Controversies in the Management of ST Elevation Myocardial Infarction: Thrombin Inhibition.

Neeraj Shah MD
Lehigh Valley Health Network, Neeraj_N.Shah@lvhn.org

David A. Cox MD
Lehigh Valley Health Network, David.Cox@lvhn.org

Published In/Presented At

Shah, N., & Cox, D. (2016). Controversies in the Management of ST Elevation Myocardial Infarction: Thrombin Inhibition. *Interventional cardiology clinics*, *5*(4), 497–511. https://doi.org/10.1016/j.iccl.2016.06.008

Controversies in the Management of ST Elevation Myocardial Infarction

Thrombin Inhibition

Neeraj Shah, MD, MPH, David Cox, MD, FSCAI*

KEYWORDS

- ST elevation myocardial infarction (STEMI)
- Primary percutaneous coronary intervention (primary PCI) • Fibrinolysis • Bivalirudin
- Direct thrombin inhibitors • Unfractionated heparin (UFH)

KEY POINTS

- Anticoagulation is essential in patients with ST elevation myocardial infarction (STEMI) in order to prevent further thrombosis and to maintain patency of the infarct-related artery after reperfusion.
- In patients with STEMI undergoing primary percutaneous coronary intervention (PCI), bivalirudin provides a mortality benefit over unfractionated heparin (UFH), predominantly via a reduction in major bleeding with bivalirudin compared to UFH.
- In clinical situations such as radial artery access, use of newer oral antiplatelet agents or provisional (rather than routine) glycoprotein IIb/IIIa inhibitor use, the bleeding advantage of bivalirudin over UFH may not be as apparent.
- There is an increase in risk of stent thrombosis with bivalirudin compared with UFH in the first 24 hours after primary PCI, which can potentially be mitigated by preadministration of UFH or prolonging full-dose bivalirudin infusion after PCI for up to 4 hours.
- UFH is the preferred anticoagulant for patients with STEMI undergoing fibrinolysis. For those in whom a PCI is not planned, enoxaparin and fondaparinux may be reasonable alternatives.

INTRODUCTION

Acute ST elevation myocardial infarction (STEMI) occurs when there is rupture of a coronary artery atherosclerotic plaque with a superimposed fibrin-rich clot resulting in occlusion of the lumen of an epicardial coronary artery. The treatment of STEMI involves either emergent percutaneous coronary intervention (PCI), which involves balloon angioplasty and/or stenting, or fibrinolysis, which involves lysis of the clot with intravenous (IV) fibrinolytic agents. The role of antithrombotic therapy in the setting of STEMI is to prevent extension or propagation of the coronary artery thrombosis and to maintain patency of the infarct-related artery after successful reperfusion.

A brief review of the coagulation cascade reveals that the intrinsic and extrinsic pathways converge to activate Factor X to Factor Xa, which converts prothrombin to thrombin. Activated thrombin converts fibrinogen to fibrin, ultimately resulting in cross-linked clot formation.[1] Antithrombin (AT)-III, a naturally occurring regulator of the coagulation cascade, inactivates both thrombin and Factor Xa. The anticoagulants

Disclosures/Conflicts of Interest: Dr D. Cox is on the medical advisory board of The Medicines Company.
Department of Cardiology, Lehigh Valley Heath Network, 1250 S Cedar Crest Boulevard, Allentown, PA 18103, USA
* Corresponding author.
E-mail address: david.cox@lvhn.org

Intervent Cardiol Clin 5 (2016) 497–511
http://dx.doi.org/10.1016/j.iccl.2016.06.008

used in the setting of myocardial infarction (MI) can, therefore, be divided into the following classes:

1. Indirect thrombin inhibitors: These inhibitors include unfractionated heparin (UFH); low-molecular-weight heparin (LMWH), which includes enoxaparin; and fondaparinux, which is a synthetic heparin pentasaccharide. These medications complex with AT-III and alter its conformation to result in either rapid inactivation of thrombin (eg, UFH) or Factor Xa (eg, LMWH and fondaparinux).
2. Direct thrombin inhibitors (DTIs): These medications directly inactivate thrombin. Bivalirudin, hirudin, and lepirudin are all direct thrombin inhibitors. Bivalirudin is the only clinically used DTI.

Anticoagulation in STEMI is divided into the following sections:

1. Patients with STEMI receiving primary PCI: This topic is reviewed in the context of different clinically relevant scenarios, such as access site (radial vs femoral), antiplatelet agent use (clopidogrel vs newer oral agents, such as prasugrel or ticagrelor), and glycoprotein IIb/IIIa inhibitor (GPI) use (routine vs provisional).
2. Patients with STEMI receiving fibrinolysis: In areas with limited access to health care, fibrinolysis is a frequently used option for revascularization.
3. Patients with STEMI not eligible for fibrinolysis or PCI (no reperfusion): This scenario is uncommon, and the role of anticoagulation in this setting is discussed briefly.

Primary Percutaneous Coronary Intervention

Use of anticoagulant therapy in the setting of primary PCI is a class I indication according to all major guidelines.[2,3] The following anticoagulants have been studied in this clinical setting: UFH, bivalirudin, fondaparinux, and enoxaparin.

Unfractionated heparin versus bivalirudin

For several years, UFH was the only anticoagulant available for PCI, and it was the standard medication used for primary PCI in STEMI for a long time.[4] However, UFH has several pharmacologic limitations, including high variability in action among different individuals and in the same individual over time.[5] The efficacy of UFH needs to be monitored by activated clotting time (ACT) measurements during PCI, with repeat boluses often necessary to maintain an ACT range of 200 to 250 seconds. In the recent years, bivalirudin has emerged as a formidable alternative to UFH. Bivalirudin is administered in a fixed weight-based dose as a bolus followed by an infusion. ACT measurements do not correlate with the level of thrombin inhibition with bivalirudin and are performed simply to assure the drug has been properly given. Routine ACT monitoring with bivalirudin is not recommended except in the presence of renal failure.[6,7] Several multicenter trials have been conducted comparing bivalirudin with UFH with conflicting results (Table 1).

RANDOMIZED CONTROLLED TRIALS

Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial published in 2008 was the first major trial comparing bivalirudin with provisional GPI to UFH with routine GP IIb/IIIa inhibition. In contrast to contemporary therapy, femoral access and clopidogrel were used in most patients and UFH was combined with a GPI in a routine rather than a provisional fashion.[8] Bivalirudin had a significant mortality benefit over UFH plus GPI with reduction in cardiac death (1.8% vs 2.9%, $P = .03$) and all-cause mortality at 30 days (2.1% vs 3.1%, $P = .047$). Similar mortality benefits with bivalirudin were maintained at the 1- and 3-year follow-up.[9] There was no difference in major adverse cardiovascular events (MACE) in the two arms; however, the primary outcome of net adverse clinical events (NACE; composite of MACE and major bleeding) was significantly lower in the bivalirudin arm (4.9% vs 8.3%, $P<.001$), largely driven by a reduction in major bleeding. An increase in the rate of acute (within 24 hours) stent thrombosis was observed in the bivalirudin arm (1.3% vs 0.3%, $P<.001$). Criticisms of this trial include high proportion (94%) of femoral arterial access and GPI use in the UFH arm (94.5%), which may have contributed to the increased bleeding rates with UFH.

European Ambulance Acute Coronary Syndrome Angiography

In the European Ambulance Acute Coronary Syndrome (ACS) Angiography (EUROMAX) trial,[10] patients were randomly assigned to receive either heparin or bivalirudin (with post-PCI infusion up to 4 hours) during emergency transport for PCI. In the heparin group, 41.5% of patients did not receive routine GPI

Table 1
Patient characteristics of randomized controlled trials comparing bivalirudin with unfractionated heparin for primary percutaneous coronary intervention in ST elevation myocardial infarction

Trial	Author, Year	Country	n	n (Bival)	n (UFH)	Age[a] (y)	Men (%)	GPI Use (Bival) (%)	GPI Use (UFH) (%)	Radial Access (%)	Clopidogrel (%)	Prasugrel/ Ticagrelor (%)
HORIZONS AMI	Stone et al,[8] 2008	United States, Italy, Poland, Israel, United Kingdom, Argentina, Norway, Netherlands, Germany, Austria, Spain	3602	1800	1802	60.2	76.6	7.2	94.5	5.9	99.8	0
EUROMAX	Steg et al,[10] 2013	France, Germany, Italy, Denmark, Netherlands, Poland, Slovenia, Austria, Czech Republic	2218	1089	1109	61.0	76.4	11.5	69.1	47.0	50.7	49.1
HEAT PPCI	Shahzad et al,[12] 2014	United Kingdom (single center)	1812	905	907	63.2	72.3	13.0	15.0	81.1	10.9	89.4
BRIGHT[b]	Han et al,[13] 2015	China (82 sites)	2194	735	1459 (729/730)[c]	57.9	82.1	4.4	5.6/100[d]	78.5	100	0
BRAVE-4	Schulz et al,[14] 2014	Germany (3 centers)	546	271	277	61.4	77.4	3.0	6.1	0.2	In UFH arm[e]	In bival arm[e]
MATRIX	Valgimigli et al,[15] 2015	Italy, Netherlands, Spain, Sweden	7213[f]	3610	3603	65.4	76.2	4.6	25.9	49.9[g]	45.9	36.5

Abbreviations: Bival, bivalirudin; n, sample size/number of patients.
[a] Age expressed as mean or median age in years in the study population.
[b] Bivalirudin compared with UFH plus provisional tirofiban (UFH-alone arm) and UFH plus routine tirofiban.
[c] A total of 729 in the UFH-alone arm and 730 in the UFH-plus-tirofiban arm.
[d] GPI use was 5.6% in UFH-alone arm and 100% in UFH-plus-tirofiban arm.
[e] Only clopidogrel used in the UFH arm, and only prasugrel used in the bivalirudin arm.
[f] Only 4010 (55.6%) had STEMI.
[g] Originally randomized to radial versus femoral access (hence 50% of each); bivalirudin versus UFH comparison was nested within the original trial.

(n = 460). The patient population was more reflective of contemporary clinical practice, with 47.0% radial access and 49.1% use of prasugrel or ticagrelor. There was no significant difference in the all-cause mortality or cardiac death with bivalirudin compared with heparin. The primary outcome of major bleeding and death was reduced with bivalirudin compared with heparin (5.1% vs 8.5%, $P = .007$); once again this was driven by a reduction in major bleeding (2.6% vs 6%, $P<.001$). Notably, 8.5% patients in the heparin group received LMWH; however, rates of primary end point were not different between UFH and LMWH.[11]

In a prespecified subanalysis of the EUROMAX trial,[11] bivalirudin was compared with heparin with routine GPI use and heparin with bailout GPI use (25.4% GPI use). Bivalirudin reduced the composite outcome of death or major bleeding compared with heparin irrespective of type of GPI use. The advantage of bivalirudin over heparin persists, regardless of planned or provisional GPI use. However, it should be kept in mind that the decision of routine versus bailout GPI use was not randomized but left at the discretion of the trial investigators.

How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention

The How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT PPCI) trial was a single-center trial comparing bivalirudin with UFH.[12] In this trial, GPI use was strictly provisional and, therefore, similar in the bivalirudin and UFH arms (13% vs 15%, see Table 1). Most patients in this trial had radial access (81%) and newer antiplatelet agent use (89%). Surprisingly, there was a significantly higher incidence of death, stroke, reinfarction, or target vessel revascularization (TVR) at 28 days with bivalirudin (8.7%) compared with the UFH (5.7%, $P = .01$). There was no difference in major bleeding (3.5% vs 3.1%, $P = .59$). Incidence of acute stent thrombosis (AST) was higher with the bivalirudin arm compared with UFH (2.9% vs 0.9%, $P = .007$). The beneficial effect of UFH over bivalirudin was driven by a significant increase in reinfarction rate (due to stent thrombosis) in the bivalirudin group. The higher rate of stent thrombosis in this trial was attributed to a high-risk study population and lack of UFH administration before randomization. Criticisms of the single-center HEAT PPCI trial include short duration of bivalirudin infusion and a lower ACT achieved with bivalirudin compared with prior studies.[13]

Bivalirudin in Acute Myocardial Infarction Versus Heparin and Glycoprotein IIb/IIIa Inhibitor Plus Heparin

The Bivalirudin in Acute Myocardial Infarction versus Heparin and GPI plus Heparin (BRIGHT) trial[13] was designed with 3 arms: bivalirudin with post-PCI infusion (30 minutes to 4 hours), UFH alone (100 units per kilogram), and UFH with routine GPI (tirofiban). Provisional use of GPI was allowed in the bivalirudin and UFH-alone arms; but unlike EUROMAX, routine versus provisional use of GPIs with UFH was randomized in this trial. In the bivalirudin arm, after 4 hours, reduced dose infusion at 0.2 mg/kg/h could be administered up to 20 hours at physician discretion. All patients received clopidogrel and 78% had radial access. The primary outcome of NACE (death, stroke, reinfarction, TVR, or major bleeding) was 8.8% with bivalirudin compared with 13.2% with UFH alone ($P = .008$) and 17% with UFH plus tirofiban ($P<.001$). Again, this effect was driven by a reduction in major bleeding with bivalirudin compared with UFH (4.1% vs 7.5% vs 12.3%, $P<.001$). Interestingly, the rate of AST was not different with bivalirudin compared with the two UFH groups. The benefit of bivalirudin over UFH persisted at 1 year. Criticisms of this trial include use of a high dose of UFH (100 U/kg) in the UFH alone arm, which may have been responsible for the higher bleeding rates seen with UFH. Notably, 12% of patients in the BRIGHT trial did not have an STEMI but had a non-STEMI (NSTEMI) requiring emergent PCI.

Bavarian Reperfusion Alternatives Evaluation 4

The Bavarian Reperfusion Alternatives Evaluation (BRAVE)-4 trial was designed to compare prasugrel plus bivalirudin with clopidogrel plus UFH.[14] Routine GPI use was not permitted; therefore, only 3% of patients in the bivalirudin arm and 6.1% of patients in the UFH arm received GPI. The access site was femoral in all but one patient. The trial was stopped prematurely, enrolling only 548 out of a target of 1240 patients, because of slow recruitment. There was no different in the primary end point of death, MI, TVR, stent thrombosis, stroke, or bleeding at 30 days in the two arms (15.6% vs 14.5%, $P = .68$). No differences were observed in MACE (4.8% vs 5.5%, $P = .89$), major bleeding (14.1% vs 12.0%, $P = .54$), or stent thrombosis (1.1% vs 1.5%, $P = .98$) at 30 days between the two arms. Given the limited sample size and premature termination of this trial, these results must be interpreted with caution.

Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox

The Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial[15] was designed to compare radial with femoral access in acute coronary syndromes as well as bivalirudin versus UFH use. Initially, 8404 patients with ACS were randomized to femoral versus radial access; of those, 7213 patients were further randomized to receive either bivalirudin or UFH. Patients in the bivalirudin group were randomized to receive or not to receive post-PCI bivalirudin infusion; however, the dose and duration of post-PCI bivalirudin infusion was not randomized and was left at the discretion of the physician. Almost 50% of patients had radial access, and 36.5% of patients received either prasugrel or ticagrelor. Provisional GPI use was 4.6% with bivalirudin and 25.9% with UFH. The rates of MACE (10.3% vs 10.9%, $P = .44$) or NACE (11.5% vs 12.6%, $P = .15$) were not significantly different between bivalirudin and UFH. Post-PCI infusion of bivalirudin did not significantly decrease the rate of urgent TVR, definite AST, or NACE. Only 4010 (55.9%) of patients in the MATRIX trial had an STEMI. In the STEMI subgroup of the MATRIX trial (MATRIX-STEMI), there was a significant reduction in all-cause mortality with bivalirudin compared with UFH (2.1% vs 3.1%, $P = .05$) as well as a significant reduction in major bleeding with bivalirudin (1.6% vs 2.7%, $P = .02$).

POOLED ANALYSES

Several meta-analyses have been conducted comparing bivalirudin to UFH pooling the results from prior data. The comparisons between bivalirudin and UFH can be broken down into the following sections.

Bivalirudin and Mortality

Compared with UFH, bivalirudin is associated with a significantly reduced risk of 30-day mortality after primary PCI in pooled analyses.[16] In the HORIZONS AMI and MATRIX-STEMI trials, there was a significant reduction in the risk of all-cause mortality at 30 days with bivalirudin compared with UFH by 1% (Fig. 1). Bivalirudin was also associated with reduced risk of cardiac death at 30 days in the HORIZONS AMI trial (Fig. 2).[16] One of the reasons for the mortality benefit of bivalirudin over UFH is a reduction in major bleeding with bivalirudin. Among all patients undergoing PCI, patients with STEMI are at the highest risk of developing major bleeding[17]; occurrence of major bleeding is an independent predictor of mortality in these patients.[18] Hence, a significant reduction in major bleeding with bivalirudin translates into a mortality benefit. Of note, in the HORIZONS AMI trial, reduction in cardiac death with bivalirudin was observed even in patients who did not experience a major bleeding event, suggesting a yet-undefined pleiotropic effect of bivalirudin.[19] The mortality benefit with bivalirudin persists over time, as seen in 3-year follow-up data of the HORIZONS AMI trial.[9]

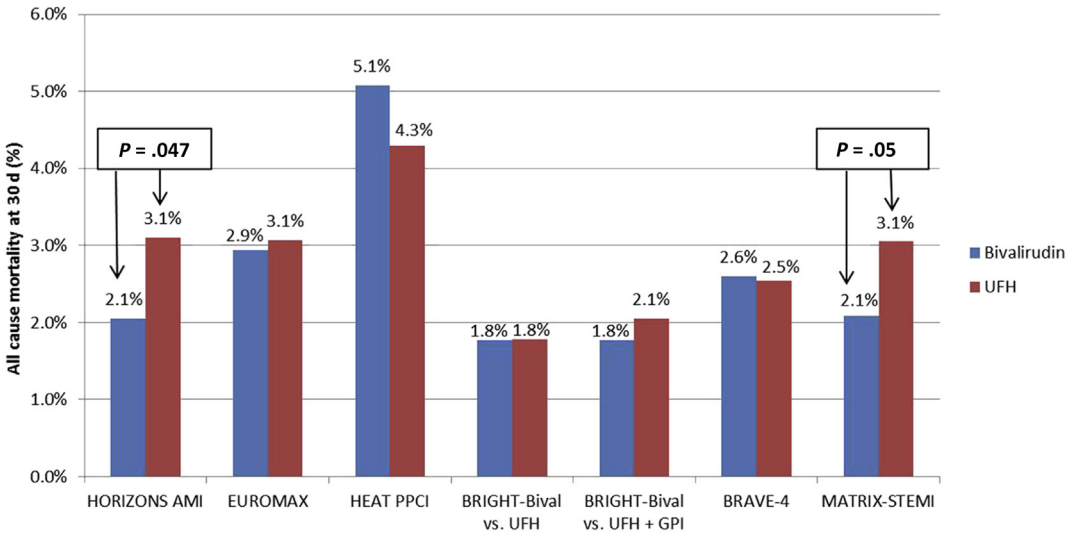

Fig. 1. Comparison of all-cause mortality at 30 days between bivalirudin and UFH arms in patients with STEMI undergoing primary PCI across major randomized controlled trials. Note: Only significant *P*-values (<.05) are shown. *P*-values for the remaining comparisons are not statistically significant. bival, bivalirudin.

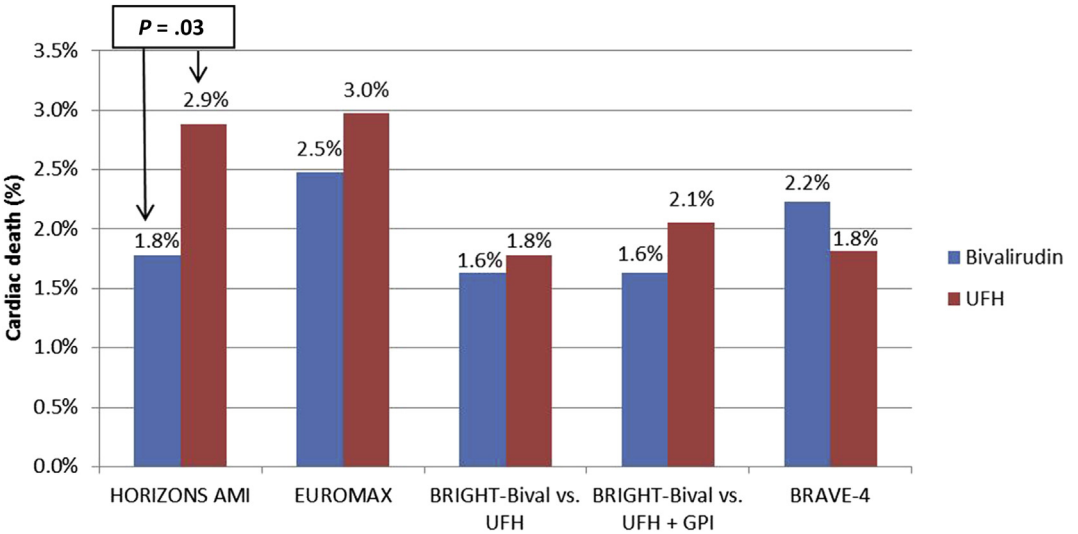

Fig. 2. Comparison of cardiac mortality at 30 days between bivalirudin and UFH arms in patients with STEMI undergoing primary PCI across major randomized controlled trials. Note: Only significant *P*-values (<.05) are shown in the figure. *P*-values for the remaining comparisons are not statistically significant. bival, bivalirudin.

Bivalirudin and Major Adverse Cardiovascular Events

Several meta-analyses have shown that compared with UFH, bivalirudin has similar rates of MACE, reinfarction, and target vessel revascularization.[16,20,21] In most of the previously discussed randomized controlled trials (RCTs), 30-day MACE rates did not differ significantly between bivalirudin and UFH (Fig. 3). Thus, bivalirudin does not seem to have any benefit over UFH in reducing ischemic events after PCI.

Bivalirudin and Bleeding

Several studies and meta-analyses confirm that bivalirudin significantly lowers the risk of major bleeding compared with UFH ± GPI (Fig. 4).[8,10,13,15,16,20,21] Reduction in major bleeding with bivalirudin is independent of the

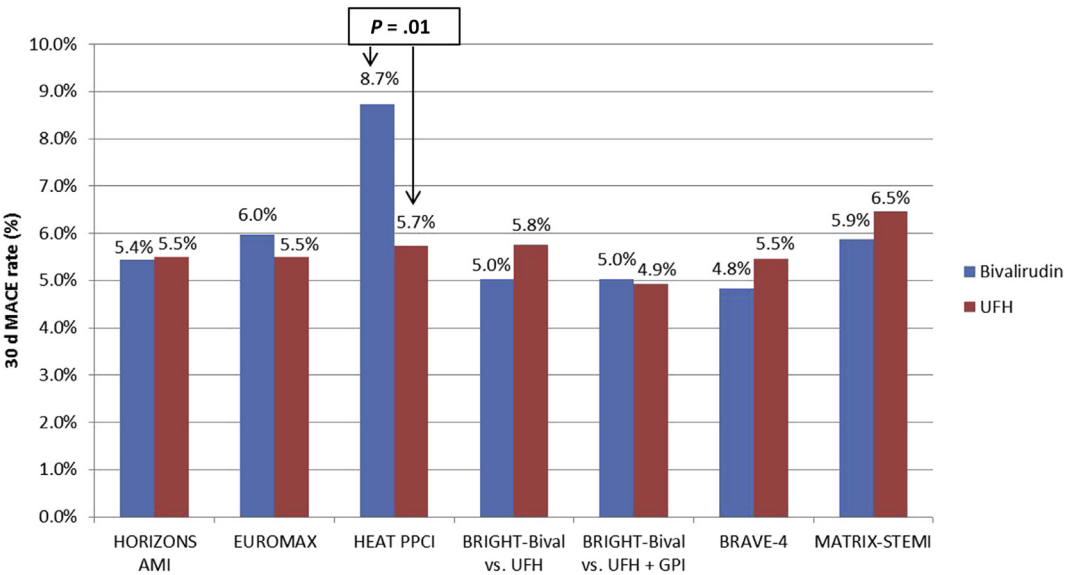

Fig. 3. Comparison of MACE at 30 days between bivalirudin and UFH arms in patients with STEMI undergoing primary PCI across major RCTs. Note: Only significant *P*-values (<.05) are shown. *P*-values for the remaining comparisons are not statistically significant. bival, bivalirudin.

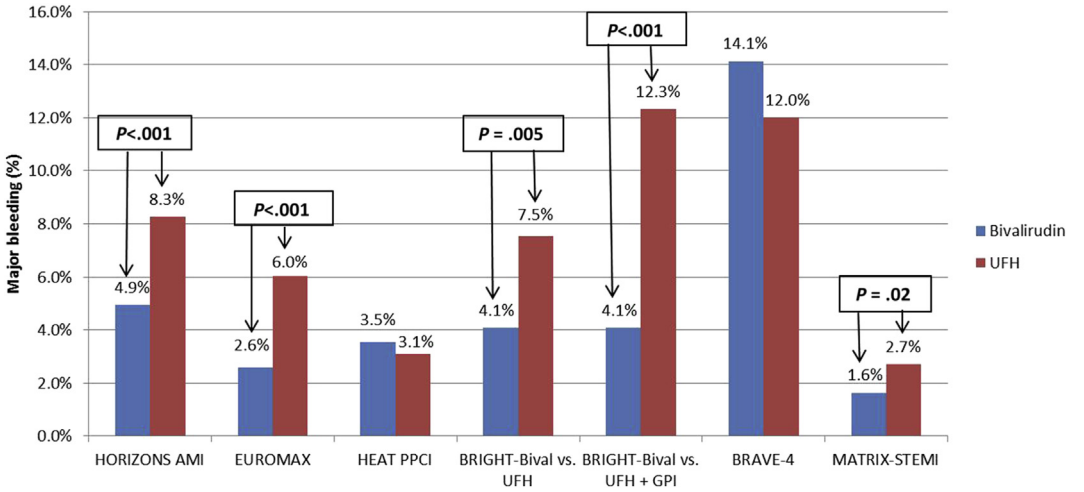

Fig. 4. Comparison of major bleeding rates at 30 days between bivalirudin and UFH arms in patients with STEMI undergoing primary PCI across major RCTs. Note: Only significant *P*-values (<.05) are shown. *P*-values for the remaining comparisons are not statistically significant. bival, bivalirudin.

baseline bleeding risk. The effect of bivalirudin on bleeding is modified by GPI use, access site, and antiplatelet agent use, with studies showing that bailout GPI use, transradial access, and newer oral P2Y12 inhibitors reduce the bleeding advantage of bivalirudin over UFH.[16,22]

The presence of bailout (rather than routine) GPI use was associated with no difference in major bleeding between bivalirudin and UFH in a few studies.[16,23] On the other hand, in the bailout GPI arm of the EUROMAX[10] and BRIGHT[13] trials, and the MATRIX-STEMI trial (whereby GPI use was not routine),[15] bivalirudin continued to exhibit a significant bleeding advantage over UFH.

Analysis of trials with predominantly radial access reveals no difference in major bleeding rates between bivalirudin and UFH.[16] Subgroup analysis of the MATRIX trial showed no bleeding advantage with bivalirudin when radial access was used[15]; however, this should be interpreted with caution because the interaction *P*-value was not significant. Of note, bivalirudin is shown to reduce both access site as well as nonaccess site bleeding[15,24] and nonaccess site bleeding is more likely to be associated with mortality.[24] Hence, the influence of the choice of access site in modifying the effect of bivalirudin on the overall bleeding risk remains controversial.

Meta-analysis of trials using predominantly prasugrel or ticagrelor showed no difference in major bleeding rates between bivalirudin and UFH[16]; however, these results were largely driven by the HEAT PPCI trial. The BRAVE-4 trial[14] also showed that using prasugrel with bivalirudin compared with clopidogrel with UFH resulted in similar major bleeding rates in the two arms; however, these results must be interpreted with caution given the small sample size and premature termination of this study.

Bivalirudin and Acute Stent Thrombosis

Several studies have shown that the risk of AST is significantly increased with bivalirudin after primary PCI[16,20,21] (Fig. 5), even though the 30-day mortality is lower. The risk of AST seems to be highest in the first 4 hours following PCI and may be related to the discontinuation of bivalirudin infusion before full effect of antiplatelet medications.[8,10] Bivalirudin has a short half-life with rapid renal clearance, resulting in quick loss of drug effect once the infusion is turned off,[11] which in combination with delayed absorption, bioavailability, and onset of action of oral antiplatelet medications[25,26] in the setting of STEMI sets the stage for early stent thrombosis. Increase in AST has resulted in higher reinfarction and TVR rates in the EUROMAX[10] and HEAT PPCI[12] trials with bivalirudin.

Preadministration of UFH in the bivalirudin arm was shown to be protective for AST in the HORIZONS AMI trial.[27] Because bivalirudin has antithrombotic properties, it was theorized that prolonged (up to 4 hours) infusion of bivalirudin after PCI may provide additional protection against AST in the early risk period.[28] The lack of difference in AST between bivalirudin and UFH in the BRIGHT trial was attributed to high-dose post-PCI bivalirudin infusion for a median duration of 3 hours in the bivalirudin arm.[13] However, in the EUROMAX[10] and MATRIX[15] trials, bivalirudin infusion after PCI did not reduce the risk of

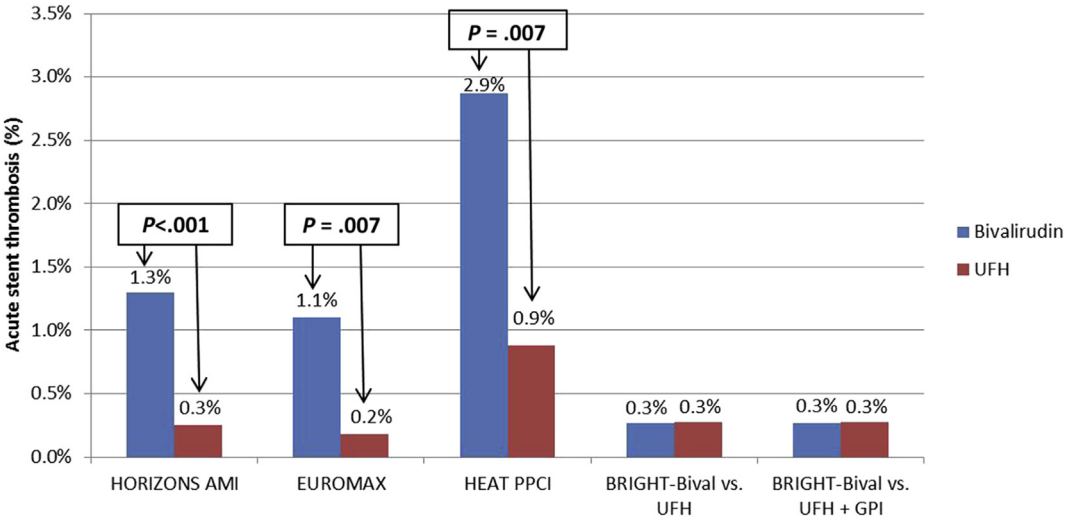

Fig. 5. Comparison of acute (within 24 hours) stent thrombosis rates between bivalirudin and UFH arms in patients with STEMI undergoing primary PCI across major RCTs. Note: Only significant *P*-values (<.05) are shown. *P*-values for the remaining comparisons are not statistically significant. bival, bivalirudin.

AST. In both trials, investigators had the option of either continuing bivalirudin infusion at the full PCI dosage of 1.75 mg/kg/h or reduced dosage of 0.25 mg/kg/h. In a subanalysis of the EUROMAX trial, it was observed that patients who got a full dosage (1.75 mg/kg/h) post-PCI infusion of bivalirudin for a median of 4 hours had a significantly reduced risk of developing AST.[29] Similarly, explorative analysis from the MATRIX trial[15] showed that patients who received full-dose bivalirudin infusion for up to 4 hours after PCI had a significantly lower risk of AST (0.2%) compared with no post-PCI infusion (0.6%) or low-dose prolonged post-PCI infusion (0.8%), without any excess bleeding risk. However, it must be noted that in all of the aforementioned trials, the dose and duration of post-PCI bivalirudin infusion were not randomized but were at the discretion of the study investigators.

Theoretically, pretreatment with newer oral P2Y12 inhibitors (prasugrel and ticagrelor) should potentially mitigate the excess risk of AST with bivalirudin. However, subanalysis of the EUROMAX trial[29] and a recently conducted meta-analysis[22] failed to demonstrate any reduction in the risk of early stent thrombosis with bivalirudin compared with UFH with the use of newer oral P2Y12 inhibitors. Impaired gastric emptying, reduced oral absorption, and a delay in onset of antiplatelet action by 4 to 6 hours in the setting of STEMI have been proposed as possible explanations behind the lack of benefit of newer oral P2Y12 inhibitors in preventing bivalirudin-associated AST.[26,30] In this scenario, the use of an intravenous P2Y12 inhibitor with a rapid onset of action (ie, cangrelor) becomes an attractive option. In a subgroup analysis of the CHAMPION PHOENIX trial (Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention)[31] including 2059 patients who received bivalirudin, there was a trend toward less stent thrombosis at 48 hours with cangrelor compared with clopidogrel (0.7% vs 1.4%, $P = .10$). Hence, cangrelor infusion after PCI seems to be a promising option to reduce the excess risk of AST with bivalirudin after primary PCI.

MEDICATION DOSING

Bivalirudin is administered as an initial bolus of 0.75 mg/kg followed by an IV infusion of 1.75 mg/kg/h for at least the duration of PCI. Routine ACT monitoring with bivalirudin is not recommended, but checking an ACT value 5 minutes after bolus may have some role in confirmation of drug administration; in some trials, an additional 0.3 mg/kg bolus of bivalirudin was administered if the ACT 5 minutes after the initial bolus was less than 225 seconds.[12,13] UFH is administered as an IV bolus ranging from 60 to 100 U/kg, with higher doses (100 U/kg) used when a GPI is not coadministered. Subsequent boluses of UFH are targeted to an ACT measurement of 200 to 250 seconds.

Summary

- Bivalirudin significantly reduces the risk of major bleeding after primary PCI for

STEMI compared with UFH. It reduces both access and nonaccess site bleeding.
- Bleeding advantage of bivalirudin over UFH may be reduced with bailout (rather than routine) GPI use, radial access, or use of newer oral antiplatelet agents; however, more evidence is needed on this topic.
- Bivalirudin has no benefit over UFH for reduction in MACE or ischemic events after primary PCI.
- Bivalirudin has a significant mortality benefit over UFH after primary PCI for STEMI, which persists over time. This benefit may be explained partly by a reduction in major bleeding and a partly by a yet-undefined pleiotropic effect of bivalirudin.
- Bivalirudin significantly increases the risk of AST compared with UFH.
- The risk of AST with bivalirudin can be potentially reduced by preadministration of UFH or prolonging bivalirudin infusion at 1.75 mg/kg/h for up to 4 hours after PCI; however, more evidence is needed before a clear recommendation can be made.
- Use of newer oral P2Y12 inhibitors with bivalirudin should theoretically reduce the excess risk of AST; however, current evidence does not show any benefit with these drugs. Use of an IV P2Y12 inhibitor (cangrelor) is an attractive option to reduce the risk of AST; however, more evidence is needed to support its use.
- The choice between bivalirudin and UFH for anticoagulation in the setting of primary PCI varies among different centers. It is often dictated by availability, cost, ease of administration, and experience with a particular medication. Clinical situations, such as the use of GPI, radial versus femoral access, and the type of oral antiplatelet agent used, may influence the choice of anticoagulation.
- In summary, bivalirudin is a relatively expensive alternative to UFH for primary PCI, and it provides a significant mortality benefit at the cost of a potentially higher rate of AST.

Enoxaparin

Enoxaparin has been compared with UFH in the ATOLL trial (STEMI Treated With Primary Angioplasty and Intravenous Lovenox or Unfractionated Heparin) in 2011 involving 910 patients with STEMI undergoing primary PCI.[32] Patients were randomly assigned to receive either enoxaparin as an IV bolus of 0.5 mg/kg or UFH as an IV bolus of 70 to 100 U/kg (if no GPI) or 50 to 70 U/kg (with GPI) before primary PCI. There was a high proportion of clopidogrel use (93%), GPI use (80%), and radial access (67%) in this trial. There was no significant difference in the primary outcome of 30-day mortality, MI complication, procedure failure, or major bleeding in enoxaparin compared with UFH (28% vs 34%, $P = .06$). There was a reduction in the secondary end point of death, recurrent MI or urgent TVR with enoxaparin (7%) compared with UFH (11%, $P = .015$). The major bleeding rates did not differ between the two groups. Thus, enoxaparin significantly reduces ischemic outcomes compared with UFH, without increasing the risk of bleeding. This study is limited by the high proportion of GPI use (80%) in both arms. Two meta-analyses have revealed that LMWH significantly reduces bleeding and mortality risk on patients with STEMI undergoing primary PCI; however, these studies are limited because of significant heterogeneity in timing, dose, and route of administration of enoxaparin in different trials.[33,34]

In summary, enoxaparin can be considered over UFH at a dose of 0.5 mg/kg IV bolus before primary PCI with radial access, if no bivalirudin use is planned. The optimal dose with femoral access is not known.

Fondaparinux

Fondaparinux is not recommended for use in STEMI in patients undergoing primary PCI based on the OASIS-6 trial (Organization for the Assessment of Strategies for Ischemic Syndromes) findings[35] (discussed later).

Fibrinolysis

Fibrinolytic agents used in the setting of STEMI include streptokinase, urokinase, or fibrin-specific agents, such as the recombinant tissue plasminogen activators (t-PAs). Recombinant t-PAs approved for STEMI include alteplase, reteplase, and tenecteplase. The various anticoagulants studied in patients with STEMI undergoing fibrinolysis are discussed later.

Enoxaparin

Several RCTs have compared UFH with enoxaparin in patients with STEMI treated with fibrinolysis.[36] These trials include Baird and colleagues 2002,[37] HART II (Second Trial of Heparin and Aspirin Reperfusion Therapy),[38] ENTIRE-TIMI 23 (Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction Thrombolysis in Myocardial Infarction

Table 2
Trials comparing different classes of anticoagulants to unfractionated heparin in ST elevation myocardial infarction patients treated with fibrinolysis

Trial	Sample Size	Agent Used	Dosing Regimen of Study Drug	Duration of UFH Infusion	Outcomes
Baird et al,[37] 2002	300	Enoxaparin	40 mg IV bolus, then 40 mg SC q8h for 4 d	4 d	Significant reduction in death, reinfarction, or readmission for angina with enoxaparin at 90 d; no difference in major bleeding
HART II, 2001	400	Enoxaparin	30 mg IV bolus, then 1 mg/kg SC q12h for ≥72 h	≥77 h	Enoxaparin noninferior to UFH with regard to infarct related artery patency rates at 90 min, and reocclusion rates 5–7 d after MI; no difference in adverse events
ENTIRE-TIMI 23, 2002	483	Enoxaparin	30 mg IV bolus, then 1 mg/kg SC q12h for 8 d or discharge	≥36 h	No difference in TIMI 3 flow at 60 min; significant reduction in death/MI with enoxaparin compared with UFH; no difference in major bleeding
ASSENT-3, 2001	6095[a]	Enoxaparin	30 mg IV bolus, then 1 mg/kg SC q12h for 7 d or discharge	≥48 h	Significant reduction in death, in-hospital reinfarction, or refractory ischemia with enoxaparin compared with UFH; no difference in major bleeding
ASSENT-3 PLUS, 2003	1639	Enoxaparin	30 mg IV bolus, then 1 mg/kg SC q12h for 7 d or discharge	≥48 h	Significant reduction in 30-d mortality, in-hospital reinfarction, or refractory ischemia with enoxaparin; increase in intracranial hemorrhage with enoxaparin, especially in those aged 75 y or older
ExTRACT TIMI 25, 2006	20,475	Enoxaparin	30 mg IV bolus, then 1 mg/kg SC q12h for 8 d or discharge[b]	≥48 h	Significant reduction in 30-d mortality or reinfarction with enoxaparin; reduction in death, reinfarction, or urgent TVR with enoxaparin. Significant increase in major bleeding with enoxaparin; no increase in intracranial hemorrhage
PENTALYSE, 2001	333	Fondaparinux	4, 8, or 12 mg initial dose IV, then SC once daily for 5–7 d	48–72 h	TIMI 3 flow rates at 90 min were similar in the 4 groups; prolonged administration of fondaparinux associated with a trend toward fewer reocclusions and revascularizations; no increase in bleeding with fondaparinux

OASIS-6, 2006	5658	Fondaparinux	2.5 mg SC once daily for 8 d (stratum I)	Compared with placebo	Significant reduction in death or reinfarction at 30 d with fondaparinux; no difference in bleeding
OASIS-6, 2006	6434	Fondaparinux	2.5 mg IV once, then SC once daily for 8 d (stratum II)	Up to 48 h	No difference in death or reinfarction; no difference in bleeding; trend toward harm in those undergoing primary PCI
GUSTO IIb, 1998	3289	Hirudin	IV infusion to maintain aPTT 60–85 s for 3–5 d	3–5 d	Reduction in death or reinfarction at 30 d with hirudin in the streptokinase group (n = 2274), but no difference between hirudin and heparin in those receiving t-PA (n = 1015)
HIT-4, 1999	1208	Hirudin	IV bolus 0.2 mg/kg, then 0.5 mg/kg SC q12h for 5–7 d	12,500 U SC q12h for 5–7 d	All patients received streptokinase; no difference in initial TIMI 3 flow, death, reinfarction, or bleeding
HERO, 1997	412	Bivalirudin	Low dose: 0.125 mg/kg bolus followed by 0.25 mg/kg/h infusion for 12 h, then 0.125 mg/kg/h for total duration of 60 h; high dose: 0.25 mg/kg bolus followed by 0.5 mg/kg/h infusion for 12 h, then 0.25 mg/kg/h for total duration of 60 h	60 h	All patients received streptokinase; TIMI 3 flow at 90–120 min higher with bivalirudin compared with heparin; no difference in death, reocclusion, or reinfarction Lower incidence of major bleeding with both high- and low-dose bivalirudin
HERO-2, 2001	17,073	Bivalirudin	0.25 mg/kg IV bolus, then infusion at 0.5 mg/kg/h for 12 h, then 0.25 mg/kg/h for 36 h	48 h	All patients received streptokinase; no difference in mortality at 30 d; significantly fewer reinfarctions within 96 h in the bivalirudin group; higher rates of mild to moderate bleeding with bivalirudin compared with heparin; however, no difference in rates of severe bleeding and intracerebral bleeding

Abbreviations: aPTT, activated partial thromboplastin time; q12h, every 12 hours; q8h, every 8 hours; SC, subcutaneous.

[a] n = 2040 in enoxaparin and n = 2038 in UFH group; there were additional comparisons of full-dose tenecteplase with half-dose tenecteplase and abciximab.

[b] Reduced dose (0.75 mg/kg) in patients older than 75 years and reduced frequency (once a day) in patients with impaired renal function.

(TIMI) - Study 23),[39] ASSENT-3 (The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3),[40] ASSENT-3 PLUS (The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 PLUS),[41] and ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction - Study 25)[42] (Table 2). All trials used UFH bolus followed by infusion to adjust to an activated partial thromboplastin time (aPTT) of 2.0 to 2.5 times normal. The duration of UFH varied in among the trials, as did the dose and duration of enoxaparin. Some of the trials (ENTIRE-TIMI 23,[39] ASSENT-3[40]) involved additional comparisons of full-dose fibrinolytics with half-dose fibrinolytics combined with GPI (eg, abciximab). The newer, larger trials comparing enoxaparin with UFH in the setting of full-dose fibrinolysis (ASSENT-3 PLUS,[41] ExTRACT-TIMI 25[42]) show a benefit of week-long enoxaparin therapy compared with 48 hour UFH infusion in reducing ischemic events, but an increase in major bleeding, especially intracranial hemorrhage in patients 75 years or older.[41]

In summary, there is benefit of enoxaparin over UFH in reduction of ischemic events in patients with STEMI receiving fibrinolysis, with an increase in the risk of major bleeding. Enoxaparin can be considered as a reasonable alternative to UFH in patients with STEMI receiving fibrinolysis without a planned PCI.

Fondaparinux

The efficacy of fondaparinux in STEMI was evaluated in the PENTALYSE (Synthetic Pentasaccharide as an Adjunct to Fibrinolysis in Acute Myocardial Infarction)[43] and OASIS-6 trials[35] (see Table 2). The OASIS-6 trial enrolled 12,092 patients with STEMI who could be treated with fibrinolytic therapy, primary PCI, or no reperfusion. Patients were stratified based on whether or not there was an indication for heparin. Stratum 1 consisted of 5658 patients without planned PCI in whom heparin was not indicated. Most of these patients (78%) received fibrinolytic therapy with streptokinase. They were randomly assigned to receive fondaparinux 2.5 mg/d subcutaneously (SC) for up to 8 days versus placebo. In stratum 2, there were 6434 patients with an indication for heparin, such as fibrinolytic therapy with t-PA, primary PCI, or no reperfusion (eligible for heparin). These patients were either randomly assigned to receive fondaparinux (as discussed earlier) or UFH for 24 to 48 hours. The following outcomes were observed:

- For the entire population, there was a reduction in the primary end point of death or reinfarction at 30 days (9.7% vs 11.2%, $P = .008$). There was no difference in major bleeding rates.
- In stratum 1, compared with placebo, there was significant reduction in death or reinfarction at 30 days with fondaparinux (11.2% vs 14.0%, $P = .002$), which persisted in a subgroup analysis of patients receiving streptokinase.
- In stratum 2, there was no benefit with fondaparinux over UFH (primary end point 8.3% vs 8.7%, $P = .58$). There was a trend toward worse outcomes in patients undergoing primary PCI with fondaparinux (incidence of death or MI at 30 days was 6.1% with fondaparinux vs 5.1% with UFH). There was an increased incidence of guide-catheter–related thrombosis in those who received fondaparinux and underwent primary PCI.
- In a prespecified subgroup analysis, benefits of fondaparinux over UFH/placebo were confined to those receiving either fibrinolytic therapy or no reperfusion. There was a trend towards harm in those undergoing primary PCI.

Based on these findings, fondaparinux may be used in patients with STEMI undergoing fibrinolysis when a PCI is not planned or in those in whom no reperfusion therapies are planned. Of note, the US Food and Drug Administration has not approved it for use in STEMI.

Direct Thrombin Inhibitors

Studies comparing direct thrombin inhibitors with UFH in patients with STEMI undergoing fibrinolysis include GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb),[44] HIT-4 (Hirudin for the Improvement of Thrombolysis (HIT)-4),[45] HERO (Hirulog Early Reperfusion/Occlusion Study),[46] and HERO-2 (Hirulog Early Reperfusion/Occlusion Study (HERO)-2)[47] (see Table 2). There is some evidence of benefit of hirudin over UFH in patients with STEMI receiving streptokinase.[44] In the HERO-2 trial,[47] whereby streptokinase was used for fibrinolysis, there was a reduction in reinfarction rates at 96 hours with bivalirudin compared with UFH (1.6% vs 2.3%, $P = .001$). There was a trend of higher severe bleeding (0.7% vs 0.5%, $P = .07$) and intracerebral bleeding (0.6% vs 0.4%, $P = .09$) as well as significantly increased mild to moderate bleeding with bivalirudin compared

with UFH. Because streptokinase is rarely used for fibrinolysis in the United States in the current era, there is no good evidence supporting the use of direct thrombin inhibitors over UFH for anticoagulation in patients with STEMI receiving fibrinolysis with fibrin-specific agents.

No reperfusion

There is a lack of randomized trials comparing UFH with placebo in patients with STEMI who are not reperfused. It is reasonable to use systemic anticoagulation with UFH in the presence of severe left ventricular (LV) dysfunction, large anterior MI, LV thrombus, atrial fibrillation, or a high risk for systemic or pulmonary embolism. Reviparin, an LMWH, administered SC twice daily for 7 days, was shown to significantly reduce the primary outcome of death, reinfarction, or stroke when compared with placebo (15.0% vs 18.3%) in a subset of 3225 patients not undergoing reperfusion in the CREATE trial (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation).[48] Compared with UFH, enoxaparin showed similar incidence of death, reinfarction, or recurrent angina in a trial of 1225 patients with STEMI not receiving reperfusion.[49] The OASIS-6 trial provides evidence of benefit with fondaparinux 2.5 mg SC once daily compared with placebo in patients with STEMI undergoing no reperfusion[35] (see earlier discussion). Direct thrombin inhibitors have not been evaluated in this setting.

SUMMARY

Anticoagulation is essential in all patients with STEMI. In patients undergoing primary PCI, bivalirudin compared with UFH provides a mortality benefit, predominantly via reduction in major bleeding. Bailout (rather than routine) GPI use, transradial access, and use of newer oral P2Y12 inhibitors can potentially lessen the bleeding advantage of bivalirudin over UFH. There is an increase in the risk of acute (within 24 hours) stent thrombosis with bivalirudin compared with UFH, which can potentially be reduced by prolonging full-dose bivalirudin infusion after PCI for 4 hours. With the advent of newer oral (prasugrel and ticagrelor) and IV (cangrelor) P2Y12 inhibitors, several potential combinations can arise, which makes the choices challenging. For instance, IV cangrelor is a potentially attractive option to reduce the risk of AST with bivalirudin; however, more studies need to be undertaken to explore its role in this setting. In patients with STEMI undergoing fibrinolysis, UFH is the preferred anticoagulant, with enoxaparin and fondaparinux being reasonable alternatives for those in whom a PCI is not planned. In patients with STEMI not undergoing reperfusion, UFH, enoxaparin or fondaparinux can be used for anticoagulation.

For the clinician, the choices of antithrombin therapy for primary PCI can be daunting. In most of the clinical trials, the choice was dichotomous; but in real-world practice, it becomes a complex calculus after factoring in decisions about radial versus femoral access, provisional versus routine GPI use, which oral antiplatelet agent to use, timing of the oral antiplatelet agent, and whether an IV P2Y12 inhibitor should be used. It is, therefore, little wonder that an individual interventional cardiologist struggles to determine if a given clinical trial fits into an algorithm to choose the optimal antithrombin strategy for a particular patient in the cardiac catheterization laboratory. There is no doubt that continued hearty debate will surround this controversy.

REFERENCES

1. Davie EW, Fujikawa K, Kisiel W. The coagulation cascade: initiation, maintenance, and regulation. Biochemistry 1991;30(43):10363–70.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127(4):e362–425.
3. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33(20):2569–619.
4. Rao SV, Ohman EM. Anticoagulant therapy for percutaneous coronary intervention. Circulation 2010;3(1):80–8.
5. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 2001;119(1S):64S–94S.
6. Cho L, Kottke-Marchant K, Lincoff AM, et al. Correlation of point-of-care ecarin clotting time versus activated clotting time with bivalirudin concentrations. Am J Cardiol 2003;91(9):1110–3.
7. Koster A, Chew D, Grundel M, et al. Bivalirudin monitored with the ecarin clotting time for

anticoagulation during cardiopulmonary bypass. Anesth Analg 2003;96(2):383–6. table of contents.
8. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358(21):2218–30.
9. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377(9784):2193–204.
10. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369(23):2207–17.
11. Zeymer U, van 't Hof A, Adgey J, et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. Eur Heart J 2014;35(36):2460–7.
12. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384(9957):1849–58.
13. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA 2015;313(13):1336–46.
14. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J 2014;35(34):2285–94.
15. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med 2015;373(11):997–1009.
16. Shah R, Rogers KC, Matin K, et al. An updated comprehensive meta-analysis of bivalirudin vs heparin use in primary percutaneous coronary intervention. Am Heart J 2016;171(1):14–24.
17. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010;55(18):1923–32.
18. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123(23):2736–47.
19. Stone GW, Clayton T, Deliargyris EN, et al. Reduction in cardiac mortality with bivalirudin in patients with and without major bleeding: the HORIZONS-AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). J Am Coll Cardiol 2014;63(1):15–20.
20. Barria Perez AE, Rao SV, Jolly SJ, et al. Meta-analysis of effects of bivalirudin versus heparin on myocardial ischemic and bleeding outcomes after percutaneous coronary intervention. Am J Cardiol 2016;117(8):1256–66.
21. Zhang S, Gao W, Li H, et al. Efficacy and safety of bivalirudin versus heparin in patients undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials. Int J Cardiol 2016;209:87–95.
22. Bittl JA, He Y, Lang CD, et al. Factors affecting bleeding and stent thrombosis in clinical trials comparing bivalirudin with heparin during percutaneous coronary intervention. Circulation 2015;8(12):e002789.
23. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet 2014;384(9943):599–606.
24. Kilic S, Van't Hof AW, Ten Berg J, et al. Frequency and prognostic significance of access site and non-access site bleeding and impact of choice of antithrombin therapy in patients undergoing primary percutaneous coronary intervention. The EUROMAX trial. Int J Cardiol 2016;211:119–23.
25. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61(15):1601–6.
26. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012;5(6):797–804.
27. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. Circulation 2011;123(16):1745–56.
28. Kimmelstiel C, Zhang P, Kapur NK, et al. Bivalirudin is a dual inhibitor of thrombin and collagen-dependent platelet activation in patients undergoing percutaneous coronary intervention. Circulation 2011;4(2):171–9.
29. Clemmensen P, Wiberg S, Van't Hof A, et al. Acute stent thrombosis after primary percutaneous coronary intervention: insights from the EUROMAX trial (European Ambulance Acute Coronary Syndrome Angiography). JACC Cardiovasc Interv 2015;8(1 Pt B):214–20.
30. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing

primary percutaneous coronary intervention. Circ Cardiovasc Interv 2015;8:e001593.
31. White HD, Bhatt DL, Gibson CM, et al. Outcomes with cangrelor versus clopidogrel on a background of bivalirudin: insights from the CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention [PCI]). JACC Cardiovasc Interv 2015;8(3):424–33.
32. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet 2011;378(9792):693–703.
33. Navarese EP, De Luca G, Castriota F, et al. Low-molecular-weight heparins vs. unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis. J Thromb Haemost 2011;9(10):1902–15.
34. Silvain J, Beygui F, Barthelemy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ 2012;344:e553.
35. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA 2006;295(13):1519–30.
36. McCann CJ, Menown IB. New anticoagulant strategies in ST elevation myocardial infarction: trials and clinical implications. Vasc Health Risk Manag 2008;4(2):305–13.
37. Baird SH, Menown IB, McBride SJ, et al. Randomized comparison of enoxaparin with unfractionated heparin following fibrinolytic therapy for acute myocardial infarction. Eur Heart J 2002;23(8):627–32.
38. Ross AM, Molhoek P, Lundergan C, et al. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). Circulation 2001;104(6):648–52.
39. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. Circulation 2002;105(14):1642–9.
40. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358(9282):605–13.
41. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108(2):135–42.
42. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 2006;354(14):1477–88.
43. Coussement PK, Bassand JP, Convens C, et al. A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction. The PENTALYSE study. Eur Heart J 2001;22(18):1716–24.
44. Metz BK, White HD, Granger CB, et al. Randomized comparison of direct thrombin inhibition versus heparin in conjunction with fibrinolytic therapy for acute myocardial infarction: results from the GUSTO-IIb Trial. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb) Investigators. J Am Coll Cardiol 1998;31(7):1493–8.
45. Neuhaus KL, Molhoek GP, Zeymer U, et al. Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. J Am Coll Cardiol 1999;34(4):966–73.
46. White HD, Aylward PE, Frey MJ, et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. Circulation 1997;96(7):2155–61.
47. White H. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. Lancet 2001;358(9296):1855–63.
48. Yusuf S, Mehta SR, Xie C, et al. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. JAMA 2005;293(4):427–35.
49. Cohen M, Gensini GF, Maritz F, et al. The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and tirofiban versus placebo in the treatment of acute ST-segment elevation myocardial infarction patients ineligible for reperfusion (TETAMI): a randomized trial. J Am Coll Cardiol 2003;42(8):1348–56.