ABSTRACT

More than 1.2 million percutaneous coronary intervention (PCI) procedures are performed each year in the United States, with average hospital costs of more than $10 000 per procedure. Balloon inflation and stent placement rupture atherosclerotic plaque and damage the vascular endothelium, both of which stimulate platelet activation and thrombus formation within the target vessel. Antiplatelet and antithrombin agents prevent thrombus formation in patients who undergo PCI and reduce the incidence of ischemic complications but require complex drug administration regimens and increase the cost of care. The results of the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) clinical trial demonstrated that the direct thrombin inhibitor bivalirudin plus provisional glycoprotein (GP) IIb/IIIa inhibitor for selected patients could be used in place of a conventional strategy of heparin and routine use of a GP IIb/IIIa inhibitor, with no loss of efficacy and a significant reduction in the number of patients with bleeding complications. A subsequent economic analysis using data from 4651 patients who participated in REPLACE-2 and who were enrolled at study centers in the United States found that patients who were assigned to the bivalirudin and provisional GP IIb/IIIa inhibitor strategy had anticoagulation costs during PCI that were approximately $400 per patient lower than with heparin plus routine GP IIb/IIIa inhibition. Bivalirudin also produced corresponding decreases in total in-hospital costs and total treatment costs during the first 30 days after enrollment in the study. Despite improvements in antithrombin and antiplatelet therapies used in PCI, ischemic and bleeding complications are still common. In the REPLACE-2 study, bivalirudin was also associated with a decrease in the costs required to manage bleeding complications in PCI, whereas costs associated with ischemic complications were largely unchanged. In an economic analysis of the use of bivalirudin in 2 other clinical trials, bivalirudin was associated with decreases in the costs of treatment for ischemic and bleeding complications. The results of the REPLACE-2 trial thus suggest that conventional treatment with heparin and a GP IIb/IIIa inhibitor may be replaced by a strategy of bivalirudin and provisional GP IIb/IIIa inhibitor treatment for selected patients with similar effects on ischemic events, significantly reduced incidence of major bleeding complications, and lower overall cost. (Adv Stud Pharm. 2005;2(3):80-89)
which increases the likelihood of ischemic complications and the need for additional treatment. As a result, antithrombotic therapy has been a mainstay of PCI since its inception. Unfortunately, many of the therapies that are intended to prevent thrombosis create a significant risk of bleeding complications.

Many large, randomized, controlled clinical trials have been conducted to define adjunctive pharmacotherapy regimens that improve coronary perfusion and reduce the incidence of complications associated with PCI. In contemporary practice, patients who undergo PCI typically receive pharmacotherapy regimens that include aspirin, oral antiplatelet therapy with clopidogrel or ticlopidine, antithrombin therapy with heparin, and a platelet glycoprotein (GP) IIb/IIIa inhibitor such as abciximab or epifibatide. Although these treatment regimens have been shown to reduce rates of ischemic complications (particularly periprocedural myocardial infarction [MI]) and improve long-term clinical outcomes, they are costly, complex to administer, and they may also increase the risk of bleeding. Thus, there is considerable interest in identifying simpler, safer, and less costly adjunctive pharmacotherapy regimens for PCI.

**ANTITHROMBIN AND ANTIPLATELET THERAPY IN PCI**

The process of balloon inflation and stent implantation usually results in the rupture of atherosclerotic plaque deposits that lie within the arterial wall. Plaque rupture exposes substances within the plaque that promote the activation of platelets and increase the ability of platelets to aggregate into thrombi. Balloon inflation and stent placement can also damage the arterial endothelium and the underlying media, triggering platelet adhesion and thrombus formation at the site of injury. Thrombi may obstruct blood flow through the target vessel or embolize into the distal microcirculation, resulting in ischemic complications such as MI or the need for another procedure. The deployment of a stent across the lesion site, which prevents the vessel from recoiling after withdrawal of the balloon, improves short-term and long-term clinical outcomes in comparison with balloon angioplasty alone, and stents are now used in more than 70% of patients who undergo PCI in the United States. However, stent implantation also exposes the circulating blood to stainless steel, which can incite local thrombus formation. Thrombosis at the stent site increases the risk of ischemic complications and is often difficult to treat. In early studies, stent thrombosis occurred in approximately 4% to 5% of patients who received stents.

Two classes of medications—antithrombin and antiplatelet agents—are generally used to prevent thrombus formation and reocclusion of a coronary artery after PCI. The principal antithrombin agent currently used is heparin, an indirect inhibitor of the enzyme thrombin. Thrombin promotes blood coagulation by catalyzing the conversion of fibrinogen to fibrin, which is an important structural component of thrombus. Heparin binds with thrombin and a naturally occurring thrombin inhibitor (antithrombin-III), and this complex accelerates the inactivation of thrombin. Heparin also inactivates a second important enzyme in the blood coagulation process, factor Xa.

Although heparin is widely used in PCI, it possesses several potentially important limitations. Heparin is highly bound to plasma proteins, and the degree of anticoagulation that it produces varies considerably from patient to patient. Heparin also stimulates platelet aggregation, and is associated with a risk of heparin-induced thrombocytopenia. In view of these limitations, other anticoagulants have been developed in recent years, including low molecular weight heparin (LMWH; eg, enoxaparin) and the direct thrombin inhibitors (DTIs; eg, bivalirudin, argatroban). LMWH consists of shorter heparin chains that have greater specificity for factor Xa than for thrombin, in comparison with conventional heparin. LMWH preparations produce more predictable anticoagulation with a longer duration of action than heparin, and they do not require the use of anticoagulation monitoring. DTIs inhibit thrombin directly, without requiring antithrombin as an intermediate. Heparin and LMWHs cannot inactivate thrombin that is bound to fibrin within blood clots, or circulating thrombin bound to fibrin degradation products. In contrast, DTIs can inactivate circulating and clot-bound thrombin.

Antiplatelet agents include several oral and injectable medications. Aspirin irreversibly inactivates the platelet enzyme cyclo-oxygenase, which prevents the formation of thromboxane A₂, one of several factors that stimulate platelet aggregation. Aspirin improves clinical outcomes in patients who are being treated for acute coronary artery disease, but it is a relatively weak inhibitor of platelet function.
Thienopyridine derivatives (ticlopidine or clopidogrel) prevent platelet aggregation that is caused by another platelet-derived mediator, adenosine diphosphate. Platelet GP IIb/IIIa inhibitors prevent clot formation by binding to specific molecules (GP IIb/IIIa receptors) on the platelet surface. When platelets are activated, a conformational change in the GP IIb/IIIa receptor allows circulating fibrin molecules to bind to these GP IIb/IIIa receptor sites and form stable cross-links between platelets. These cross-linked fibrin strands are required for the platelets to aggregate into a cohesive thrombus. GP IIb/IIIa inhibitors thus block this fibrin-mediated cross-linking and inhibit platelet aggregation. Clinical practice guidelines published in September 2004 by the American College of Chest Physicians recommend a combination regimen of aspirin, clopidogrel, and a GP IIb/IIIa inhibitor (abciximab or eptifibatide) for most patients who undergo PCI. The DTI bivalirudin is recommended for patients who do not receive heparin or a GP IIb/IIIa inhibitor, for patients at low risk of complications, and for those considered to be at high risk of bleeding complications.

Several studies published during the past decade have found that treatment regimens that include heparin and platelet GP IIb/IIIa inhibitors can significantly reduce the incidence of ischemic complications and improve long-term clinical outcomes in patients undergoing PCI. In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study, the combination of heparin and abciximab produced a lower rate of ischemic events than heparin plus placebo among patients with high-risk features (severe acute coronary artery disease or blood vessels with high-risk characteristics) who underwent balloon angioplasty. At 30 days, the incidence of a composite endpoint of death, MI, urgent repeat PCI or coronary artery bypass grafting (CABG) surgery, or insertion of intra-aortic balloon pump for refractory ischemia was 12.8% for the placebo group and 8.3% for patients who received abciximab (P = .008). In the Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa blockade (EPILOG) trial, which examined lower-risk patients, the incidence of the primary endpoint (a composite of death from any cause, MI, or the need for urgent revascularization within 30 days of randomization) was significantly lower among patients who received abciximab and low-dose heparin (5.2%) or abciximab and standard-dose heparin (5.4%) than among patients who received placebo plus standard-dose heparin (11.7%; P < .001 vs both abciximab treatment groups). More recently, GP IIb/IIIa inhibitors have been shown to reduce the risk of ischemic complications in patients undergoing PCI and stent placement. In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial, the use of abciximab on top of background aspirin plus low-dose heparin reduced the incidence of ischemic endpoints (death, MI, or the need for repeat revascularization) from 10.8% to 5.3% (P < .001). Similarly, in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy Trial (ESPRIT) study, in which patients also received stents, eptifibatide (with heparin, aspirin, and a thienopyridine) reduced the same triple endpoint from 10.5% in the placebo group to 6.8% in the eptifibatide group (P = .0034). Long-term follow-up studies have demonstrated sustained clinical benefits when GP IIb/IIIa inhibitors are also added to the PCI treatment regimen. However, in patients with low risk of ischemic complications who underwent elective PCI and were treated with clopidogrel (600 mg), the addition of abciximab did not produce significantly greater improvement in clinical outcomes than placebo.

With the introduction of these combination pharmacotherapy approaches in PCI along with prolonged administration of aspirin and a thienopyridine, the incidence of stent thrombosis has been reduced to approximately 1% to 2% or less.

In contrast to the antithrombotic benefits proven in these trials, heparin and GP IIb/IIIa inhibitors have each been associated with increased risk of bleeding complications. In the EPILOG trial, the incidence of minor bleeding complications was highest when patients received a standard dose of heparin and a GP IIb/IIIa inhibitor (7.4%). The incidence of bleeding was lower when patients received standard-dose heparin and placebo (3.7%) or reduced-dose heparin and abciximab (4.0%). A randomized controlled trial of GP IIb/IIIa inhibition in patients receiving stents found that the GP IIb/IIIa inhibitor tirofiban increased the risk of minor, but not major, bleeding complications.

These combination regimens also require prolonged intravenous infusions and high drug purchase costs, which significantly increase the cost of PCI. The average per-procedure hospital charges for PCI are approximately $28,000 in the United States. Estimates of actual costs, based on hospital resource use, equipment and supplies, physician fees, and other expenses, have suggested that per-procedure costs may reach $8500 for expenses related to the catheterization.
laboratory itself, and typically average approximately $10,000 to $12,000 per procedure when all in-hospital expenses are included. When the need for additional long-term evaluation and treatments are included, it has been estimated that the cumulative costs during a year following PCI average approximately $22,000 per patient. As a result of the high per-patient cost and the total number of procedures performed, the total economic impact of PCI in the US healthcare system has been estimated to exceed $10 billion per year. Therefore, treatment strategies that produce even relatively modest cost savings could have a significant impact on the costs associated with PCI to the healthcare system as a whole. Some experts have also suggested that cost has been a significant barrier to the more widespread use of abciximab in PCI, despite general agreement among clinicians that it improves clinical outcomes.

DTIs have recently emerged as an alternative to more complex antithrombin and antiplatelet strategies in PCI. Injectable DTIs approved for use in the United States include bivalirudin, argatroban, and lepirudin. An additional oral DTI, ximelagatran, is not yet approved for use in the United States. Of the available DTIs, bivalirudin possesses several pharmacologic properties that make it well suited for PCI. Unlike heparin and the LMWHs, bivalirudin inhibits circulating and clot-bound thrombin. Bivalirudin produces a more consistent and predictable anticoagulant effect than heparin, with less need for dosage adjustment, and it has a relatively low rate of elimination via the renal route. Unlike other DTIs, bivalirudin is a reversible inhibitor of thrombin, which may contribute to its lower incidence of bleeding complications (Figure 1). The efficacy of bivalirudin was recently evaluated in the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-1) pilot study, in which 1056 patients undergoing PCI received heparin or bivalirudin, usually in combination with a stent (85% of patients) and a GP IIb/IIIa inhibitor (72% of patients). The effect of bivalirudin on ischemic outcomes was similar to that of heparin: the combined endpoint of death, MI, or repeat revascularization occurred in 5.6% and 6.9% of patients in the bivalirudin and heparin groups, respectively (P = not significant). The incidence of bleeding complications also did not differ between the 2 treatments, although there was a trend toward less bleeding in the bivalirudin group. This study demonstrated that bivalirudin could be used effectively and safely as an alternative to heparin in patients receiving stents and GP IIb/IIIa inhibitors.

REPLACE-2: CLINICAL AND ECONOMIC IMPLICATIONS OF BIVALIRUDIN USE IN PCI

A recent large, randomized, double-blind clinical trial, REPLACE-2, was designed to examine whether bivalirudin could replace the combination of heparin and a GP IIb/IIIa antagonist for most patients who undergo PCI. The rationale for that approach was several-fold. First, the use of oral antiplatelet agents, including aspirin and clopidogrel, can achieve modest levels of platelet inhibition in most patients. In addition, by avoiding the platelet activation that occurs with unfractionated heparin, the need for additional platelet inhibitors may be reduced. Finally, by eliminating the need for heparin and GP IIb/IIIa inhibition, bivalirudin offered the possibility to simplify the PCI anticoagulation regimen and reduce cost.

A total of 6010 patients from 233 hospitals in 9 countries were randomized to one of 2 treatments: a conventional strategy of heparin plus a GP IIb/IIIa inhibitor or bivalirudin plus "provisional" use of a GP IIb/IIIa inhibitor if needed for complications during the procedure. Patients with ongoing acute MI were excluded from the study. All patients received aspirin and most also received clopidogrel before the PCI procedure. Physicians could select eptifibatide or abciximab as...
GP IIb/IIIa therapy, when used. For patients in the bivalirudin group, the physician was allowed to “cross-over” to open-label GP IIb/IIIa inhibition in the event of angiographic complications suggesting ongoing thrombus formation, which occurred in approximately 7% of patients in the bivalirudin group.

The primary study endpoint was the combined incidence of 4 clinical outcomes during the first 30 days after the procedure: death from any cause, MI, severe myocardial ischemia that required surgery or a repeat PCI, or major bleeding. The incidence of the primary outcome was similar for the 2 treatment strategies: 10% with heparin plus GP IIb/IIIa inhibitor, and 9.2% with bivalirudin plus provisional GP IIb/IIIa inhibitor, a difference that was not statistically significant. Moreover, formal statistical analysis indicated that compared with heparin plus routine GP IIb/IIIa inhibition, the strategy of bivalirudin with provisional GP IIb/IIIa inhibition was noninferior with respect to the quadruple endpoint noted earlier in this paragraph and the more traditional “triple composite” endpoint of death, MI, or urgent repeat revascularization. The incidence of ischemic events, and especially of non–Q-wave MI, tended to be slightly higher among patients in the bivalirudin group, although the difference between the bivalirudin and heparin groups was not statistically significant (5.8% vs 6.6% of patients in the conventional treatment and bivalirudin groups, respectively; \( P = .43 \)). However, the incidence of major bleeding complications (intracranial or retroperitoneal hemorrhage, clinically overt blood loss that resulted in a decrease in hemoglobin value \( >3 \) g/dL, any decrease in hemoglobin value \( >4 \) mg/dL, or the transfusion of at least 2 units of packed red blood cells) was significantly lower among the group of patients who received bivalirudin (2.4%) than among patients who received the conventional treatment (4.1%; \( P < .001 \)). A subsequent long-term follow-up study found that clinical outcomes for up to 1 year after randomization remained similar for the 2 treatment strategies.23

These results suggested that the reduced incidence of bleeding complications and the need for fewer infusions of GP IIb/IIIa inhibitors with bivalirudin may lower treatment cost in comparison with conventional treatment. To test this possibility, the costs associated with the 2 treatments were evaluated in a prospective-ly planned economic analysis that was performed using data from 4651 patients enrolled in the REPLACE-2 study at US study centers.24 The primary endpoint of the economic analysis was the total cost accrued during hospitalization and continuing through the first 30 days of treatment. Costs were calculated for the cardiac catheterization laboratory, for other hospital services, and for any other cardiac hospitalizations during the 30-day study period.

In the bivalirudin and provisional GP IIb/IIIa inhibitor group, only 7.7% of the patients received a GP IIb/IIIa inhibitor, and the total anticoagulation-related costs were lower for the bivalirudin group by an average of approximately $400 per patient. Other costs associated with the procedure (eg, devices, medical supplies, physician fees) were similar for the 2 groups (Table 1). Primarily as a result of lower anticoagulation costs, mean procedural costs were significantly lower for patients in the bivalirudin group ($4606) than for the heparin plus GP IIb/IIIa inhibitor group ($4941; \( P < .001 \)). The total costs incurred during the initial hospitalization were also significantly lower in the bivalirudin group, with a mean difference of $405 per patient. During the period of time from hospital discharge until the end of the 30-day study period, resource utilization and clinical outcomes were similar for the 2 groups. As a result, overall treatment costs for the first 30 days after enrollment remained lower, by an average of $374 per patient, in the bivalirudin group.

<table>
<thead>
<tr>
<th></th>
<th>Bivalirudin Group</th>
<th>Heparin + GP IIb/IIIa</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All anticoagulants</td>
<td>530</td>
<td>932</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>453</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abciximab*</td>
<td>130</td>
<td>1467</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eptifibatide†</td>
<td>42</td>
<td>580</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Devices</td>
<td>2075</td>
<td>2024</td>
<td>.38</td>
</tr>
<tr>
<td>Supplies</td>
<td>715</td>
<td>709</td>
<td>.30</td>
</tr>
<tr>
<td>Room/overhead</td>
<td>1162</td>
<td>1153</td>
<td>.61</td>
</tr>
<tr>
<td>Nonphysician personnel</td>
<td>123</td>
<td>122</td>
<td>.61</td>
</tr>
<tr>
<td>Total procedure cost</td>
<td>4606</td>
<td>4941</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Among patients preselected for abciximab (1949).
† Among patients preselected for eptifibatide (2792).
GP = glycoprotein; REPLACE-2 = Randomized Evaluation of PCI Linking Angiomax in Reduced Clinical Events.
Separate analyses of subgroups of patients found that cost savings were observed independent of gender, age (>75 vs ≤75 years), and type of presentation (unstable angina/recent MI vs other; Figure 2). Because the physician was required to prespecify the type of GP IIb/IIIa inhibitor that would be used before enrollment, it was also possible to perform stratified analyses for patients receiving abciximab or eptifibatide on an intention-to-treat basis. The extent of cost savings tended to be somewhat greater for patients treated with abciximab than eptifibatide ($559 vs $185 per patient)—a finding that was not surprising given the difference in acquisition costs between the 2 GP IIb/IIIa inhibitors.

Because approximately 1 million PCI procedures are performed in the United States each year, even savings on the order of $400 per procedure could translate into substantial overall cost savings to the healthcare system as a whole. An editorial that accompanied the publication of the REPLACE-2 economic analysis suggested that the complete replacement of heparin and GP IIb/IIIa inhibitors with a strategy of bivalirudin and provisional GP IIb/IIIa inhibition, although unlikely, could result in cost savings of $80 million per year in the United States. Equally important, given the prospective Diagnosis Related Group payment system in place throughout the United States at this time, most of the cost savings achieved by bivalirudin in PCI accrue directly to the hospital rather than to the third-party payer.

The investigators noted several limitations of the REPLACE-2 economic analysis. Although resource utilization was assessed for the entire study cohort, actual cost data were obtained from approximately 2500 patients who were selected at random from the US participants; for the remaining patients, hospital costs were estimated using statistical modeling. The time period evaluated in the economic study (30 days) was relatively brief, although there was no suggestion from the clinical analysis of any late “catch-up” of clinical events. Patients with acute MI were excluded from the study, and it is unclear whether these results would also apply to those patients. Finally, because of the double-blind nature of the trial, patients who were randomized to receive bivalirudin also received placebo infusions to mimic administration of a GP IIb/IIIa inhibitor to ensure that the physicians remained unaware of the patients’ actual treatment. In actual clinical practice, the additional expense associated with maintaining this 12-hour infusion would be eliminated, which may further improve the relative economic benefit of bivalirudin therapy.

**ECONOMIC IMPACT OF BLEEDING AND ISCHEMIC COMPLICATIONS IN PCI**

Despite continued improvement in device technology and adjunctive pharmacotherapy, ischemic complications still occur in approximately 5% to 15% of patients undergoing PCI, and bleeding complications in 4% to 15%. Complications contribute directly to

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**Table 2. The REPLACE-2 Study: Stratified Analyses of Aggregate 30-Day Costs by Treatment Group According to Prespecified Patient Characteristics**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mean 20-Day Cost</th>
<th>Bivalirudin</th>
<th>Heparin + GP IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 4851)</td>
<td>$10,668</td>
<td>$11,242</td>
<td></td>
</tr>
<tr>
<td>Men (n = 3383)</td>
<td>$11,197</td>
<td>$11,489</td>
<td></td>
</tr>
<tr>
<td>Women (n = 1268)</td>
<td>$10,787</td>
<td>$11,263</td>
<td></td>
</tr>
<tr>
<td>Ages &gt;75 (n = 669)</td>
<td>$11,605</td>
<td>$11,314</td>
<td></td>
</tr>
<tr>
<td>Ages ≤75 (n = 3982)</td>
<td>$10,995</td>
<td>$11,360</td>
<td></td>
</tr>
<tr>
<td>ACS (n = 1116)</td>
<td>$12,415</td>
<td>$12,308</td>
<td></td>
</tr>
<tr>
<td>No ACS (n = 3452)</td>
<td>$10,582</td>
<td>$11,010</td>
<td></td>
</tr>
<tr>
<td>Eptifibatide (n = 2792)</td>
<td>$10,671</td>
<td>$10,756</td>
<td></td>
</tr>
<tr>
<td>Abciximab (n = 1949)</td>
<td>$11,549</td>
<td>$12,408</td>
<td></td>
</tr>
</tbody>
</table>

In the Randomized Evaluation of PCI-Linking Angiomax in Reduced Clinical Events (REPLACE-2) study, bivalirudin and provisional use of a glycoprotein IIb/IIIa inhibitor reduced total treatment costs in men and women; in younger and older patients; and in patients with or without unstable angina or myocardial infarction after percutaneous coronary intervention. The graph shows the mean difference between the 2 groups (black squares) and the 95% confidence interval (bars). ACS = acute coronary syndromes; GP = glycoprotein.

the cost of treatment because of increased length of stay and ancillary costs, and also increase morbidity and mortality. Over the past decade, several studies have attempted to examine how these common complications affect the cost of percutaneous procedures in the United States. Ellis et al, who examined in-hospital costs associated with PCI in a consecutive series of 1086 patients (with a total of 1237 procedures) at a single hospital, found that 2 factors that were highly predictive of total costs were the need for CABG and the need for blood transfusion. Lauer et al reported that it costs an average of $11 784 to treat an episode of bleeding that requires transfusion, and that the cost of a repeat PCI adds an average of $4667 to the cost of treatment (Figure 3).

During the past few years, as a result of innovations in PCI procedures and adjunctive therapies, ischemic complications have become less common, resulting in an increase in the relative importance of bleeding complications on patient outcomes and cost. Fewer patients now require repeat revascularization procedures in the hospital as a result of abrupt closure of the artery, and the economic consequences of PCI complications have increasingly been because of hemorrhagic events. For example, in the EPIC clinical trial, which was conducted in 1991 and 1992, ischemic complications accounted for approximately 80% of complication-related costs. However, in the more recent REPLACE-2 trial, which was conducted in 2002 and 2003, ischemic complications accounted for less than 40% of the costs associated with the treatment of complications. Therefore, strategies that reduce hemorrhagic complications may have a relatively large impact on the total costs associated with PCI procedures in contemporary practice.

In the economic analysis of the REPLACE-2 study described earlier in this article, the average estimated costs associated with specific PCI-related complications are shown in Table 2. On a per-event basis, the most expensive complications were the need for bypass surgery or repeat PCI before discharge from the hospital. Although costly, these events are relatively uncommon in contemporary practice. When viewed on an average cost per patient basis, major and minor bleeding events were the most costly complications, with associated per-patient costs of $342 and $151, respectively. On average, ischemic and bleeding complications together contributed $907 per patient to the cost of the initial hospitalization in the heparin plus GP IIb/IIIa group. Ischemic complications were somewhat more likely in the bivalirudin group, resulting in slightly higher costs due to moderate-sized MIs (mean increase of $21 per patient). This increase in ischemic complications was more than offset by statistically significant savings associated with a reduced incidence of major bleeding complications (mean reduction of $107 per patient), thrombocytopenia ($47 per patient), and minor bleeding complications ($52 per patient). The overall treatment costs associated with procedural complications were lower by an average of $84 per patient in the bivalirudin plus provisional GP IIb/IIIa inhibitor group than in the conventional treatment group. Of note, the extent of cost savings was less than may have been expected because of a relative excess of patients undergoing multivessel PCI in the bivalirudin group.

Several other studies have examined the specific contributions of bleeding and ischemic complications...
to the costs associated with PCI. Another recent economic analysis of bivalirudin in 2 large, randomized clinical trials found that this agent reduced the costs of ischemic and bleeding complications, in comparison with heparin alone. In the Bivalirudin Angioplasty Trial, heparin administration was associated with costs of $714 per patient to treat ischemic complications and $753 per patient for transfusions (costs associated with all bleeding complications were not specifically assessed in this analysis). For patients who received bivalirudin, these costs decreased to $548 and $283 for ischemic complications and transfusions, respectively. In the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET), heparin was associated with costs of $452 and $632 for ischemic and bleeding complications, respectively, whereas in the bivalirudin group, the mean cost of ischemic complications was $94, and the mean cost of bleeding complications was $283. These cost differences represent only the differences between heparin and bivalirudin groups in the economic impact of complications; they do not include drug acquisition or other costs.

Finally, an economic analysis of data from the EPIC trial, which examined the efficacy and safety of abciximab in high-risk coronary angioplasty, found that abciximab reduced the costs associated with ischemic complications by an average of $622 per patient, but increased bleeding-related costs by $521. In the EPILOG trial, which examined a lower weight-adjusted heparin dose in a lower-risk patient population, abciximab plus standard-dose heparin produced cost savings of $484 in ischemic complications, and an increase in bleeding-related costs of $40, compared with standard heparin and placebo. Abciximab plus low-dose heparin produced a mean savings of $603 in ischemic complications and a cost increase of $2 in bleeding complications.

### Conclusions

Patients who undergo PCI typically receive complex anticoagulation regimens that incorporate antithrombin agents and antiplatelet agents. The combination of heparin and a GP IIb/IIIa inhibitor reduces the incidence of ischemic complications but...
increases treatment complexity, bleeding risk, and cost. In the REPLACE-2 clinical trial the incidence of ischemic events was similar for patients randomized to conventional treatment (with heparin and a parenteral GP IIb/IIIa inhibitor) or to treatment with the direct thrombin inhibitor bivalirudin and a GP IIb/IIIa inhibitor only when needed. The incidence of major bleeding complications was significantly lower with bivalirudin. A subsequent economic analysis found that anticoagulation-related costs were significantly lower, by a mean of approximately $400 per patient, with the bivalirudin-based strategy. Total in-hospital costs and 30-day treatment costs were also significantly lower with bivalirudin. Although much of the cost difference was driven by differences in acquisition costs for the drugs, approximately 20% of the cost savings were directly attributable to the substantial reductions in major and minor bleeding with bivalirudin.

REFERENCES


