Antithrombotic Therapy for PCI

Alternatives that may surpass current UFH pathophysiology.

BY SEAN JAVAHERI, MD, AND SUNIL V. RAO, MD

Percutaneous coronary intervention (PCI) is an integral component of therapy for coronary artery disease. Evolution in pharmacotherapy and device technology have led to substantial reductions in periprocedural complications, including abrupt closure, myocardial infarction (MI), and emergency coronary artery bypass grafting (CABG).[1] The goal of pharmacotherapy during PCI is to reduce thrombotic events that may originate from coronary plaque, intravascular equipment (eg, catheters and guidewires), or both. Since the introduction of coronary angioplasty, the target for antithrombotic therapy is thrombin, also known as factor II, and the most commonly used antithrombin agent for PCI is unfractionated heparin (UFH).[2] UFH has several recognized limitations, and one focus of drug development during the last 2 decades has been to introduce alternatives to heparin that overcome these limitations. This article explains the role of thrombin inhibition during PCI, reviews the risks and benefits of UFH, and examines currently available alternatives to heparin for PCI.

THE ROLE OF THROMBIN INHIBITION

During PCI, there is iatrogenic damage to the endothelium, which leads to increased expression of tissue factor and activation of coagulative proteins. The cumulative result of this endothelial damage is the formation of activated factor X (FXa). This results in the conversion of prothrombin to thrombin, which then leads to the conversion of fibrinogen to fibrin, and to thrombus formation.[3] The effect of thrombin is not merely isolated to the coagulation cascade because once thrombin is formed, it participates in platelet activation via its effects on the protease-activated receptor 1. In addition, thrombin activates certain integrins on the platelet surface that promote platelet aggregation.[4]

> "The goal of pharmacotherapy during PCI is to reduce thrombotic events that may originate from coronary plaque . . ."

Antithrombin, produced by the liver, is a potent inhibitor of coagulation with the ability to bind thrombin, factor Xa, and factor 1Xa. When heparin chains bind antithrombin, the ability of antithrombin to inhibit coagulation is dramatically increased. The role of thrombin inhibition in the treatment of acute coronary syndrome (ACS) was well established even before PCI became a part of the ACS management strategy.[5] Based on its actions that promote thrombosis, the role of thrombin inhibition during PCI is to address balloon- and stent-induced vascular damage and to prevent catheter-related thrombosis.

UFH

UFH is a heterogeneous group of glycosaminoglycans with a wide range of lengths (5,000 to 30,000 Da). UFH, as previously mentioned, has a profound effect on accelerating the action of antithrombin, which subsequently inactivates thrombin. Although UFH remains the most widely used anticoagulant during PCI, there are no prospective randomized trials demonstrating efficacy over placebo. Dosing regimens range from 70 to 140 U/kg, and some recent trials suggest that with aggressive parenteral antiplatelet therapy, antithrombin therapy may not be required at all.[6] Despite the lack of rigorous data, clinical experience and knowledge of the role of thrombin in thrombosis supports the past, current, and likely future need for anticoagulation during PCI. There

are some important pharmacokinetic limitations to the use of UFH that have been well described, including unpredictable and poor bioavailability resulting in significant variability in its anticoagulant response, platelet activation at low doses, and development of heparin-induced thrombocytopenia with or without thrombosis (HIT or HIT[TS]).[7]

In the setting of percutaneous transluminal coronary angioplasty, observational data show an association between greater inhibition of thrombin (measured using the activated clotting time [ACT]) and a lower rate of abrupt closure. A pooled analysis of six randomized controlled (heparin only) trials evaluating the optimal ACT during PCI demonstrated that higher ACT values were associated with a greater reduction in ischemic events but also with an increase in the risk of bleeding.[8] This analysis demonstrated the lowest ischemic events at an ACT >350 seconds, with the risk of bleeding lowest between 300 to 350 seconds. It is significant that these data were generated in the era before the use of glycoprotein IIb/IIIa inhibitors (GPI). Because UFH activates platelets, the use of GPI with heparin has been shown to reduce periprocedural ischemic events,[9] especially when heparin is used as the antithrombin agent in patients with ACS.[10] The addition of these antiplatelet agents can increase bleeding risk above that seen with heparin alone, therefore, a series of post hoc analyses of clinical trial data demonstrated that lower heparin doses to achieve ACT values <250 are also appropriate to achieve the balance between ischemia reduction and bleeding reduction.[11]

LOW-MOLECULAR-WEIGHT HEPARINS (ENOXAPARIN)

Due to the limitations of heparin outlined previously, alternative antithrombin agents have been introduced during the last decade. One class of agents that has been extensively studied, in both ACS and PCI, is the low-molecular-weight heparins, the most studied of which is enoxaparin. Low-molecular-weight heparins are produced through a depolymerization process of UFH, resulting in molecular weights between 3,000 to 5,000 Da. Although UFH has a 1:1 ratio of anti-Xa: anti-IIa activity, the in vivo ratio for enoxaparin is 4:1, and the ex vivo ratio is 10:1. Enoxaparin has less nonspecific plasma protein binding, platelet activation, and PF-4 interaction (leading to a potentially lower risk of HIT[TS]), resulting in a more predictable dose-response relationship.[12] Initial pharmacokinetic investigation for PCI was undertaken by Martin et al, who found that patients receiving a standard 1 mg/kg twice-daily regimen subcutaneously showed adequate anti-Xa levels 2 to 8 hours after the last dose. If the last dose was administered between 8 to 12 hours, an intravenous booster dose of 0.3 mg/kg was required.[13]

The SYNERGY trial randomized 10,027 high-risk ACS patients to either enoxaparin or UFH.[14] An early invasive strategy was recommended, and the overall results demonstrated that enoxaparin was statistically noninferior to UFH with respect to the primary endpoint of death or MI at 30 days. Among the patients who underwent cardiac catheterization, enoxaparin was supposed to be continued on the morning of the procedure (ie, the morning dose was not held). At the time of PCI, a supplemental intravenous dose of 0.3 mg/kg was given if the last enoxaparin dose was >8 hours prior. In the final analysis, there was no significant difference in the rate of unsuccessful PCI, abrupt closure, or emergency CABG between the enoxaparin and UFH arms. The overall bleeding results demonstrated no significant difference in the rate of GUSTO (Global Use of Strategies to Open Occluded Arteries) severe bleeding, thrombolysis in myocardial infarction (TIMI) minor bleeding, or blood transfusions between the two arms; however, there was a statistically significant excess of TIMI major bleeding among patients assigned to enoxaparin (9.1% vs 7.6%; *P*=.008), which may have been driven by patients who received both UFH and enoxaparin.[15] These data demonstrate that enoxaparin may be a reasonable alternative to UFH in high-risk ACS patients undergoing an early invasive strategy, with the caveat that there may be a modest excess of bleeding seen with enoxaparin therapy. The EXTRACT-TIMI 25 study compared enoxaparin to UFH with thrombolysis in STEMI.[16] In this trial, 4,670 patients underwent PCI at some point during their hospitalization, and examination of this subgroup showed a reduction in death or MI (10.7% vs 13.8%; *P*=.001) without an increase in bleeding complications. These should be viewed as hypothesis-generating results because this is a subgroup analysis, although they do support the role of enoxaparin for elective PCI in patients with STEMI who underwent fibrinolysis.

Several studies have examined the role of intravenous enoxaparin for elective PCI. The initial experience was reported by the National Investigators Collaborating on Enoxaparin (NICE) study group.[17] NICE-1 evaluated enoxaparin alone, and NICE-4 evaluated enoxaparin with the GPI, abciximab. In NICE-1 (n=828), the primary endpoint was 30-day major bleeding. No vascular closing devices were allowed, and vascular sheaths were removed at 4 to 6 hours after the procedure. Major bleeding only occurred in 1.1% of patients, and minor hemorrhage occurred in 6.2%. The dose of enoxaparin (without GPI) in NICE-1 was 1 mg/kg intravenously. In NICE-4 (n=818), enoxaparin was given at a dose of 0.75 mg/kg intra-

venously with abciximab at standard dose, and again, vascular closure devices were not allowed. Similar to NICE-1, major bleeding was low at 0.4%, and minor bleeding occurred in 7%, with 1.8% needing a transfusion. In the NICE-1 and NICE-4 registries, the composite endpoint of death or MI urgent revascularization occurred in 7.7% of patients. In the NICE-1 and NICE-4 registries, the rates of the composite endpoint of death, MI, or urgent revascularization occurred in 7.7% and 6.8% of patients, respectively. Compared with the historical control of the EPISTENT trial,[17] these data suggested superior efficacy to UFH alone and similar efficacy to UFH plus abciximab. The NICE-3 registry examined 671 ACS patients treated with either eptifibatide, tirofiban, or abciximab. Of the 671 patients, 43% underwent PCI, and death, MI, and urgent revascularization at 30 days were 1.6%, 5.1%, and 6.8% across the respective GPI. Major bleeding was seen in 1.9% of patients at 30 days. In summary, the NICE studies were uncontrolled observational studies showing the feasibility of utilizing enoxaparin with or without GPI during PCI.

> "The current ACC/AHA guidelines recommend against the use of fondaparinux as the sole anticoagulant if PCI is planned."

Two randomized trials examining enoxaparin for elective PCI are the CRUISE trial and the STEEPLE trial.[18,19] The CRUISE study randomized 261 patients to enoxaparin (1 mg/kg intravenously) or weight-adjusted UFH (60 IU/kg). In this trial, major and minor bleeding complications were similar in the two groups (6.3% vs 6.2%). There was no difference in ischemic endpoints at 48 hours and at 30 days. A subsequent meta-analysis of studies comparing enoxaparin to UFH showed no overall difference between enoxaparin versus UFH during PCI with respect to ischemic complications or bleeding.[19] However, this meta-analysis was generated prior to the STEEPLE trial, which is the largest trial comparing enoxaparin to UFH in elective PCI.[20]

The STEEPLE trial randomly assigned 3,528 patients to one of three arms: 0.5 mg/kg intravenous enoxaparin, 0.75 mg/kg intravenous enoxaparin, or weight-adjusted UFH (target ACT 200 to 300/s if a GPI was used, or 300 to 350/s if no GPI was used). The primary endpoint of the STEEPLE trial was non–CABG-related major bleeding at 48 hours (Table 1). The main secondary efficacy endpoint was the proportion of patients who achieved therapeutic anticoagulation as measured by the anti-Xa level (0.5 to 1.8 IU/mL) or ACT at the beginning and end of PCI. Other secondary endpoints were incidences at 48 hours of non–CABG-related major bleeding, death, MI, or urgent target vessel revascularization (TVR) (the so-called net clinical benefit), as well as purely ischemic events such as death, MI, or urgent TVR.

Baseline characteristics were balanced across the three groups, although there were slightly fewer anemic patients in the 0.5 mg/kg enoxaparin arm. The lowest rate of non–CABG-related major bleeding at 48 hours was seen in the 0.5 mg/kg enoxaparin arm (5.9% in the 0.5 mg/kg enoxaparin arm vs 6.5% in the 0.75 mg/kg enoxaparin arm vs 8.5% in the UFH arm; P=.01 for comparison between the 0.5 mg/kg arm and UFH, P=.051 for comparison between the 0.75 mg/kg arm and UFH). In terms of the key efficacy endpoint of achieving therapeutic anticoagulation during PCI, 78.8% of patients assigned to the 0.5 mg/kg arm, 91.8% of patients in the 0.75 mg/kg arm, and 19.7% of patients in the UFH arm met this goal (P<.001 for comparison of enoxaparin arms to UFH arm). One interesting development was that an interim analysis of the data before the trial had completed enrollment demonstrated an increase in mortality in the 0.5 mg/kg arm compared to the other arms (1% vs 0.4% in the 0.75 mg/kg arm vs 0.2% in the UFH arm), which led to early termination of enrollment in the 0.5 mg/kg arm. Although the initial results of the STEEPLE trial showed that intravenous bolus dose enoxparin reduced major bleeding compared to weight-adjusted heparin, the mortality data failed to demonstrate the overall superiority of enoxaparin over UFH. This, coupled with the fact that the anticoagulant effect of enoxaparin cannot be measured with a bedside assay, has led to concerns over the widespread use of enoxaparin for elective PCI.[21]

In summary, despite the proposed pharmacokinetic advantages of enoxaparin over UFH (ease of administration, potential lack of need for monitoring, and more rapid and consistent therapeutic effect), there appears to be a lack of consistent data regarding the efficacy or safety of enoxaparin over UFH for PCI. When used for ACS patients, a regimen of subcutaneous dosing with intravenous supplementation for PCI appears to be noninferior to UFH with respect to ischemic outcomes but may carry a risk for bleeding.[14] In contrast, use of intravenous bolus dosing of enoxaparin for elective PCI appears to be associated with less bleeding than weight-adjusted UFH; however, the best dose of intravenous enoxaparin is still not clear.

FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa without any effect on factor IIa.

Therefore, it is not an antithrombin agent per se. However, because factor Xa catalyzes the formation of Factor IIa (thrombin), there has been great interest in its development as an anticoagulant for ischemic heart disease. A phase 2 trial of intravenous fondaparinux in 350 patients undergoing elective or urgent PCI demonstrated statistical noninferiority of two different doses of fondaparinux (2.5 and 5 mg) and UFH with respect to major and minor bleeding, as well as the composite of death, MI, urgent TVR, or use of bailout CPI.[22] This pilot trial suggested that fondaparinux might have a role in the therapy of ACS patients. The large phase 3 OASIS-5 trial compared fondaparinux with enoxaparin in 20,078 patients with non–ST-segment elevation ACS.[23] OASIS-5 was a noninferiority trial assessing the composite of death, MI, and refractory ischemia at 9 days, with a test for superiority with respect to the outcome of major bleeding. Major bleeding was defined as clinically overt bleeding that was either fatal, a symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, an intraocular hemorrhage leading to significant vision loss, a decrease in hemoglobin of at least 3 g/dL (with each blood transfusion unit counting for 1 g/dL of hemoglobin), or bleeds requiring transfusion of two or more units of red blood cells or the equivalent of whole blood. The rate of major bleeding at 9 days was significantly lower with fondaparinux than with enoxaparin (2.2% vs 4.1%; *P*<.001). Patients undergoing PCI in the enoxaparin arm received supplemental UFH if they had not received enoxaparin in the last 6 hours. This additional UFH may have contributed to the higher rates of bleeding seen in the enoxaparin arm. Fondaparinux was also associated with a significantly reduced number of deaths at 30 days (3.5% vs 2.9%; *P*=.02) and at 180 days (6.5% vs 5.8%; *P*=.05). A total of 6,889 patients underwent PCI, and although no increase in ischemic complications was noted, more patients in the fondaparinux arm developed catheter-related thrombosis (1.3% vs 0.5%; *P*=.001), prompting a protocol change to mandate the use UFH at the time of PCI in the fondaparinux arm. This increase in PCI-related complications was underscored by the OASIS-6 trial that examined the role of fondaparinux in patients with STEMI.[24] Fondaparinux was associated with an increase in mortality among STEMI patients undergoing primary PCI with fondaparinux as the anticoagulant. The current American College of Cardiology/American Heart Association guidelines recommend against the use of fondaparinux as the sole anticoagulant if PCI is planned.[25]

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors can form stable noncovalent bonds with thrombin and have a smaller molecular size. They have several potential advantages, including a greater level of thrombin inhibition due to lack of dependence on antithrombin and virtually no risk of HIT(TS). Based on the type of interaction they exhibit with thrombin, direct thrombin inhibitors can be broadly classified as univalent and bivalent. The univalent agents only inhibit fibrin-bound thrombin and include argatroban, dabigatran, melagatran, and ximelagatran. The bivalent compounds are bivalirudin and hirudin. The direct thrombin inhibitor that has the most supportive data in ischemic heart disease is bivalirudin, and therefore, it is the focus of this section. Bivalirudin is an irreversible inhibitor of thrombin but has a half-life of approximately 25 minutes. The first trial of bivalirudin in PCI was the Bivalirudin Angioplasty Trial (BAT).[26] In this trial, 4,098 patients with unstable angina or recent MI were randomized in a double-blind fashion to either UFH or bivalirudin. The primary endpoint of this trial was in-hospital mortality, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin. Using a higher-than-current-standard bivalirudin bolus (1 mg/kg vs 0.75 mg/kg) and infusion (2.5 mg/kg/hr vs 1.75 mg/kg/hr), bivalirudin did not significantly reduce the incidence of the primary endpoint (11.4% for bivalirudin vs 12.2% for UFH) but did result in a lower incidence of bleeding (3.8% vs 9.8%; *P*<.001). Interestingly, in a prespecified subgroup of 704 patients with postinfarction angina, bivalirudin therapy resulted in a lower incidence of the primary endpoint (9.1% vs 14.2%; *P*=.04) and a lower incidence of bleeding (3% vs 11.1%; *P*<.001). The BAT trial was conducted prior to the use of GPI and stents, therefore, the role of bivalirudin in the modern era of PCI was evaluated in the REPLACE-2 trial.[27] REPLACE-2 randomly assigned 6,010 patients undergoing urgent or elective PCI in a double-bind, double-dummy fashion to either UFH plus planned GPI or bivalirudin (at a dose lower than that in the BAT trial) with provisional use of GPI given only for procedural complications. The trial was statistically powered to show noninferiority of the bivalirudin strategy to the UFH plus GPI strategy with respect to the primary quadruple composite endpoint of 30-day death, MI, urgent TVR, or major bleeding (the net clinical benefit). Major bleeding was defined as intracranial, intraocular or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dL, any decrease in hemoglobin of more than 4 g/dL, or transfusion of two or more units of packed red blood cells or whole blood. Approximately 7.2% of patients in the bivalirudin arm received GPI for bailout use. Bivalirudin proved to be statistically noninferior to UFH plus GPI with respect to the net clinical benefit at 30 days (9.2% bivalirudin vs 10.0% UFH plus GPI; *P*=.32), a

result that was driven by a substantial reduction in major bleeding (2.4% vs 4.1%; *P*<.001). There was a slight nonsignificant excess of periprocedural MI in the bivalirudin arm, but the 1-year mortality rates were statistically similar in both arms.[28] The ISAR-REACT 3 trial examined whether bivalirudin was superior to UFH alone with respect to 30-day death, MI, urgent TVR, or major bleeding (as defined in the REPLACE-2 trial) in elective PCI when patients were aggressively pretreated with thienopyridines.[29] In this study, 4,570 patients were pretreated with 600 mg of clopidogrel at least 2 hours before PCI and were randomized to either 140 IU/kg of intravenous heparin or bivalirudin. There was no significant difference in the primary endpoint between bivalirudin and UFH (8.3% vs 8.7%; *P*=.57). Major bleeding, however, was again significantly lower in the bivalirudin arm (3.1% vs 4.6%; *P*=NS). Thus, bivalirudin is a viable alternative to either UFH alone or UFH plus GPI in elective PCI and is safer with respect to bleeding.

The ACUITY trial examined the role of bivalirudin in non–ST-segment elevation ACS.[30] This open-label trial randomized 13,800 patients with moderate-risk ACS to one of three arms: UFH or enoxaparin plus GPI, bivalirudin plus GPI, or bivalirudin with provisional GPI during PCI. The dose of bivalirudin used for medical management before cardiac catheterization was a much lower dose than that studied in the REPLACE-2 trial; the dose during PCI was the same dose used in REPLACE-2 (the FDA-approved dose). The trial was powered for superiority of the bivalirudin-alone strategy with respect to the 30-day incidence of death, MI, urgent TVR, or major bleeding. The definition of major bleeding in ACUITY was intracranial or intraocular bleeding, hemorrhage at the access site requiring intervention, hematoma with a diameter of at least 5 cm, a reduction in hemoglobin levels of at least 4 g/dL without an overt bleeding source or at least 3 g/dL with such a source, reoperation for bleeding, or transfusion of a blood product. There were no significant differences in baseline characteristics across the three arms; the median time from randomization to catheterization was approximately 4 hours. Approximately 9.1% of patients in the bivalirudin arm received GPI during the study. At 30 days, the arms that used planned GPI had similar outcomes (11.8% bivalirudin plus GPI vs 11.7% UFH/enoxaparin plus GPI), however, bivalirudin was superior to either arm (10.1% bivalirudin alone vs 11.7% UFH/enoxaparin plus GPI; *P*=.02). In terms of ischemic complications defined as death, MI, or urgent TVR, bivalirudin was deemed statistically noninferior to UFH/enoxaparin plus GPI, but the noninferiority margin was 25%, which is much wider than in previous trials.[31] With respect to protocol-defined major bleeding, however, bivalirudin again demonstrated a significant advantage over UFH plus GPI (3% vs 5.7%; *P*<.001). Given these results, it is unclear whether bivalirudin is as efficacious as UFH/enoxaparin plus GPI for the management of patients with ACS. It is clear, however, that bivalirudin is associated with significantly less bleeding. One possible strategy is switching patients from UFH or enoxaparin to bivalirudin during PCI. Post hoc analyses of the REPLACE-2 trial[32] and the ACUITY trial[33] demonstrate that switching to bivalirudin during PCI from either UFH or enoxaparin (used with or without GPI) is associated with statistically similar rates of ischemic events and statistically significant lower rates of bleeding. A trial of 91 patients with ACS treated with enoxaparin and undergoing PCI randomized to receive bivalirudin within 4 hours, 8 hours, or 12 hours of the last enoxaparin dose demonstrated no increase in major bleeding, regardless of when the bivalirudin was administered.[34]

TABLE 1. DEFINITION OF MAJOR BLEEDING IN THE STEEPLE TRIAL

- Fatal bleeding
- Retroperitoneal, intracranial, or intraocular bleeding
- Bleeding that causes hemodynamic compromise requiring specific treatment
- Bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event
- Clinically overt bleeding, requiring any transfusion of ≥1 unit of packed red cells or whole blood
- Clinically overt bleeding, causing a decrease in hemoglobin of ≥ 3 g/dL (or, if hemoglobin level is not available, a decrease in hematocrit of ≥ 10%)

The most recent trial of bivalirudin is the HORIZONS AMI trial that randomly assigned 3,602 patients with STEMI undergoing primary PCI to either UFH plus GPI or bivalirudin.[35] The trial examined two primary endpoints: 30-day major bleeding (as defined in the ACUITY trial) and composite of death, MI, urgent TVR, stroke, and major bleeding. There were no significant differences in baseline patient or procedure characteristics between the two arms; the use of GPI in the bivalirudin arm was 7.5%. At 30 days, there was a significantly lower rate of both the primary bleeding endpoint (4.9% bivalirudin vs 8.3% UFH plus GPI; *P*<.001) and the primary composite endpoint (9.2% vs 12.1%; *P*=.005). There was no difference in the rate of death, MI, urgent TVR, or stroke between the two groups (5.4% vs 5.5%; *P*=.95). Offsetting this reduc-

tion in bleeding was an increase in acute (ie, within 24 hours of the PCI) stent thrombosis (1.3% vs 0.3%; *P*<.001). Interestingly, there was a significant reduction in mortality at 30 days among bivalirudin-treated patients despite the increase in acute stent thrombosis (2.1% vs 3.1%; *P*=.047). Some of the differences in mortality rates are likely explained by a lower rate of bleeding among bivalirudin-treated patients.

Based on these trial summaries, a strategy of bivalirudin with provisional use of GPI for procedural complications is a viable alternative to UFH alone and may be preferred over UFH plus planned GPI when reduction in bleeding risk is a priority. The mortality reduction with the bivalirudin-alone strategy in primary PCI is intriguing and suggests that with modern PCI procedural techniques and equipment, reduced bleeding is of paramount importance and affects survival. The increase in acute stent thrombosis is an issue that needs to be dealt with; however, evidence supporting an optimal strategy is lacking. Options include prolonging the infusion of bivalirudin or aggressive use of thrombectomy after the procedure,[36] but these should be tested in prospective trials employing bivalirudin as the antithrombin.

CONCLUSION

Thrombin plays an important prothrombotic role in the pathophysiology of PCI-related ischemic complications. Historically, these complications have been addressed with UFH. Retrospective and observational data have determined that weight-adjusted dosing of UFH is important in minimizing ischemic and bleeding complications; however, UFH has several limitations, including unreliable antithrombin activity, platelet activation, and potential for HIT(TS). Alternatives to UFH for PCI include enoxaparin, fondaparinux, and bivalirudin. Several trials have evaluated the role of enoxaparin in ACS and PCI. For ACS patients undergoing an early invasive strategy, enoxaparin appears to be as efficacious as UFH, with a potentially modest increase in bleeding. Intravenous enoxaparin for PCI appears to be superior to UFH with respect to bleeding and provides similar protection against ischemic complications. Bivalirudin has been extensively studied for elective PCI, PCI in the setting of ACS, and primary PCI for STEMI. Overall, it is associated with significantly less bleeding than UFH alone or UFH plus GPI regardless of patient population studied. In the setting of primary PCI, the bleeding advantage of bivalirudin is offset by a slight increase in acute stent thrombosis. Despite this finding, bivalirudin is associated with a significant decrease in 30-day mortality among patients undergoing primary PCI. New strategies to address the acute stent thrombosis with bivalirudin in primary PCI are needed. ■

Sean Javaheri, MD, is from the Duke University Medical Center, in Durham, North Carolina. Financial interest disclosure information was not available at the time of publication.

Sunil V. Rao, MD, is from the Duke University Medical Center and the Duke Clinical Research Institute, in Durham, North Carolina. Financial interest disclosure information was not available at the time of publication. Dr. Rao may be reached at (919) 286-0411; sunil.rao@duke.edu.

1. Singh M, Rihal CS, Gersh BJ, et al. Twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention: a single-institution experience. Circulation. 2007;115:2835-2841.
2. Rao SV, Dai D, Mehta SK, et al. Randomized trials have varying impact on antithrombin use among patients with non ST-segment elevation acute coronary syndromes (NSTEACS) undergoing percutaneous coronary intervention (PCI) in clinical practice: Data from the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR). Abstract presented at: The American College of Cardiology Annual Scientific Sessions; Chicago, IL: March 29-April 1, 2008.
3. Davie EW, Kulman JD. An overview of the structure and function of thrombin. Semin Thromb Hemost. 2006;32(suppl 1):3-15.
4. Coughlin SR. Thrombin signalling and protease-activated receptors. Nature. 2000;407:258-264.
5. Williams DO, Kirby MG, McPherson K, et al. Anticoagulant treatment of unstable angina. Br J Clin Pract. 1986;40:114-116.
6. Stabile E, Nammas W, Salemme L, et al. The CIAO (Coronary Interventions Antiplatelet-based Only) Study: a randomized study comparing standard anticoagulation regimen to absence of anticoagulation for elective percutaneous coronary intervention. J Am Coll Cardiol. 2008;52:1293-1298.
7. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 1: Heparin. American Heart Association. Circulation. 1994;89:1449-1468.
8. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. Circulation. 2001;103:961-966.
9. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet. 2000;356:2037-2044.
10. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes: Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. N Engl J Med. 1998;339:436-443.
11. Tolleson TR, O'Shea JC, Bittl JA, et al. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. J Am Coll Cardiol. 2003;41:386-393.
12. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. Circulation. 1998;97:251-256.
13. Martin JL, Fry ET, Sanderink GJ, et al. Reliable anticoagulation with enoxaparin in patients undergoing percutaneous coronary intervention: the pharmacokinetics of enoxaparin in PCI (PEPCI) study. Cathet Cardiovasc Interv. 2004;61:163-170.
14. The SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA. 2004;292:45-54.
15. Cohen M, Mahaffey KW, Pieper K, et al. A subgroup analysis of the impact of pre-randomization antithrombin therapy on outcomes in the SYNERGY trial: enoxaparin versus unfractionated heparin in non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol. 2006;48:1346-1354.
16. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med.

(Continued on page 38)

(Continued from page 37)

2006;354:1477-1488.
17. Hermiller JB. Role of enoxaparin in the invasive management of the ACS patient. J Invasive Cardiol. 2004;16:52-53.
18. Bhatt DL, Lee BI, Casterella PJ, et al. Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. J Am Coll Cardiol. 2003;41:20-25.
19. Borentain M, Montalescot G, Bouzamondo A, et al. Low-molecular-weight heparin vs. unfractionated heparin in percutaneous coronary intervention: a combined analysis. Cathet Cardiovasc Interv. 2005;65:212-221.
20. Montalescot G, White HD, Gallo R, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. N Engl J Med. 2006;355:1006-1017.
21. O'Neill WW. Risk of bleeding after elective percutaneous coronary intervention. N Engl J Med. 2006;355:1058-1060.
22. Mehta SR, Steg PG, Granger CB, et al. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. Circulation. 2005;111:1390-1397.
23. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354:1464-1476.
24. 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;295:1519-1530.
25. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation. 2007;116:e148-304.
26. Bittl JA, Strony J, Brinker JA, et al. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. N Engl J Med. 1995;333:764-769.
27. Lincoff AM, Bittl JA, Harrington RA, et al. 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.
28. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. JAMA. 2004;292:696-703.
29. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N Engl J Med. 2008;359:688-696.
30. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006;355:2203-2216.
31. Kaul S, Diamond GA. Making sense of noninferiority: a clinical and statistical perspective on its application to cardiovascular clinical trials. Prog Cardiovasc Dis. 2007;49:284-299.
32. Gibson CM, Ten Y, Murphy SA, et al. Association of prerandomization anticoagulant switching with bleeding in the setting of percutaneous coronary intervention (A REPLACE-2 analysis). Am J Cardiol. 2007;99:1687-1690.
33. White HD, Chew DP, Hoekstra JW, et al. Safety and efficacy of switching from either unfractionated heparin or enoxaparin to bivalirudin in patients with non-ST-segment elevation acute coronary syndromes managed with an invasive strategy: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol. 2008;51:1734-1741.
34. Waksman R, Wolfram RM, Torguson RL, et al. Switching from enoxaparin to bivalirudin in patients with acute coronary syndromes without ST-segment elevation who undergo percutaneous coronary intervention. Results from SWITCH—a multicenter clinical trial. J Invas Cardiol. 2006;18:370-375.
35. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008;358:2218-2230.
36. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med. 2008;358:557-567.