue and reduce mortality. Reperfusion therapy can be provided mechanically with primary percutaneous coronary intervention (PCI), or pharmacologically with fibrinolysis. Regardless of the reperfusion strategy selected, the appropriate use of anticoagulant therapy is critical to its success. There have been a number of clinical trials evaluating the different anticoagulants in patients with STEMI, as well as recent updates to the guidelines for management of patients with STEMI and on the use of PCI. When making clinical decisions on the use of anticoagulant therapy in the management of patients with STEMI, it is important to not only understand the contents of these consensus guidelines but to also have an appreciation of the details of the clinical trials that have evaluated the different anticoagulants. In this review, the reader will find an evaluation of the current guidelines concerning the use of anticoagulant therapy in patients with STEMI as well as a detailed examination of the literature with critical analysis on issues that should be considered when deciding on the appropriate implementation of anticoagulant therapy in patients with STEMI undergoing either mechanical or pharmacologic reperfusion.

Keywords

acute coronary syndrome, anticoagulation, cardiology, coronary artery disease, myocardial infarction, percutaneous coronary intervention, fibrinolysis, unfractionated heparin, low-molecular-weight heparin, enoxaparin, fondaparinux, bivalirudin

Introduction

Acute coronary syndrome (ACS) represents a spectrum of disease in which patients may present with unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI). Patients with UA or NSTEMI are commonly grouped together and referred to as NSTE ACS. In 2005, there were 1.4 million emergency room visits for ACS.[1] Of these, approximately 40% were UA, 40% were NSTEMI, and 20% were STEMI.[1] Over 100 000 patients with ACS die before even reaching the hospital, many of whom are thought to be STEMI. While the mortality rate for patients with MI has consistently gone down over the last 2 decades, it is still a leading cause of death in the United States. The first-year cost for patients with ACS is approximately $285 billion, with over 70% of the cost due to hospitalizations and less than 10% attributed to pharmacy costs.[2]

The pathophysiology of STEMI is similar to that of NSTE ACS and is briefly discussed in the accompanying review on the use of anticoagulants in the management of NSTE ACS.[3] Patients with STEMI typically have a more extensive thrombus formation, and therefore, more extensive myocardial cell death.[4,5] The total, or near total, coronary artery occlusion typically produces significant chest pain, ST-segment elevation on the electrocardiogram, elevated cardiac markers, and mortality. Based on the similar pathophysiology to NSTE ACS, a number of antithrombotic agents have been investigated and currently recommended for use in these patients. While platelets play a dominate role in the pathophysiology of STEMI, there is also a critical role for anticoagulant therapy. Due to the central role of thrombin in both platelet aggregation and the clotting cascade, inhibition of thrombin or its production through inhibition of factor Xa are popular targets for anticoagulant agents in the management of STEMI.

When evaluating the literature for anticoagulant agents, it is important to note whether the study population is NSTE ACS,

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Table 1. Bleeding Definitions

TIMI Minor[9]	TIMI Major[9]	GUSTO Severe[10]	ACUITY Major[11]
• 3 to $\leq$5 g/dL hemoglobin drop with overt bleed • 9% to $\leq$ 15% drop in hematocrit	• More than 5 g/dL hemoglobin drop with overt bleed • More than 15% drop in hematocrit • Intracranial bleed	• Intracranial bleed • Bleed resulting in hemodynamic compromise requiring treatment	• More than 3 g/dL hemoglobin drop with overt bleed • More than 4 g/dL hemoglobin drop without overt bleed • Intraocular bleed • Access site bleed intervention • Hematoma >5 cm • Reoperation for bleeding • Any blood transfusion

Abbreviations: TIMI, Thrombolysis in Myocardial Infarction; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Arteries; ACUITY, Acute Catheterization and Urgent Intervention Triage strategY

Table 2. ACC/AHA ST-Segment Elevation Myocardial Infarction Anticoagulation Guidelines[6]

Level of Recommendation	Anticoagulation Recommendations
Class I level of evidence A	Pharmacologic reperfusion—Enoxaparin for duration of hospitalization
Class I	Pharmacologic reperfusion—Fondaparinux for duration of hospitalization, PCI after receiving anticoagulant
Level of evidence B	therapy—Enoxaparin
Class I	Pharmacologic reperfusion—UFH for up to 48 hours, PCI after receiving anticoagulant therapy—UFH or
Level of evidence C	bivalirudin
Class III	PCI after receiving anticoagulant therapy—avoid fondaparinux as sole anticoagulant during PCI

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; UFH, unfractionated heparin; PCI, percutaneous coronary intervention.

STEMI, or both. It is also important to note the management strategy utilized in the trial. In STEMI, immediate reperfusion therapy may be provided pharmacologically with fibrinolytics or mechanically with primary percutaneous coronary intervention (PCI).[6-8] In this review, we will describe the evidence for the various anticoagulant agents that have been evaluated and available for the management of STEMI with the different approaches to reperfusion therapy.

Finally, it is also important when evaluating the safety of anticoagulant agents to carefully examine the definition of major bleeding used in the trial. Unfortunately, there has not been consistent definition of major bleeding used in the clinical trials, making the evaluation of relative safety of the anticoagulant options challenging (Table 1).[9-11]

Treatment of patients with STEMI differs from NSTE ACS in that patients with STEMI need to receive immediate reperfusion therapy. While the preferred mechanism of reperfusion therapy for the management of STEMI would be primary PCI, fewer than 25% of hospitals can provide primary PCI, and even less can do it in a timely manner (within 90 minutes).[7,12] Therefore, there are still a number of patients, especially in rural areas, who receive pharmacologic reperfusion with fibrinolytics. Similar to the management of patients with NSTE ACS, the use and evidence among anticoagulants differs between an invasive compared to a conservative approach, the use and evidence with anticoagulants differs in STEMI between reperfusion with fibrinolytics and primary PCI (Table 2). There are currently no guideline recommendations for the use of anticoagulants at the time of primary PCI, but only recommendations regarding how to manage anticoagulation if anticoagulants were started in the emergency department.[6,8]

Unfractionated Heparin

The evidence supporting the routine use of unfractionated heparin (UFH) in the setting of STEMI is less clear than in the setting of NSTE ACS. Indeed, controversy still exists as to the role of UFH in currently available guidelines as well as in current daily practice.[6,7,13] In an overview of 21 small randomized STEMI trials, totaling approximately 5500 patients, UFH therapy demonstrated a significant reduction in mortality as compared to placebo (11.4% vs 14.9%, $P = .002$).[14] The use of UFH in this analysis also resulted in a reduction in recurrent MI, stroke, and venous thromboembolism (VTE). However, no patients received aspirin, and fibrinolytic therapy was largely absent in these investigations. As such, while the significant reduction in the rate of in-hospital VTE is noteworthy, the true effect of UFH in STEMI on arterial outcomes within the context of contemporary management remained unclear.

Studies designed to investigate the effect of intravenous (IV) UFH therapy at achieving patency of the infarct-related artery have consistently demonstrated that in the setting of fibrinolysis, UFH therapy increases the rate of reperfusion.[15,16] Despite this benefit, clinical outcomes for patients receiving UFH appear to be minimally affected. When looking at available trials comparing IV UFH with no UFH in the setting of fibrinolysis, there were no statistically significant differences in hospital mortality, reinfarction, or rates of recurrent ischemia.[17]

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In examining the effect of UFH when administered with aspirin to patients with STEMI (93% of whom also received fibrinolysis), a very modest mortality benefit was observed (approximately 5 fewer deaths per 1000 patients), and an even smaller reinfarction benefit was demonstrated (approximately 3 fewer per 1000 patients). On the other hand, patients receiving UFH also had a higher risk of bleeding and a small increase in the rate of stroke (approximately 1 more per 1000 patients).[14] Complicating the interpretation of the data further, the role of UFH in the setting of fibrinolysis may also vary depending on the specific fibrinolytic agent used. Data suggests that UFH therapy may be more important when a fibrin-specific agent is used (alteplase, reteplase, tenecteplase) as opposed to a nonspecific agent such as streptokinase.[7,10]

While much of the available data regarding the use of UFH in STEMI comes from trials assessing its role as an adjunct to fibrinolysis, there are no available randomized trials investigating UFH compared to no anticoagulant therapy in the setting of primary PCI. Despite the lack of supporting trial data compared to placebo, UFH is commonly employed in primary PCI as it has always been a constant in the evolution of PCI in the treatment of STEMI, NSTE ACS, as well as elective PCI.[6-8,18]

Despite the limitations on supporting evidence, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend the use of UFH in STEMI. Anticoagulant therapy with UFH is recommended to maintain infarct-related artery patency when fibrin-specific fibrinolytic agents are used.[7] Similar to NSTE ACS, careful attention to appropriate dosing is crucial for ensuring safety and efficacy. Patients receiving fibrin-specific fibrinolysis should receive UFH as a 60 unit/kg bolus (maximum bolus dose 4000 units), followed by a 12 unit/kg per h infusion (max initial infusion 1000 units/h). Therapy should be titrated based on the activated thromboplastin time response and continued for up to 48 hours.[6,7]

In patients receiving primary PCI, UFH therapy is recommended, and the dose depends on the presence or absence of a glycoprotein (GP) IIb/IIIa inhibitor. When a GP IIb/IIIa is present, UFH should be dosed as a 50 to 70 unit/kg 1 time dose, with the goal of achieving an activated clotting time of >200 seconds (Table 3). In the absence of a GP IIb/IIIa, the dose of UFH can be increased (range 60-100 units/kg 1 time dose) with a target activated clotting time of 250 to 350 seconds (Table 3).[6,7,13]

Low-Molecular-Weight Heparin

Due to the lack of phase III evidence evaluating the efficacy and safety of dalteparin or tinzaparin, enoxaparin is the only low-molecular-weight heparin (LMWH) currently recommended in the ACC/AHA STEMI guidelines.[6] Evidence to support the use of enoxaparin in patients receiving pharmacologic reperfusion comes from 2 main trials. In the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial, 6095 patients with STEMI were randomized to full-dose tenecteplase plus UFH, full-dose tenecteplase plus enoxaparin, or half-dose tenecteplase plus abciximab plus low-dose UFH.[19] Dosing of enoxaparin was slightly different from dosing in NSTE ACS trials. Enoxaparin was given as an initial 30 mg IV bolus followed immediately by 1 mg/kg subcutaneously (SC) every 12 hours, with the first 2 SC doses being capped at 100 mg. The primary composite outcome of 30 day mortality, in-hospital MI, or in-hospital refractory ischemia was significantly lower for the investigational arms with enoxaparin (11.4%; $P = .0009$) or abciximab (11.1%; $P = .0002$) compared to traditional UFH (15.4%). Major bleeding was significantly higher in the abciximab group (4.3%; $P = .0002$) compared to UFH (2.2%) but not in the enoxaparin group (3.0%). When combining efficacy and safety into net clinical outcome, only patients receiving enoxaparin had a significant benefit over UFH (13.7% vs 17.0%; $P = .0146$), and abciximab patients did not (14.2%; $P = .057$).

The results of the ASSENT-3 trial, as well as a meta-analysis of smaller STEMI trials comparing UFH to enoxaparin, led to the development of the Enoxaparin and Thrombolysis for Acute Myocardial Infarction Treatment (ExTRACT-TIMI 25) trial.[20,21] In the ExTRACT-TIMI 25 trial, patients with STEMI initially receiving reperfusion with fibrinolytics (n = 20 506) were randomized to UFH with an IV bolus of 60 U/kg (maximum 4000 U) followed by an IV infusion of 12 U/kg per h (initial max of 1000 U/h) or to a similar dosing of enoxaparin as in the ASSENT-3 trial, with some changes for patients with reduced renal function and for patients over the age of 75 (Table 3). Data from the ASSENT-3 Plus trial demonstrated patients over the age of 75 receiving full-dose fibrinolytic and enoxaparin had an intracranial hemorrhage rate of 6.7% compared to 0.8% with UFH and full-dose fibrinolytic ($P = .001$), and therefore, a dosing change was necessary for this age group of patients receiving enoxaparin with a fibrinolytic agent (Table 3).[22]

A regimen of 5 days of enoxaparin significantly reduced death and MI by 17% compared to 2 days of UFH (Table 4).[21] The relative reduction of 17% is interesting as it represents approximately the same relative risk reduction demonstrated in the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events), TIMI 11B (Thrombolysis in Myocardial Infarction), and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; consistent therapy group) trials in NSTE ACS with the use of enoxaparin across the spectrum of ACS.[23-26] Most of the benefit of enoxaparin came in the 33% reduction in MI at 30 days, while mortality was only reduced by 8%. There was also a significant 26% reduction in the need for urgent revascularization in patients receiving enoxaparin compared to UFH (Table 4).[21] While the benefit in reducing ischemic end points with enoxaparin came at a price of significantly higher incidence of major bleeding, importantly there was no difference in the incidence of intracranial hemorrhage between the groups and less than 1% (Table 4).[21] Furthermore, the difference in major bleeding between the 2 agents may be due to the unusually low bleeding rate for UFH in the trial. Data from a meta-analysis

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Table 3. Anticoagulant Dosing in ST-Segment Elevation Myocardial Infarction

Drug	Primary PCI Reperfusion	Fibrinolysis Reperfusion
Unfractionated heparin	Without GPI give 60-100 IV bolus, followed by repeated boluses to maintain an ACT of 250-350 seconds With GPI give 50-70 units/kg IV bolus followed by repeated boluses to maintain an ACT of greater than 200 seconds	60 units/kg IV bolus (max 4000 units, followed by IV infusion of 12 unit/kg per h (max initial infusion of 1000 units/h)
Enoxaparin	No recommendation If patient initially received anticoagulation with enoxaparin If PCI within 8 hours of last SC dose, no additional anticoagulation needed. If PCI 8-12 hours after last SC dose, give an additional IV bolus of 0.3 mg/kg	30 mg IV bolus, followed within 15 minutes by 1 mg/kg SC q 12 hours with the first 2 doses capped at 100 mg
Enoxaparin with CrCl <30 mL/min	No recommendation If patient initially received anticoagulation with enoxaparin If PCI within 8 hours of last SC dose, no additional anticoagulation needed. If PCI 8-12 hours after last SC dose, give an additional IV bolus of 0.3 mg/kg	30 mg IV bolus, followed within 15 minutes by 1 mg/kg SC q 24 hours with the first 2 doses capped at 100 mg
Enoxaparin with age $\geq$75 years	No recommendation If patient initially received anticoagulation with enoxaparin If PCI within 8 hours of last SC dose, no additional anticoagulation needed. If PCI 8-12 hours after last SC dose, give an additional IV bolus of 0.3 mg/kg	No IV bolus 0.75 mg/kg q 12 hours with the first 2 doses capped at 75 mg
Fondaparinux	If previous UFH plus GPI given, then give 2.5 mg IV bolus followed by 2.5 mg SC q 24 hours If previous UFH without GPI given, then 5 mg IV bolus followed by 2.5 mg SC q 24 hours If no UFH, but did get a GPI, then give 2.5 mg IV bolus followed by 2.5 mg SC q 24 hours If no UFH and no GPI, give 5 mg IV bolus followed by 2.5 mg SC q 24 hours All PCI patients should also receive UFH 40-50 mg/kg at the time of PCI	2.5 mg SC q 24 hours with the first dose given IV.
Bivalirudin	IV bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/hr to be discontinued at the conclusion of PCI	No recommendation

Abbreviations: PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; ACT, activated clotting time; SC, subcutaneous; q, every; CrCl, creatinine clearance; UFH, unfractionated heparin

demonstrates a typical major bleeding rate of about 2% with the use of UFH and a fibrinolytic, while patients receiving UFH in the ExTRACT-TIMI 25 trial were able to keep major bleeding at an impressive rate of only 1.4%.[17] Results in patients with severe renal dysfunction or age greater than 75 years were consistent with the overall trial results.[27,28]

Controversy exists over the unequal duration of anticoagulation between the groups. Some have suggested that there may not have been a significant difference between the 2 arms had UFH been given for the same duration as enoxaparin. Adding to this issue is the increased amount of separation between the groups after the discontinuation of UFH. There are 2 points that may help address this issue. First, there is no data supporting the use of UFH for more than 48 hours with fibrinolysis, and this is the duration of UFH therapy recommended in the ACC/AHA STEMI guidelines.[6,7] Second, it should be noted that while the difference in event rates between the groups definitely increased after the discontinuation of UFH, there was already a difference between the groups at the 48-hour time point in death or MI (4.7% vs 5.2%; $P = .8$), MI (0.9% vs 1.4%; $P = .002$), urgent revascularization (0.7% vs 0.9%; $P = .09$), and the composite of death, MI, or urgent revascularization (5.3% vs 6.1%; $P = .02$).[21]

Patients randomized to enoxaparin were less likely to undergo PCI through day 30 compared to patients randomized to UFH (22.8% vs 24.2%; $P = .027$).[29] Patients randomized to enoxaparin, received enoxaparin during PCI using the dosing established in the SYNERGY trial, in which no additional anticoagulation was given if PCI was within 8 hours of the last dose of SC enoxaparin.[25] If PCI was 8 hours or more since the last dose of SC enoxaparin, then a supplemental IV bolus of 0.3 mg/kg was given. There was a significant 22% relative risk reduction in the incidence of death or MI; the patients in the PCI subgroup had an even more dramatic 66% relative risk reduction (Table 4).[29] These benefits were demonstrated without an increase in major bleeding (Table 4). These data provide adequate support for the recommendation of enoxaparin in patients undergoing PCI in the ACC/AHA STEMI guidelines.

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Table 4. ExTRACT-TIMI 25 Trial Results at 30 Days[21,29]

Outcome	Unfractionated Heparin (%)	Enoxaparin (%)	*P* Value
Death/MI	12.0	9.9	<.0001
Death	7.5	6.9	<.11
Myocardial infarction	4.5	3	<.0001
Urgent revascularization	2.8	2.1	.008
Major bleeding	1.4	2.1	<.001
Nonfatal major bleeding	0.9	1.3	.014
Intracranial hemorrhage	0.7	0.8	.14
PCI patients (n = 4,676)			
Death/MI	13.8	10.7	.001
Stroke	0.9	0.3	.006
Major Bleeding	1.6	1.4	NS

Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; NS, not significant.

It should be noted that these data do not support the use of enoxaparin for primary PCI, but instead for PCI that may need to be done following fibrinolysis. Enoxaparin has not been evaluated in the setting of primary PCI. An IV bolus of greater than 30 mg, such as the IV bolus doses of 0.5 or 0.75 mg/kg evaluated in the Safety and Efficacy of Enoxaparin in PCI Patients (STEEPLE) trial, would probably need to be investigated in the setting of primary PCI.[30]

Fondaparinux

Phase III evidence evaluating the use of fondaparinux in patients with STEMI comes from the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-6 trial. Patients with STEMI (n = 12 092) were randomized in a double-blinded fashion to fondaparinux 2.5 mg SC daily (first dose given IV) or control for up to 8 days.[31] The initial separation of patients into the 2 groups was not random. Rather, patients were first stratified based on the investigator's decision on whether UFH should be used. If the investigator decided that the STEMI patient should not receive UFH, the patient was then randomized to fondaparinux 2.5 mg SC daily or placebo. These patients were considered to be in stratum 1. Stratum 1 included patients receiving reperfusion with streptokinase (78%) and patients receiving no reperfusion therapy. If the investigator decided that the STEMI patient should receive UFH, the patient was then randomized to fondaparinux 2.5 mg SC daily or IV UFH given as a bolus of 60 U/kg (max 4000 U) and followed by an infusion of 12 U/kg per h (initial max of 1000 U/h). These patients were considered to be in stratum 2. Stratum 2 included patients receiving primary PCI (53%), a fibrin-specific fibrinolytic (16%), and patients receiving no reperfusion therapy. The primary outcome of the OASIS-6 trial was the occurrence of death or MI at 30 days.

Results of the OASIS-6 trial are shown in Table 5.[31] Overall, patients receiving fondaparinux demonstrated a 13% relative risk reduction in the primary end point of death or MI compared to control. However, much controversy surrounds the methodology of the OASIS-6 trial. One point of concern is the initial stratification, rather than randomization, of the patients into 2 groups, which then received 2 different controls (placebo or UFH). Should the 2 groups be combined together in a final analysis? When evaluating the strata separately, there was a significant 20% relative risk reduction with the use of fondaparinux compared to placebo in stratum 1, but no difference between fondaparinux and UFH in stratum 2. A second point of concern is the external validity of the trial. Patients in stratum 1 have very little relevance to the treatment of patients with STEMI in the United States, because streptokinase in not used as a fibrinolytic for STEMI and most patients not receiving reperfusion therapy would still be given anticoagulation. Patients in stratum 2 of the OASIS-6 trial are more reflective of those receiving management of STEMI in the United States, but the outcomes were no different between fondaparinux and UFH. As in the OASIS-5 trial (see manuscript on NSTE ACS), catheter thrombosis was significantly higher in patients receiving fondaparinux.[31,32] Therefore, the evidence for fondaparinux in the management of patients with STEMI supports its use as an alternative to UFH in patients receiving a fibrinolytic or no reperfusion therapy. Because there is no advantage to the use of fondaparinux besides simpler dosing, the difference in cost may limit the utilization of fondaparinux in these patients.

Bivalirudin

Unlike the anticoagulant agents discussed above, bivalirudin has not been extensively investigated in conjunction pharmacologic reperfusion. One study of bivalirudin given with streptokinase did not provide positive results and the combination is not recommended.[33] Currently, there is no evidence to support the use of bivalirudin with any of the fibrin-specific fibrinolytic agents. Bivalirudin was evaluated in a large phase III trial in patients with STEMI undergoing primary PCI in the Harmonizing Outcomes with Revascularization with Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial.[34] In the HORIZONS-AMI trial, patients with STEMI and planned primary PCI (n = 3602) were randomized in an open-label fashion to IV UFH with a GP IIb/IIIa inhibitor or bivalirudin alone. Patients randomized to UFH received an IV bolus of 60 IU/kg followed by additional boluses to achieve and maintain an activated clotting time of 200 to 250 seconds. The choice of GP IIb/IIIa inhibitor as well as the loading dose of clopidogrel (300 mg vs 600 mg) was left up to the investigator, with abciximab (52%) and eptifibatide (46%) being most commonly selected. The bolus dose of bivalirudin was higher in the HORIZONS-AMI trial (0.75 mg/kg) compared to the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial (0.5 mg/kg), but the infusion dose and duration were similar.[32,34]

As with the ACUITY trial (see manuscript on NSTE ACS), the primary end point of the HORIZONS-AMI was defined as net adverse clinical events and included both ischemic end points (death, MI, target vessel revascularization, and stroke)

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Table 5. OASIS-6 Trial Results at 30 Days[31]

Outcome	Placebo or UFH (%)	Fondaparinux (%)	HR (95% CI)	*P* Value
All patients (n = 12 092)				
Death/MI	11.2	9.7	0.86 (0.77–0.96)	.008
Death	8.9	7.8	0.87 (0.77–0.98)	.03
Myocardial infarction	3.0	2.5	0.81 (0.65–1.01)	.06
Severe hemorrhage	1.3	1.0	0.77 (0.55–1.08)	.13
Major bleeding	2.1	1.8	0.83 (0.64–1.06)	.14
Stratum 1—Placebo (n = 5658)				
Death/MI	14	11.2	0.79 (0.68–0.92)	
Death	NA	NA		
Myocardial infarction	NA	NA		
Severe hemorrhage	1.6	1.0	0.63 (0.40–1.02)	.06
Major bleeding	2.0	1.4	0.68 (0.45–1.02)	.07
Stratum 2—UFH (n = 6434)				
Death/MI	8.7	8.3	0.96 (0.81–1.13)	
Death	NA	NA		
Myocardial infarction	NA	NA		
Severe hemorrhage	1.1	1.1	0.95 (0.59–1.52)	.82
Major bleeding	2.3	2.1	0.93 (0.67–1.30)	.69
Stratum 2 No PCI—UFH (n = 2666)				
Death/MI	13.8	11.5	0.82 (0.66–1.02)	.08
Death	10.9	9.6	0.88 (0.69–1.12)	.29
Myocardial infarction	4.3	2.6	0.60 (0.39–0.93)	.02
Severe hemorrhage	2.2	1.5	0.69 (0.39–1.22)	.20
Major bleeding	3.2	2.2	0.66 (0.41–1.07)	.09
Stratum 2 PCI—UFH (n = 3768)				
Death/MI	5.1	6.1	1.20 (0.91–1.57)	.19
Death	3.9	4.5	1.16 (0.85–1.58)	.36
Myocardial infarction	1.6	2.0	1.25 (0.77–2.05)	.36
Severe hemorrhage	0.3	0.7	2.18 (0.83–5.74)	.11
Major bleeding	1.7	2.2	1.30 (0.81–2.08)	.27

Abbreviations: UFH, unfractionated heparin; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention.

and bleeding end points. At 30 days, net adverse clinical events were reduced by 24% with the use of bivalirudin alone compared to UFH with a GP IIb/IIIa inhibitor (Table 6).[34] As in the ACUITY trial, the impressive reduction in major bleeding (41%) with the use of bivalirudin alone was the reason for the difference in the combined end point, and there was a similar amount of ischemic end points between the groups (Table 6).[34] An interesting finding in the HORIZONS-AMI trial was a significant 33% reduction in all-cause mortality and a 38% significant reduction in cardiac mortality in patients receiving bivalirudin alone (2.9% vs 1.8%; $P = .03$). As in the OASIS-5 trial, the early reduction in major bleeding was associated with a benefit in mortality. Even when excluding patients who did not undergo primary PCI (7.2%, n = 262), there was still a 31% reduction in all-cause mortality (2.9% vs 2.0%; $P = .067$) and a 36% reduction in cardiac mortality (2.8% vs 1.8%; $P = .045$), with the use of bivalirudin alone compared to the use of UFH with a GP IIb/IIIa inhibitor. This difference in all-cause mortality (4.8% vs 3.4%; $P = .029$), driven by cardiac mortality (3.8% vs 2.1%; 0.005), was still evident at the 1-year follow-up. While the HORIZONS-AMI trial was not designed or large enough to evaluate mortality alone, these results deserve consideration.

There are several issues requiring critical assessment when evaluating the design and results of the HORIZONS-AMI trial. In the HORIZONS-AMI trial, investigators could have selected any GP IIb/IIIa inhibitor for use with UFH. It should be noted there is not a similar level of evidence between the different GP IIb/IIIa inhibitors in the setting of primary PCI.[35] The ACC/AHA STEMI guidelines currently provide a Class IIa recommendation for the use of abciximab in primary PCI, and a Class IIb recommendation for eptifibatide and tirofiban.[6,8] The recommendation for abciximab is based on a number of randomized trials demonstrating a significant reduction in composite ischemic outcomes.[36-39] A meta-analysis of these trials has also demonstrated a significant reduction in mortality when abciximab is used in the setting of primary PCI.[40] The recommendation for the use of eptifibatide and tirofiban in primary PCI is based on the fact they are also GP IIb/IIIa inhibitors and have a similar mechanism of action. While there are some smaller trials evaluating the role of eptifibatide or tirofiban in surrogate end points (ST-segment resolution, myocardial perfusion, etc), there have been no trials large enough to evaluate the impact of these agents on clinical outcomes.[41-43] While the patients in HORIZONS-AMI were not randomized to abciximab or eptifibatide, and no statistical comparisons

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Table 6. HORIZONS AMI Trial Results at 30 Days[34]

Outcome	UFH + GPI (%)	Bivalirudin Alone (%)	*P* Value
Net adverse clinical events	12.1	9.2	.005
Death	3.1	2.1	.047
Myocardial infarction	1.8	1.8	.90
TVR for ischemia	1.9	2.6	.18
Stroke	0.6	0.7	.68
ACUITY major bleeding	8.3	4.9	< .001
TIMI major bleeding	5.0	3.1	.002
GUSTO severe bleeding	0.6	0.4	.49
Stent thrombosis	1.9	2.5	.30
Acute (≤24 hours)	0.3	1.3	<.001
Subacute (>24 hours to 30 days)	1.7	1.2	.28

Abbreviations: UFH, unfractionated heparin; GPI, glycoprotein IIb/IIIa inhibitor; TVR, target vessel revascularization; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; TIMI, Thrombolysis in Myocardial Infarction; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Arteries.

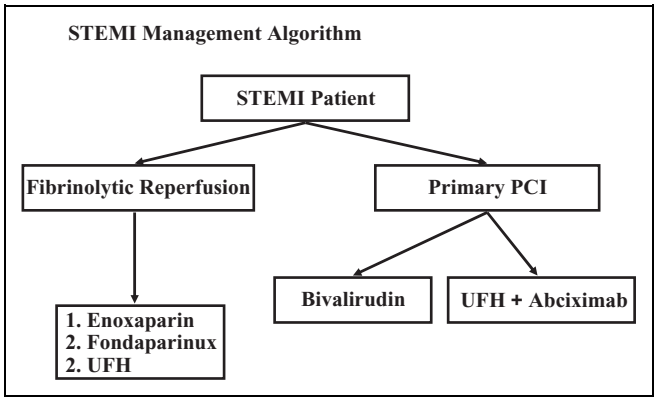

Figure 1. ST-segment elevation myocardial infarction management algorithm. PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

have been completed, patients receiving abciximab had a 0.5% reduction in ischemic end points compared to patients receiving bivalirudin alone. Patients receiving eptifibatide had a 0.5% increase in ischemic end points compared to patients receiving bivalirudin alone.[34] Thus, the investigators' effort to maximize external validity by allowing for any GP IIb/IIIa inhibitor may have resulted in a loss of internal validity.

Another issue from the HORIZONS-AMI trial deserving some consideration is the significant 4-fold increase in acute stent thrombosis demonstrated in patients receiving bivalirudin alone compared to UFH with a GP IIb/IIIa inhibitor (1.3% vs 0.3%; $P = .0009$).[34] These results are similar to the findings from the ACUITY trial, in which patients with no antiplatelet therapy beyond aspirin at the time of PCI had an increase in ischemic outcomes.[44] In the setting of primary PCI where door-to-balloon time should be less than 90 minutes, there would be inadequate time for even a pre-PCI loading dose of 600 mg of clopidogrel to provide sufficient antiplatelet protection.[45] It should be remembered that despite the significant increase in the rate of acute stent thrombosis demonstrated with the use of bivalirudin alone, there was not a significant increase in death or MI in the study overall. Therefore, unless an episode of acute stent thrombosis would be considered catastrophic, as defined in the ACC/AHA PCI guidelines, an anticoagulation strategy of bivalirudin alone in primary PCI is reasonable.[8]

Summary

Developing protocols for the use of anticoagulants in the setting of STEMI requires a critical evaluation of current guidelines and the clinical literature to decide how the evidence applies to the practice setting. An example of applying guidelines and clinical literature into acceptable anticoagulation options for STEMI is demonstrated in Figure 1. The reperfusion strategy of the institution needs to be considered when developing a STEMI protocol. While rural institutions that can only provide pharmacologic reperfusion do not have to develop a primary PCI protocol, institutions performing extensive primary PCI still may have an occasional situation in which primary PCI cannot be done (laboratory is full, bad weather and the team cannot get in, etc), and it may be helpful to have a second protocol for pharmacologic reperfusion. For pharmacologic reperfusion, enoxaparin would be the preferred agent based on the ExTRACT-TIMI 25 trial, with UFH and fondaparinux being alternatives based on OASIS-6.[21,31] Because patients receiving initial pharmacologic reperfusion often end up undergoing PCI, the evidence from the PCI patients in ExTRACT-TIMI 25 support a role for enoxaparin.[29]

If primary PCI is selected as the reperfusion modality, one option would be the use of UFH with a GP IIb/IIIa inhibitor, preferably abciximab. Another reasonable option would be the use of bivalirudin alone, based on the results of the HORIZONS-AMI trial.[34] Due to the issue of catheter thrombosis in OASIS-6 trial, fondaparinux should not be utilized at this time in patients undergoing primary PCI.[31] Enoxaparin has not been fully evaluated in the setting of primary PCI and should not be used until more data are available. As in NSTE ACS, the development of protocols for appropriate and safe use of anticoagulants requires special attention be placed on dosing. Table 3 describes anticoagulant dosing based on the different management approaches in ACS patients.

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Declaration of Conflicting Interests

Dr. Dobesh serves as a consultant for The Medicines Company and Sanofi-Aventis. Dr. Trujillo has no conflict to declare.

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