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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

# Scientific Update™

## Defining the Role of Bivalirudin in Percutaneous Coronary Intervention: Further Insights from REPLACE-2

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Anticoagulation therapy plays an important role during percutaneous coronary intervention (PCI) in preventing intravascular thrombosis and acute closure, inhibiting thrombi formation on equipment, and reducing distal thromboembolization. The Randomized Evaluation in PCI Linking Angiomax® (bivalirudin) to Reduced Clinical Events (REPLACE)-2 trial was recently published. It demonstrated that bivalirudin combined with provisional glycoprotein (GP) IIb/IIIa receptor inhibitors reduced the composite endpoint of death, myocardial infarction (MI), and urgent target vessel revascularization (TVR) at 30 days, as well as in-hospital major bleeding, compared to unfractionated heparin (UFH) alone in a historical control group. In addition, this strategy was not inferior to current state-of-the-art therapy with UFH and GP IIb/IIIa receptor blockade. This issue of *Cardiology Scientific Update* will review new data from the REPLACE-2 study (including the economic substudy) and examine its clinical applications and future directions.

### Overview of anti-thrombotics in PCI

Thrombin plays a central role in the complex coagulation cascade and is a potent platelet activator. Thrombin activation results in the release of potent cytokines and the activation of GP IIb/IIIa receptors, further catalyzing the thrombotic process.

UFH, an indirect thrombin inhibitor, is the standard anticoagulant used during PCI. However, there remain important limitations to its use (Table 1), including the stimulation of platelet aggregation.<sup>1</sup> Modifications to UFH therapy, including weight adjustments and dose reductions, combined with the addition of potent antiplatelet agents like the thienopyridines and GP IIb/IIIa receptor inhibitors, have resulted in reduced PCI-associated ischemic and bleeding complications. Despite these advances, there is growing evidence that procedure-related complications remain a substantial clinical and economic problem for patients undergoing PCI, thus prompting the search for a better thrombin inhibitor.

Direct thrombin inhibitors have several important characteristics that make them an attractive alternative to UFH (Table 1). They result in more effective and reliable thrombin inhibition, predictable pharmacokinetics, and less platelet activation. Bivalirudin is a synthetic analog of hirudin, with a plasma half-life of 25 minutes after intravenous administration. It is a bivalent thrombin inhibitor that binds to thrombin at the substrate recognition site and the active site. Once bound, thrombin slowly cleaves the Arg-Pro bond of bivalirudin, freeing the active site.<sup>2</sup> This allows bivalirudin to initially act as a noncompetitive inhibitor of thrombin; it then becomes a competitive inhibitor, enabling thrombin to subsequently participate in hemostatic reactions. This, theoretically, reduces the risk of bleeding. In addition, bivalirudin has antiplatelet activity via its ability to

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**Table 1: Potential advantages of direct thrombin inhibitors over UFH**

Unfractionated heparin	Direct thrombin Inhibitors
Requires a cofactor, antithrombin (AT) III, therefore cannot be used in AT-III deficient patients	No cofactor required
Non-specific binding to plasma proteins and endothelial cells, leading to unpredictable anticoagulant effect.	No binding to plasma proteins, leading to a more predictable anticoagulant response
Inability to inactivate fibrin-bound thrombin	Able to inhibit clot-bound thrombin, potentially important in situations of angiographically-visible thrombus
Induces platelet activation	No platelet activation, profound inhibitor of thrombin-mediated platelet aggregation
Platelet activation induces release of PF 4, with subsequent heparin neutralization	No binding to PF4, thus retaining activity in vicinity of platelet-rich thrombi
Primarily renal excretion, thus potential for increased bleeding in patients with renal insufficiency	Mainly extra-renal excretion, potentially safer in the setting of renal insufficiency

inhibit thrombin-mediated platelet aggregation, without causing platelet activation.

Bivalirudin has been previously studied in patients with unstable angina,<sup>3</sup> as an adjunct to thrombolysis,<sup>4</sup> and in patients undergoing PCI.<sup>5-7</sup> On re-evaluation of the negative Bivalirudin Angioplasty Study,<sup>5</sup> a 22% reduction ( $p=0.04$ ) in the post-hoc composite endpoint of death, MI, and TVR was demonstrated when bivalirudin was used in patients undergoing PCI, along with a 62% reduction ( $p<0.001$ ) in hemorrhagic complications.<sup>6</sup> This re-analysis resulted in the approval of the use of bivalirudin in PCI by the U.S. Food and Drug Administration in December 2000. Subsequently, a pilot study<sup>7</sup> using bivalirudin with provisional use of GP IIb/IIIa inhibitor in patients undergoing contemporary PCI (88% stent use) demonstrated similar clinical efficacy, but less bleeding complications compared to UFH and GP IIb/IIIa inhibitors. These observations led to the design and implementation of the REPLACE-2 study.

### The REPLACE-2 study

The REPLACE-2 study was a large-scale, international, randomized trial designed to determine whether the strategy of bivalirudin combined with the provisional use of GP IIb/IIIa inhibitors would be as efficacious as the current “standard” approach of low-dose UFH and routine GP IIb/IIIa blockade, for the prevention of ischemic and bleeding complications of PCI. The design and principle results have been recently published.<sup>8</sup> In brief, a total of 6010 patients undergoing elective or urgent PCI in 233 hospitals across North America and Europe were enrolled in the study. Patients >21 years and scheduled to undergo PCI with an approved device were eligible for entry into the study. Standard exclusion criteria were used, including primary or rescue PCI for acute MI, PCI within 1 month or planned staged PCI within the subsequent month, platelet count

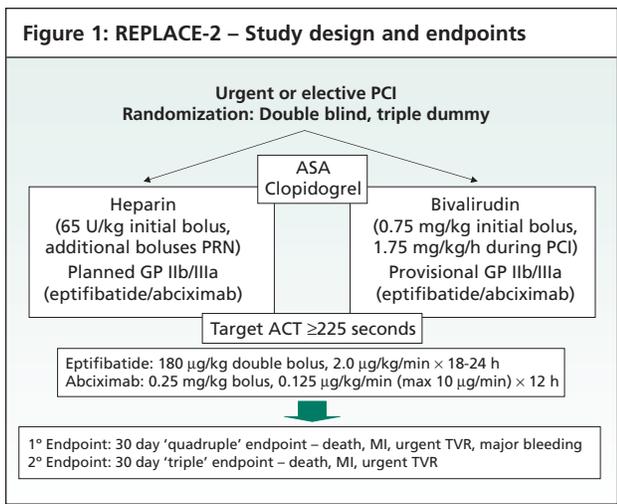
<100,000/ $\mu$ L, or serum creatinine >353  $\mu$ mol/L. Patients were also ineligible if they were on coumadin therapy or had received UFH within 6 hours (unless the aPTT was  $\leq 50$  seconds or the activated clotting time (ACT) was  $\leq 175$  seconds), low molecular weight heparin (LMWH) within the previous 8 hours, bivalirudin within the previous 24 hours, abciximab within the previous 7 days, or eptifibatid within the previous 12 hours.

The trial design is shown in Figure 1. All patients received aspirin. Pretreatment with clopidogrel 300 mg was strongly encouraged, followed by 75 mg daily for at least 30 days. Prior to randomization, physicians were required to specify whether abciximab or eptifibatid was the GP IIb/IIIa being used in the study. Patients were randomized to receive either bivalirudin (plus provisional GP IIb/IIIa) or UFH plus GP IIb/IIIa blockade. Additional boluses of bivalirudin or UFH were given if the ACT was <225 seconds.

The primary outcome was the 30-day composite endpoint of all-cause death, MI, urgent TVR, or in-hospital major bleeding. The main secondary endpoint was the 30-day composite endpoint of death, MI and urgent TVR. The trial design also included both:

- a non-inferiority statistical analysis for the comparison of the two randomized treatment strategies (primary hypothesis; Figure 2);
- a superiority analysis for the bivalirudin arm versus an imputed control group of heparin without GP IIb/IIIa inhibitor use, based on historical data from control arms of the ESPRIT<sup>9</sup> and EPISTENT<sup>10</sup> trials (secondary hypothesis).

The inferiority boundary was set at the lower limit of the 95% confidence interval for half the benefit of GP IIb/IIIa over placebo observed in EPISTENT and ESPRIT. Non-inferiority was chosen because the current standard of treatment is very effective for ischemic outcomes. It would require a very large study

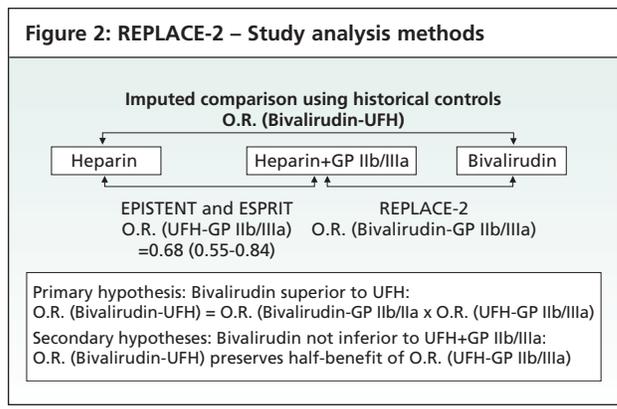


to show superiority. Non-inferiority allows the comparator to preserve the ischemic benefits of the current treatment and show additional benefits (ie, decreased bleeding).

### Main study results

Patients randomized to each of the bivalirudin (n=2994) and UFH + GP IIb/IIIa (n=3008) arms were well-matched for all major baseline characteristics. An index PCI was performed on >98% of patients, with procedural success rates over 95%. Approximately 85% of patients in both treatment groups received a stent. As mandated by protocol, the majority of patients (96.3%) in the UFH + GP IIb/IIIa arm received a GP IIb/IIIa inhibitor (43% abciximab, 53% eptifibatide), whereas in the bivalirudin arm, only 7.2% received a GP IIb/IIIa inhibitor. Thienopyridines were administered prior to PCI in >85% of patients in both arms, most receiving clopidogrel (84%).

The primary quadruple endpoint occurred in 275 (9.2%) patients in the bivalirudin arm, and 299 (10%) of patients in the UFH + GP IIb/IIIa (odds ratio [OR] 0.92, 95% confidence interval [CI], 0.77-1.09,  $p=0.32$ ). For the superiority analysis, bivalirudin met the prespecified definition of superiority over UFH alone. For the non-inferiority analysis, bivalirudin was not inferior to UFH + GP IIb/IIIa with respect to the quadruple endpoint of death, MI, urgent revascularization, and major bleeding. When individual components of the quadruple endpoint were examined, there were no significant differences in any of the 'ischemic' endpoints of mortality, MI, or urgent revascularization. There was, however, a statistically significant reduction in major bleeding in the bivalirudin arm as compared to the UFH + GP IIb/IIIa arm (Figure 3). In addition, the incidence of thrombocytopenia (platelet count <100,000/ $\mu\text{L}$ ) was significantly less in bivalirudin-treated patients compared to those treated with UFH + GP IIb/IIIa (0.7% vs 1.7% respectively,



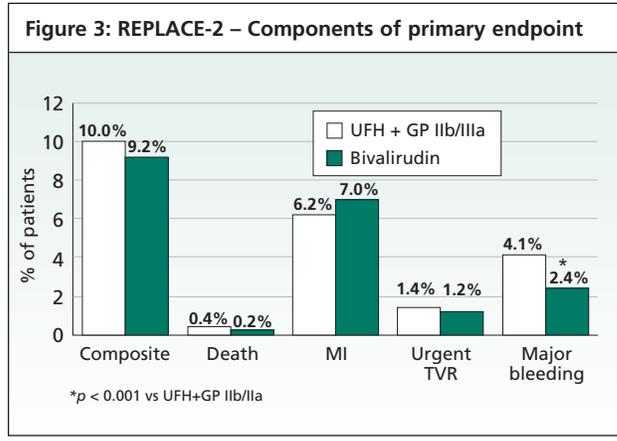
$p < 0.001$ ). For the secondary endpoint of death, MI, or urgent TVR, there was no significant difference between treatment arms. Similar to the primary endpoint, criteria for superiority of bivalirudin over imputed UFH was met, as was criteria for non-inferiority of bivalirudin as compared to UFH + GP IIb/IIIa.

### REPLACE-2: New data

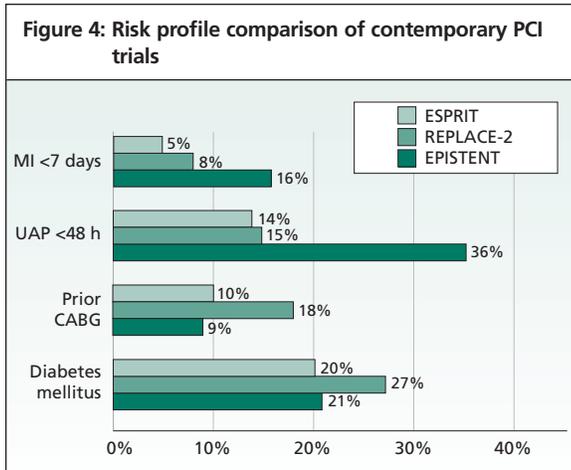
Several potentially important limitations were raised regarding the applicability of the main results of REPLACE-2. These have included:

- Patients enrolled in the study were too low-risk to allow generalization of study results to the everyday population presenting for PCI.
- There were concerns about the appropriateness of including major bleeding as a component of the primary study endpoint and the bleeding definitions used for REPLACE-2.
- There were also concerns that the ACT was too high in the UFH + GP IIb/IIIa treatment arm, accounting for the differences in bleeding outcomes.

New data addressing these questions, as well as the economic substudy results of REPLACE-2 were recently



TVR = target vessel revascularization

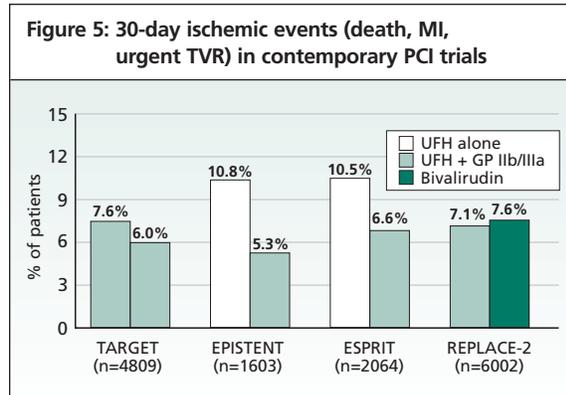


UAP = unstable angina pectoris  
CABG = coronary artery bypass graft

presented in a Satellite Symposium at the 52<sup>nd</sup> Annual Scientific Session of The American College of Cardiology. These data are not yet published and may therefore be subject to modification.

Data on the risk profile of patients enrolled in REPLACE-2, along with similar data for 2 contemporary studies of GP IIb/IIIa inhibition in PCI – the ESPRIT<sup>9</sup> and EPISTENT<sup>10</sup> trials – are illustrated in Figure 4. While the REPLACE-2 patient population had less recent MI and unstable angina, as compared to EPISTENT, they were similar to those found in ESPRIT. However, the incidence of previous coronary artery bypass graft (CABG)<sup>10</sup> surgery and diabetes was higher in REPLACE-2 as compared to ESPRIT and EPISTENT. Data for ischemic event rates from these 3 trials, as well as data for another large trial of GP IIb/IIIa inhibitors in PCI (the TARGET study<sup>11</sup>), are shown in Figure 5. The ischemic event rate in the bivalirudin arm of REPLACE-2 was within the range seen with the UFH + GP IIb/IIIa inhibitor arms of the remaining trials, and both were lower than in UFH-only arms. One factor that may have explained the slightly lower patient risk profile in REPLACE-2 was the exclusion of patients already on GP IIb/IIIa inhibitors. Regardless, the patient profile and their outcomes in the REPLACE-2 study appear comparable to other contemporary PCI trials that shape current PCI guidelines.

The majority of trials studying interventions in non-ST elevation MI (NSTEMI) have used the combined triple-endpoint of death, MI, and urgent TVR. Bleeding is often included as one of many secondary endpoints. However, there is growing evidence supporting the importance of peri-procedural bleeding complications and their contribution to



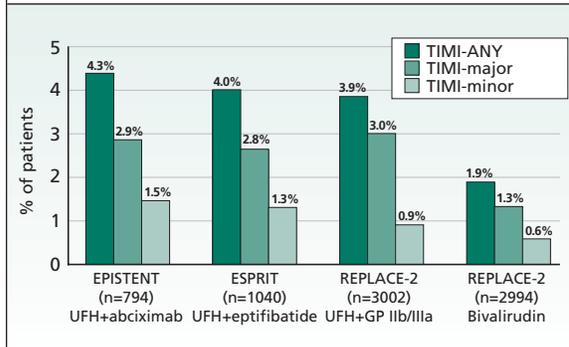
adverse clinical outcomes. Major bleeding, transfusions, and thrombocytopenia remain important and are associated with patient discomfort, risk of infection from blood products, prolonged hospitalizations, and increased costs. In REPLACE-2, the definition of major bleeding was a composite of TIMI major and minor criteria, and the requirement of a blood transfusion  $\geq 2$  units. It is important to remember that the TIMI bleeding scale was originally designed for trials of thrombolytic agents in acute MI and what was considered major and minor bleeding after administration of a lytic agent may not be similarly classified for a PCI trial in lower risk patients after NSTEMI. The clinical relevance of peri-procedural PCI bleeding complications is borne out by data from REPLACE-2 (Table 2). The occurrence of major bleeding in this study was associated with a significantly higher incidence of death and urgent TVR.

In REPLACE-2, the use of bivalirudin was associated with a relative risk reduction (RRR) of 41% in the incidence of major hemorrhage, 48% in the incidence of minor hemorrhage, 32% in the requirement for any blood transfusion, and 59% in the incidence of thrombocytopenia, as compared to UFH + GP IIb/IIIa blockade. Importantly, this

**Table 2: Major bleeding and the incidence of clinically important outcomes in REPLACE-2.**

	No major bleeding (n=5807)	Major bleeding (n=194)	P-value
Death	9 (0.2%)	10 (5.2%)	p<0.001
MI	354 (6.1%)	3 (1.6%)	p<0.01
Urgent TVR	50 (0.9%)	6 (3.1%)	p<0.01
Urgent PCI	43 (0.7%)	2 (1.0%)	p=NS
Urgent CABG	9 (0.2%)	4 (2.1%)	p<0.01

**Figure 6: Bleeding by TIMI-criteria in contemporary PCI trials**



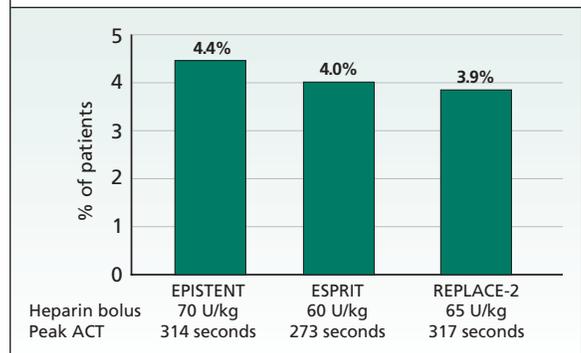
was accomplished without any significant differences in ischemic outcomes between groups. When TIMI-bleeding alone is examined and compared to similar PCI trials of GP IIb/IIIa inhibitors (Figure 6), the incidence of bleeding is lower with bivalirudin than with GP IIb/IIIa inhibitors. Were the differences in bleeding complications due to excessive use of UFH? This would seem unlikely given that the dose of UFH chosen was a median of the EPISTENT and ESPRIT UFH dosing, resulting in similar median peak ACTs and corresponded to similar TIMI bleeding complications (Figure 7).

### REPLACE-2 Economic Study

An important pre-planned substudy of REPLACE-2 was the economic study. The objectives were to compare the in-hospital and 30-day costs for patients undergoing PCI within the 2 treatment arms of REPLACE-2, and to determine the impact of both ischemic and bleeding complications on the cost of PCI in contemporary practice. The economic substudy examined only U.S. patients within the main study population (n=4651), analyzed on an intention-to-treat basis. Hospital costs (in U.S. dollars) were determined by standard methods. Similar to the main study, U.S. patients randomized to each treatment arm were well-matched for baseline characteristics. One exception was the slightly higher use of multivessel PCI in the bivalirudin arm as compared to the UFH + GP IIb/IIIa arm (17.3% vs 14.6%, p<0.05), which could tend to increase procedural costs in the bivalirudin group.

The use of bivalirudin with provisional GP IIb/IIIa (approximately 7%) compared with heparin and routine GP IIb/IIIa inhibition led to similar in-hospital and 30-day outcomes, fewer bleeding complications, and reduced total medical care costs by \$374/patient. The cost-savings were consistent across a variety of clinical subgroups, but tended to be less among patients selected for eptifibatide (\$185/

**Figure 7: Comparison of TIMI-major+minor bleeding in UFH plus GP IIb/IIIa arms of contemporary trials of PCI**



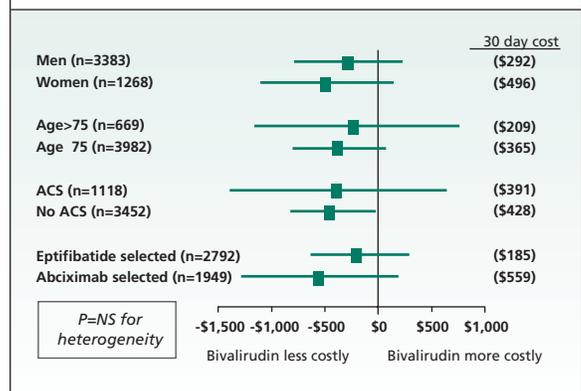
patient) and greater among patients selected for abciximab (\$560/patient) (Figure 8). While the difference in anti-coagulants accounted for a large proportion of the cost-savings, approximately 20% of the difference was related to less hematologic complications (bleeding and thrombocytopenia) with bivalirudin. In the future, substantially greater savings might be possible in selected patients by using a short infusion duration of bivalirudin.

### Discussion and clinical application

The principle findings of REPLACE-2 are that low- to moderate-risk patients undergoing PCI and randomized to bivalirudin and a low rate of provisional GP IIb/IIIa inhibitor:

- have outcomes that are not inferior to those in patients taking UFH+GP IIb/IIIa inhibitor, with similar 30-day event rates in the quadruple endpoint of death, MI, urgent TVR, and major bleeding using the protocol-defined definition of non-inferiority
- have significantly lower 30-day event rates of the same quadruple endpoint than an imputed historical estimate alone.

**Figure 8: Subgroups: 30-day cost difference**



Bivalirudin use was associated with a lower risk of major bleeding compared to treatment with UFH + GP IIb/IIIa inhibitor. Importantly, the lower rate of bleeding was achieved despite relatively high ACTs, perhaps related to cleaving of the Arg-Pro bond of bivalirudin by thrombin, enabling thrombin to subsequently participate in the clotting cascade.<sup>2</sup> Recently presented data suggest that a shorter duration of therapy (0.73 hours vs. 1.5 hours) with bivalirudin compared to UFH + GP IIb/IIIa inhibitor results in net cost-savings at 30 days.

Despite these results suggesting that the use of bivalirudin versus standard-of-care treatment for patients undergoing PCI results in similar efficacy for clinical ischemic endpoints, substantially less bleeding, a shorter duration of therapy, and lower total medical costs, the use of bivalirudin in the clinical setting remains limited. This may be related to following concerns:

- The higher rates of MI/significant CK-MB elevation in the bivalirudin-treated group, although not statistically significant, compared to the UFH + GP IIb/IIIa group (6.6% vs 5.8%, respectively,  $p=0.23$ ) and their potential effect on long-term (>30-day) clinical outcomes. The 1-year follow-up data will help to assess the long-term clinical implications of these CK-MB elevations. One possible reason why more CK-MB elevations were seen only in the 5-10  $\times$  ULN (upper limit of normal) range could be because there were significantly more multi-vessel interventions in the bivalirudin arm.

- The applicability of bivalirudin treatment to the current clinical practice of early intervention in patients with acute coronary syndromes (ACS), where GP IIb/IIIa inhibitors have been proven beneficial, particularly in high-risk patients. The exclusion of patients currently on GP IIb/IIIa inhibitors, UFH, or LMWH certainly limited enrollment of these higher risk patients into REPLACE-2.

## Conclusions

There is no doubt that UFH alone is not acceptable in the majority of patients undergoing PCI, with the possible exception of patients at the lowest risk, or those at high risk of bleeding complications. Given the results of the REPLACE-2 study, the direct thrombin inhibitor, bivalirudin, has great potential as a replacement for UFH in patients undergoing non-urgent PCI. It may result in cost-savings as compared to regimens using GP IIb/IIIa inhibitors, and the short duration of treatment may allow outpatient PCI to be performed in the future. Given the already widespread acceptance of GP IIb/IIIa inhibitors, both in the setting of ACS, as well as during PCI, another agent would have to show increased clinical efficacy and cost-effectiveness before GP IIb/IIIa receptor blockers are replaced. Thus, further clinical studies of bivalirudin in the setting of ACS and urgent

PCI are required to determine its role in contemporary clinical practice. The planned ACUITY (Acute Catheterization and Urgent Intervention Thrombotic strategy) trial will be underway soon. It will compare bivalirudin to enoxaparin, with or without upstream GP IIb/IIIa inhibition, in approximately 13,800 ACS patients undergoing early invasive assessment and management in multiple treatment arms.

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