Abstract: Cardiovascular disease is the leading cause of death in the US. For patients with ST-elevation myocardial infarction (STEMI), urgent reperfusion of the culprit arterial occlusion, often achieved via primary percutaneous coronary intervention (PCI), reduces post-MI mortality and other major adverse cardiovascular events (MACE). Adjunctive antithrombotic and antiplatelet therapies are used during PCI to reduce MACE rates. Currently, a variety of antithrombotic options are available for peri-procedural use. The most commonly used agents include unfractionated heparin or low molecular weight heparin ± glycoprotein IIb/IIIa inhibitors (GPI). These agents reduce the rates of peri-procedural ischemic and thrombotic events, though these benefits come at the cost of an increase in bleeding complications. Bivalirudin is a direct thrombin inhibitor with a short half-life and linear pharmacokinetics, which results in predictable serum concentrations and anticoagulant effect. Bivalirudin has emerged as an efficacious and safe alternative to heparin plus GP IIb/IIIa inhibitors in both stable coronary artery disease and acute coronary syndrome patients. In the HORIZONS-AMI trial, monotherapy with bivalirudin was compared with the combination of heparin and a GPI in a large population of patients with STEMI who underwent primary PCI. Bivalirudin treatment was associated with improved event-free survival at 30 days and reduced rates of major bleeding. Based on the results of the trial, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines have incorporated recommendations for bivalirudin use in the setting of STEMI. Recently, 3-year follow-up data from the HORIZONS-AMI cohort were published, demonstrating sustained benefits in patients treated with bivalirudin, including reduced rates of mortality, cardiovascular mortality, reinfarction, and major bleeding events. These results further support the use of bivalirudin in the setting of primary PCI for STEMI given that its benefits are maintained through long-term follow-up.

Keywords: bivalirudin, antithrombotic, ST-elevation myocardial infarction, acute coronary syndrome, PCI

Introduction
Cardiovascular disease is the leading cause of death in the US.1 Acute coronary syndromes (ACS) are responsible for more than 1.3 million hospitalizations in the US annually.1 Registry data indicate that nearly 30% of these cases are due to ST-elevation myocardial infarctions (STEMI).2 In patients with STEMI, timely reperfusion is the primary goal, and this is often achieved through primary percutaneous coronary intervention (PCI).3 Urgent revascularization significantly reduces the rate of cardiovascular mortality as well as other major adverse cardiovascular events (MACE) after MI.4,5
In the setting of ACS, the prothrombotic clotting cascade is activated, leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to a fibrin monomer. This fibrin production then results in platelet activation via prostaglandin and adenosine diphosphate-independent mechanisms. Antithrombotic agents, therefore, are used in conjunction with revascularization to reduce post-MI ischemic events and to minimize thrombotic events peri-procedurally. The use of antithrombotic agents to this end is frequently associated with increased rates of bleeding complications and transfusions. Bleeding events and transfusions have been shown to be independent predictors of mortality in patients with ACS and in patients undergoing PCI. The mechanisms by which post-PCI bleeding increases short- and long-term mortality are not well understood, but may include fatal or hemodynamically significant hemorrhage, temporary or permanent discontinuation of cardiovascular medications in the setting of an acute bleed, and the prothrombotic effects of blood transfusions. The ideal antithrombotic agent would therefore be effective in reducing the rates of major cardiovascular events while minimizing bleeding complications.

Unfractionated heparin (UFH) is the most commonly used antithrombotic agent in the setting of ACS. Heparin binds to and catalyzes the activity of the antithrombin, resulting in indirect inhibition of thrombin (Table 1). Heparin is associated with high rates of bleeding after primary PCI, and this may be related to its inability to bind to clot-bound thrombin, its indirect mechanism of thrombin inhibition via anti-thrombin III activation, non-specific protein binding, and non-linear pharmacokinetics. Glycoprotein IIb/IIIa inhibitors (GPIs) bind to and inhibit the platelet IIb/IIIa receptor and are used as an adjunctive therapy to heparin in primary PCI. The use of GPIs has been associated with reduced rates of subacute stent thrombosis, recurrent ischemic events, as well as with improved survival. However, GPIs are also associated with increased rates of hemorrhagic complications and significant thrombocytopenia.

Table 1 Differences in mechanisms of action between unfractionated heparin and bivalirudin

| Structure | Unfractionated heparin | Bivalirudin |
|-----------|------------------------|------------|
| Binds     | Anti-thrombin III (AT III) | Semi-synthetic, 20 amino acid polypeptide derived from hirudin |
| Mechanism of action | Indirect thrombin inhibition via binding of AT III | Direct thrombin inhibition |
| Activity against thrombin | Inhibits only thrombin that is not bound to fibrin | Inhibits bound and unbound thrombin |
| Inactivated by | Platelet factor 4 | Cleavage by thrombin |
| Pharmacokinetics | Non-linear | Linear |

Bivalirudin is a direct thrombin inhibitor that has a high affinity and specificity for binding to the active site of thrombin (Table 1). Its carboxy-terminal segment competes with fibrinogen for access to a binding site on thrombin, and its amino-terminal segment attaches to the active catalytic site of thrombin, which is responsible for the conversion of fibrinogen to fibrin and the activation of clotting factors and platelets. Bivalirudin is active against both unbound and bound thrombin. Unlike heparin, bivalirudin is not inactivated by platelet factor 4, does not require any cofactors for its activity, and does not bind to proteins or cellular matrices other than thrombin. The pharmacokinetics of bivalirudin are linear. Peak plasma concentrations with bolus dosing are achieved within minutes and steady-state concentrations are directly related to its dose. These properties of bivalirudin result in a more predictable anticoagulant effect as evidenced by linear increases in the prothrombin time, activated partial thromboplastin time, and activated clotting time with increasing intravenous bivalirudin doses. Some bivalirudin elimination occurs via proteolytic cleavage, but it is primarily renally cleared, and dose adjustments are necessary for patients with renal dysfunction. Bivalirudin’s half-life is 20–25 minutes in patients with normal renal function. The half-life is nearly 1 hour in patients with a CrCl between 10 and 30 mL/minute, and in hemodialysis patients, the half-life of bivalirudin is 3.5 hours.

In a number of randomized trials of patients with stable CAD, unstable angina or non-ST segment elevation MI (NSTEMI), bivalirudin, compared with the combination of heparin and a GPI has been demonstrated to have similar efficacy and an improved bleeding profile. The REPLACE-2 trial, which randomized 6010 patients undergoing elective or urgent PCI to bivalirudin with provisional use of a GPI versus heparin plus a GPI, found that bivalirudin treatment was non-inferior to heparin plus a GPI in terms of the primary composite endpoint of the 30-day incidence of death, MI, urgent revascularization, and in-hospital bleeding. The ACUITY trial randomized 13,819 patients with unstable angina and NSTEMI to UFH or enoxaparin plus a GPI,
bivalirudin plus a GPI, or bivalirudin alone and demonstrated that bivalirudin monotherapy, compared with heparin plus a GPI, was non-inferior in terms of the 30-day composite ischemia endpoint of death, MI, and urgent revascularization, while also significantly reducing the rates of major bleeding. These studies demonstrated the efficacy and safety of bivalirudin in low to intermediate risk ACS patients and set the stage for the evaluation of bivalirudin in high-risk STEMI patients.

The HORIZONS-AMI trial

The HORIZONS-AMI trial was an international, multicenter, prospective, open-label, randomized study designed to examine the safety and efficacy of bivalirudin monotherapy compared with UFH plus routine GPIs, and the paclitaxel-eluting TAXUS stent compared with a bare metal EXPRESS 2 stent in patients with STEMI undergoing primary PCI.

The two primary 30-day endpoints were major bleeding not related to coronary artery bypass grafting (CABG) and net adverse clinical events (NACE) defined as the composite of major bleeding and MACE, which included death, reinfarction, target vessel revascularization (TVR) for ischemia, while also significantly reducing the rates of major bleeding. These studies demonstrated the efficacy and safety of bivalirudin in low to intermediate risk ACS patients and set the stage for the evaluation of bivalirudin in high-risk STEMI patients.

Between March 2005 and May 2007, 3602 patients with STEMI were enrolled at 123 medical centers in 11 countries. Patients were randomized in a 1:1 fashion prior to primary angioplasty to UFH with a GPI versus bivalirudin with provisional use of GPIs (Figure 1). Randomization was achieved with an interactive voice response system that incorporated multiple clinical parameters into stratification including whether or not the patient received any non-protocol heparin, whether the patient was loaded with 300 mg of clopidogrel, 600 mg of clopidogrel, or 500 mg of ticlopidine, whether the patient received abciximab or eptifibatide as the GPI in the control arm, and whether the site was US or non-US. Emergency coronary angiography was performed after randomization. Subsequently, the treating physician would decide on further management with PCI, CABG, or medical management. Details of the second randomization comparing paclitaxel-eluting stents versus bare-metal stents will not be described here other than to state that after patency was established in the infarct-related vessel, eligible patients were then assigned randomly in a 3:1 ratio to either paclitaxel-eluting stents or bare-metal stents.

Bivalirudin was administered as an intravenous bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/hour. Bivalirudin was to be started before PCI, though the exact timing of bivalirudin initiation prior to PCI was not specified. When UFH was used, it was administered as an intravenous bolus of 60 IU per kg of body weight, and subsequent boluses were given to achieve a target activated clotting time of 200 to 250 seconds. Both of these antithrombin agents were to be discontinued at the completion of angiography or PCI, but they could be continued at low doses if they were clinically indicated. A GPI was administered before PCI as a bolus followed by a continuous infusion in all patients in the control group, but was to be administered in the bivalirudin group only in patients with no reflow or with large thrombus burden during PCI. The choice of GPI was left to the discretion of the operator. GPIs were continued for 12 to 18 hours post-PCI.

All patients received either 324 mg of chewed, non-enteric coated aspirin or 500 mg IV aspirin followed by 300 to 325 mg orally daily while in the hospital and then...
75 mg to 81 mg daily upon discharge. Clopidogrel was loaded at either 300 mg or 600 mg per investigator discretion and was then followed by 75 mg daily for at least 6 months. Alternatively, if clopidogrel was either unavailable or there was a documented hypersensitivity to the medication, ticlopidine was used. If neither of these thienopyridines could be tolerated, then cilostazol at a dose of 100 mg twice daily was to be administered for 6 months.²⁷

The baseline features between the two anticoagulation groups were well matched. The median age was 60.2 years, and 76.6% of the patients were men. In terms of baseline cardiovascular risk factors, 15% had diabetes, and ~30% of those patients required insulin. Over 50% had hypertension, >40% had hyperlipidemia, and nearly half the patients were current smokers. Renal insufficiency was evident in 15% of patients.

The median ejection fraction was 50% in both groups. Over 10% had previously suffered MIs, and a similar percentage had undergone previous PCI, while 3% of patients had previously undergone CABG. Twenty-seven percent of patients were on aspirin before admission, and ~4% were using thienopyridines before admission.²⁶

In terms of presentation, symptom onset to hospital arrival occurred at a median of just over 2 hours. After emergency angiography, the primary management strategy was primary PCI in 92.7% of the patients, deferred PCI in 0.2%, primary CABG in 1.7%, and medical management in 5.3%. Of those patients who underwent primary PCI, stents were implanted in 95.5%.²⁶

UFH, most often as a bolus and without a continuous infusion, was administered before cardiac catheterization in
approximately two-thirds of the patients who were assigned to treatment with bivalirudin. In addition, 2.6% of patients in the bivalirudin arm received heparin during the procedure, and 7.5% of patients in this arm received bailout GPs during primary PCI. The most common reasons for GPi use in this group were sustained absence of reflow after PCI or giant thrombus after PCI. Abciximab was used most commonly, followed by eptifibatide and then tirofiban. Only 0.2% of patients in the heparin plus GPI group received bivalirudin during the PCI.

In both groups, >99% of patients received aspirin during the hospitalization, and >97% of patients in both groups were discharged on aspirin. A 600 mg loading dose of clopidogrel was used almost twice as frequently as a 300 mg dose, and ~93% of patients in both groups were discharged on thienopyridines. Other cardiovascular medication use at discharge was similar in both arms, including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins.

With regard to the primary 30-day endpoints for the entire study population, bivalirudin monotherapy, compared with heparin plus a GPI, significantly reduced the rate of NACE (9.2% vs 12.1%, RR: 0.76, 95% CI: 0.63–0.92; P = 0.005), due, in large part, to a lower rate of major non-CABG-related bleeding (4.9% vs 8.3%, RR: 0.60, 95% CI: 0.46–0.77; P < 0.001), with similar rates of major adverse cardiovascular events (5.4% vs 5.5%, RR: 0.99, 95% CI: 0.76–1.30; P = 0.950) (Table 2). The rates of major bleeding, including CABG-related events were also lower in the bivalirudin group (6.8% vs 10.8%, P < 0.001), as were the rates of blood transfusions (2.1% vs 3.5%, P < 0.001), thrombocytopenia, and hemorrhagic complications as defined by the Thrombosis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) scales. Importantly, among patients in the heparin plus GPI arm, the peak ACT was not significantly different in those patients who suffered major bleeding and those who did not. Neither preprocedural UFH use nor clopidogrel loading dose demonstrated a significant interaction with regard to either major adverse cardiovascular events or major bleeding.26 Importantly, treatment with bivalirudin significantly reduced 30-day rates of cardiovascular mortality (1.8% vs 2.9%, RR: 0.62, 95% CI: 0.40–0.95; P = 0.030) and all-cause mortality (2.1% vs 3.1%, RR: 0.66, 95% CI: 0.44–1.00; P = 0.047).

For the subgroup of patients in whom PCI was performed, which accounted for 93% of study patients, treatment with bivalirudin as compared with heparin plus a GPI resulted in lower rates of major bleeding (5.1% vs 8.5%, RR: 0.59, 95% CI: 0.46–0.77; P < 0.001), net adverse clinical events (9.2% vs 12.2%, RR: 0.75, 95% CI: 0.62–0.92; P = 0.005), and 30-day cardiovascular mortality (1.8% vs 2.8%, RR: 0.63, 95% CI: 0.40–0.99; P = 0.045). In this PCI subgroup, there was no difference in the two arms in terms of all-cause mortality at 30 days (0.2% vs 0.1%, P = 1.000). Additionally, rates of reinfarction, TVR, and stroke were not significantly different in the two arms, whether or not PCI was performed.26

The lower rates of bleeding events in the bivalirudin arm account for the significant difference in NACE at 30 days. The reduction in bleeding rates was accompanied by significant reductions in both all-cause and cardiac mortality, although the composite of MACE, which included death, reinfarction, ischemia-driven TVR, and stroke, was not significantly different. The precise mechanism by which reduction in bleeding events is associated with lower mortality is not clear. Postulated mechanisms include reduction in fatal or hemodynamically significant hemorrhage, temporary or permanent discontinuation of cardiovascular medications in the setting of an acute bleed, and the prothrombotic effects of blood transfusions.12,13

One area of concern in the bivalirudin-treated patients was a higher rate of acute stent thrombosis occurring within 24 hours (1.3% vs 0.3%, P < 0.001). This may be related to lower loading dose of clopidogrel (300 mg vs 600 mg) and not receiving UFH bolus before randomization in those patients. However, the overall rate of stent thrombosis at 30 days was not significantly different in the two arms (2.5% vs 1.9%, P = 0.300). Furthermore, the 30-day rates of reinfarction were similar in both arms.26

The HORIZONS-AMI trial demonstrated the superior safety and efficacy profile of bivalirudin monotherapy compared with heparin plus GPI therapy in patients with STEMI undergoing primary PCI. However, a number of limitations should be acknowledged, including the open-label design, slight imbalances in baseline patient characteristics including outpatient use of thienopyridines, the lack of reporting or standardization of timing of bivalirudin initiation prior to PCI, high rate of use of heparin in the bivalirudin group, limited use of radial access which is known to be associated with lower rates of bleeding complications, higher rate of acute stent thrombosis, lack of adjustment of probability values for secondary endpoints for multiple analyses and, perhaps most importantly, relatively short-term follow-up.5,28–30
The HORIZONS-AMI trial: subgroup analyses and follow-up

Following the publication of HORIZONS-AMI, a number of studies examining high-risk subgroups were published.31–33 One-year follow-up data for the 16.5% of patients in HORIZONS-AMI with diabetes demonstrated that bivalirudin monotherapy reduced 1-year rates of cardiovascular mortality, driven largely by reduced mortality in insulin-treated diabetics, though there were no significant differences with respect to all-cause mortality, major bleeding, MACE, NACE, or stent thrombosis.31

Another 1-year follow-up study examined clinical outcomes in patients stratified by the CADILLAC risk score, a validated prognostic score for patients undergoing primary PCI. Patients were classified as low-, medium-, and high-risk based on these scores, and the CADILLAC score accurately identified high-risk patients based on receiver operator characteristic curves. In the highest risk group, bivalirudin monotherapy was associated with significantly lower rates of all-cause mortality (8.4% vs 15.9%, RR: 0.53, 95% CI: 0.32–0.89; \( P < 0.010 \)). Bivalirudin therapy reduced major bleeding rates in all three risk groups, although this reduction was only statistically significant in the lowest-risk patient group. One major limitation of this substudy was the lack of availability of data allowing for CADILLAC score calculation in ∼30% of the HORIZONS-AMI patients.32

Three year follow-up data on the chronic kidney disease (CKD) subgroup, which was defined as a precontrast CrCl of <60 mL/minute, reaffirmed CKD as an independent predictor of poor cardiovascular outcomes. In this subgroup of patients, bivalirudin monotherapy did not result in lower rates of ischemic or bleeding events.33

Importantly, all of these results should be considered hypothesis-generating only, as the HORIZONS-AMI trial was not powered for testing of superiority or non-inferiority of bivalirudin therapy in these subgroups.31–33

The HORIZONS-AMI trial: 3-year follow-up

Clinical follow-up for the original HORIZONS-AMI cohort was planned for 30 days, 6 months, 1 year, 2 years, and 3 years. Due to insufficient funding, planned follow-up to 5 years was not possible, so in June 2011, *Lancet* published the final 3-year follow-up data for the HORIZONS-AMI cohort. Pre-specified endpoints included major bleeding not related to CABG, composite MACE, which included
death, reinfarction, ischemia-driven TVR, and stroke, as well as each of these individual components, and NACE, which was the composite of MACE and non-<c>ABG related major bleeding.30</c>

During the follow-up period, aspirin was taken by more than 90% of patients in both treatment arms, whereas thienopyridine use dropped from 93% at the discharge and 30-day time points to 88% at 6 months. By 1 year, only two-thirds of patients were taking thienopyridines, and by 3 years, thienopyridine use dropped to just one-quarter of patients.30

At 3 years, bivalirudin monotherapy, compared with heparin plus a GPI, significantly reduced rates of non-<c>ABG related major bleeding (6.9% vs 10.5%, P = 0.0001), as well as a number of other bleeding safety parameters including major bleeding including CAbG-related bleeding, blood transfusion, TIMI major and minor bleeding, and any GUSTO bleeding (Table 2). Kaplan–Meier analyses confirmed that after the initial benefit in major bleeding reduction with bivalirudin at 30 days, major bleeding events occurred at similar rates in both treatment groups.30

There were no significant changes in the rates of composite MACE (21.9% vs 21.8%, P = 0.95) or NACE (25.5% vs 27.6%, P = 0.090). Importantly, bivalirudin treatment significantly reduced rates of cardiovascular mortality (2.9% vs 5.1%, P = 0.001), all-cause mortality (5.9% vs 7.7%, P = 0.030), and rates of reinfarction (6.2% vs 8.2%, P = 0.040). The mortality, cardiac mortality, and reinfarction benefits in the bivalirudin arm increased over time. This reduction in all-cause mortality equates to a number needed to treat of 54; therefore, 18 lives would be saved per 1000 patients treated with bivalirudin compared with heparin plus a GPI.30

Bivalirudin monotherapy was associated with a trend towards increased rates of ischemia-driven TVR (14.2% vs 12.1%, P = 0.06) and ischemia-driven target lesion revascularization (11.3% vs 9.7%, P = 0.010), though for the 1203 patients for whom follow-up angiographic data were available, restenosis rates were similar in both groups (12.8% vs 12.9%, P = 0.980).30

Though there were concerns over increased rates of acute stent thrombosis in the bivalirudin arm from the original 30-day data, final 3-year follow-up data demonstrated no statistically significant difference with regard to definite stent thrombosis (4.2% vs 4.1%, P = 0.870), probable stent thrombosis (0.3% vs 1.0%, P = 0.020), or their composite (4.5% vs 5.1%, P = 0.490).30

In summary, after 3 years of follow-up, bivalirudin monotherapy as compared with heparin plus a GPI in patients with STEMI, most of whom underwent primary PCI, demonstrated sustained benefits with significant reductions in all-cause mortality, cardiovascular mortality, major bleeding, and reinfarction, while the rates of MACE, stroke, TVR, and stent thrombosis were not significantly different.30

**Future directions**

Since the publication of the HORIZONS-AMI trial, registry data have indicated an increase in the use of bivalirudin in the setting of AMI, though heparin still remains the most commonly used anti-thrombotic agent.14

Based on the results of the original HORIZONS-AMI trial, both the European Society of Cardiology guidelines on acute myocardial infarction and the American College of Cardiology/American Heart Association (ACC/AHA) STEMI guidelines incorporated stronger recommendations for use of bivalirudin in primary PCI.34 The most recent guidelines from the European Society of Cardiology published in 2008 provide a Class IIa recommendation (Level of Evidence: B) for the use of bivalirudin as an anti-thrombotic therapy for primary PCI.34

Compared with the previous ACC/AHA STEMI guidelines from 2007, the 2009 guidelines incorporated bivalirudin as an acceptable anticoagulant for primary PCI based on the data from HORIZONS-AMI.35 They make a Class I recommendation (Level of Evidence: B) for the use of bivalirudin as a supportive measure for primary PCI with or without prior treatment with UFH. Additionally, a Class IIa recommendation (Level of Evidence: B) states that in STEMI patients undergoing PCI who are at high risk of bleeding, anticoagulation with bivalirudin is reasonable.3

With the most recent long-term HORIZONS-AMI follow-up data demonstrating the sustained benefits of bivalirudin compared with heparin plus a GPI in terms of bleeding, mortality and reinfarction with no loss of efficacy in ischemic outcomes, future STEMI guidelines will likely continue to support the use of bivalirudin in these high-risk patients undergoing primary PCI.

**Disclosure**

Ashish Shah has no conflicts to declare. Dmitriy N Feldman is a member of the speakers’ bureau for Abbott Vascular, the Medicines Company, a member of the advisory board/speakers’ bureau for Eli Lilly, Daiichi-Sankyo, and a consultant for Maquet Cardiovascular, Gilead Sciences.

---

**Vascular Health and Risk Management 2012:8**

---

Dovepress

Submit your manuscript | www.dovepress.com

Dovepress
References

1. WRITING GROUP MEMBERS, Lloyd-Jones D, Adams RJ, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Committee. Heart disease and stroke statistics – 2010 update: a report from the American Heart Association. Circulation. 2010;121:e46–e215.

2. Roe MT, Parsons LS, Pollack CV Jr, et al. National Registry of Myocardial Infarction Investigators. Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction. Arch Intern Med. 2005;165:1630–1636.

3. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused updated) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

4. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13–20.

5. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084–1089.

6. Sciulli TM, Mauro VF. Pharmacology and clinical use of bivalirudin. Ann Pharmacother. 2002;36:1028–1041.

7. White CM. Thrombin-directed inhibitors: pharmacology and clinical use. Am Heart J. 2005;154:S5–S60.

8. Morrow DA. Antithrombotic therapy to support primary PCI. N Engl J Med. 2008;358:2280–2282.

9. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004;292:1555–1562.

10. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006;114:774–782.

11. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55:2556–2566.

12. Wang TY, Xiao L, Alexander KP, et al. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation. 2008;118:2319–2345.

13. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation. 2007;115:813–818.

14. Kadakia MB, Desai NR, Alexander KP, et al; National Cardiovascular Data Registry. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry – GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry – Get With The Guidelines). JACC Cardiovasc Interv. 2010;3:1166–1177.

15. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest. 2001;119(1 Suppl): 64S–94S.

16. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA. 2005;293:1759–1765.

17. Lee DP, Herity NA, Hiatt BL, et al. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. Circulation. 2003;107:1497–1501.

18. Montalescot G, Barragan P, Wittenberg O, et al. ADMIRAL Investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med. 2001;344:1893–1905.

19. van ’t Hof AW, Ernst N, de Boer MJ, et al. For the On-Time Study Group. Facilitation of primary coronary angioplasty by early start of a glycoprotein IIb/IIIa inhibitor: results of the ongoing tirofiban in myocardial infarction evaluation (On-TIME) trial. Eur Heart J. 2004;25:837–846.

20. Zeymer U, Zahn R, Schiele R, et al. Early eptifibatide improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized integrilin in acute myocardial infarction (INTAMI) pilot trial. Eur Heart J. 2005;26:1971–1977.

21. Stone GW, Grines CL, Cox DA, et al; for the CADILLAC investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002;346:957–966.

22. Tcheng JE, Kandzari DE, Grines CL, et al. CADILLAC Investigators. Benefits and risks of abciximab use in primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. Circulation. 2003;108:1316–1323.

23. Gibson CM, Morrow DA, Murphy SA, et al; TIMI Study Group. A randomized trial to evaluate the relative protection against post-percutaneous coronary intervention microvascular dysfunction, ischemia, and inflammation among antiplatelet and antithrombotic agents: the PROTECT-TIMI-30 trial. J Am Coll Cardiol. 2006;47:2364–2373.

24. Lincoff AM, Bittl JA, Harrington RA, et al; for the REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA. 2003;289:853–863.

25. Stone GW, McLaurin BT, Cox DA, et al; for the ACUITY investigators. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006;355:2203–2216.

26. Stone GW, Witzenbichler B, Guagliumi G, et al; for the HORIZONS-AMI Trial Investigators. Bivalirudin during Primary PCI in Acute Myocardial Infarction. N Engl J Med. 2008;358:2218–2230.

27. Mehran R, Broduie B, Cox DA, et al. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. Am Heart J. 2008;156:44–56.

28. Mehran R, Lansky AJ, Witzenbichler B, et al. HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet. 2009;374:1149–1159.

29. Webster MW. HORIZONS-AMI. Lancet. 2010;375:375.

30. Stone GW, Witzenbichler B, Guagliumi G, et al. HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and provisional glycoprotein IIb/IIIa blockage during percutaneous coronary intervention (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet. 2011;377:2193–2204.

31. Witzenbichler B, Mehran R, Guagliumi G, et al. Impact of diabetes mellitus on the safety and effectiveness of bivalirudin in patients with acute myocardial infarction undergoing primary angioplasty. JACC Cardiovasc Interv. 2011;4:760–768.

32. Parodi G, Antonucci D, Nikolsky E, et al. Impact of bivalirudin therapy in high-risk patients with acute myocardial infarction. JACC Cardiovasc Interv. 2010;3:796–802.
33. Saltzman AJ, Stone GW, Claessen BE, et al. Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2011;4:1011–1019.

34. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. *Eur Heart J*. 2008;29:2909–2945.

35. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2007 Focused Update of the 2004 ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2007;51:210–247.