# Economic Implications of Bivalirudin in the Cardiac Catheterization Laboratory

Ameet Bakhai, MD, MRCP,*† David J. Cohen, MD, MSc†

*Harvard Clinical Research Institute, Boston, MA; †Cardiovascular Division, Beth Israel Deaconess Medical Center, Boston, MA

*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. Despite ongoing improvements in device technology and adjunct pharmacology, both ischemic complications (eg, periprocedural myocardial infarction) and bleeding complications remain relatively common and are associated with both increased costs (in the short term) and mortality (in the longer term). Recently, the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 clinical trial demonstrated that the use of the direct thrombin inhibitor, bivalirudin, with provisional glycoprotein (GP) IIb/IIIa inhibitor for selected patients in place of a conventional anticoagulation strategy of heparin and routine use of a GP IIb/IIIa inhibitor, resulted in comparable rates of ischemic complications and a significant reduction in the frequency of both major and minor bleeding complications. A prospectively designed economic analysis was performed using data from 4651 US patients who participated in REPLACE-2. In this analysis, 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 those with heparin plus routine GP IIb/IIIa inhibition. Bivalirudin also produced corresponding decreases in total in-hospital costs and aggregate 30-day medical care costs. These cost savings derived both from the lower acquisition cost of the antithrombotic therapy and the reduced rate of bleeding complications, which accounted for approximately 20% of the cost offsets. These results suggest that for patients similar to those studied in REPLACE-2 (ie, low to moderate risk PCI procedures), use of bivalirudin and provisional GP IIb/IIIa inhibition compared with heparin and routine GP IIb/IIIa inhibition can result in similar rates of ischemic complications, reduced bleeding, and substantial cost savings to both hospitals and the healthcare system. Whether these benefits can be extended to higher risk patient subsets including patients with non-ST elevation or ST elevation myocardial infarction is currently under investigation.*
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Percutaneous coronary intervention (PCI) is among the most common medical procedures performed in the United States. The number of percutaneous coronary procedures performed each year more than doubled between 1990 and 2002, and it is now estimated that more than 1 million PCI procedures are performed annually in the United States alone.[1] In recent years,

improved pharmacologic regimens along with impressive advances in device therapy have led to substantial improvements in the safety and predictability of PCI procedures. Standard pharmacologic therapy currently consists of a combination of 1 or more antiplatelet agents (eg, aspirin, clopidogrel, glycoprotein IIb/IIIa receptor antagonists) along with a thrombin inhibitor (eg, unfractionated heparin, low-molecular-weight heparin, or a direct thrombin inhibitor) to provide optimal protection against ischemic complications resulting from local arterial injury. 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.[2-4] Thus, there is considerable interest in identifying simpler, safer, and less costly adjunctive pharmacotherapy regimens for PCI.

These combination regimens also require prolonged intravenous infusions and high drug purchase costs, which significantly increase the cost of PCI. The actual costs of PCI vary widely according to the clinical setting and type of procedure. Several recent studies from the era before the introduction of drug-eluting stents found that procedural 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.[5-9] When the need for additional long-term evaluation and procedures are included, it has been estimated that the cumulative costs during the year following PCI average approximately $22,000 per patient.[10] Although drug-eluting stents have had an important impact on follow-up costs, it is less clear whether aggregate costs are reduced due to the higher acquisition costs for drug-eluting stents.[11,12] 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.[13] Therefore, treatment strategies that produce even relatively modest cost savings for each procedure could have a significant impact on annual healthcare expenditures.

## Economic Impact of Percutaneous Coronary Intervention–Related Complications

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 10%.[13] Complications contribute directly to the cost of treatment because of increased length of stay and ancillary costs, and also increase morbidity and mortality.[14] Over the past decade, several studies have attempted to examine how these common complications affect the cost of percutaneous procedures in the US healthcare environment. Ellis and colleagues[14] examined in-hospital costs associated with PCI in a consecutive series of 1086 patients (with a total of 1237 procedures) at a single hospital and found that the 2 factors that were most predictive of total costs were the need for coronary artery bypass grafting (CABG) and the need for blood transfusion. More recently, Lauer and colleagues[15] examined PCI-related costs using a large insurance database and reported that it costs an average of $11,784 to treat an episode of bleeding that requires transfusion, while repeat PCI adds an average of $4667 to the cost of treatment.

Recently, Kugelmass and colleagues[16] used data from the US Medicare system to estimate the frequency and incremental cost of specific PCI-related complications. In this analysis, based on 2002 administrative data, complications occurred in 9.5% of all PCI patients and were associated with a mean increase in hospital costs of $8540. The incremental costs associated with specific complications are summarized in Table 1. Although emergency bypass surgery was the most costly complication on a per-event basis, given its frequency of just 0.6%, the estimated economic burden of emergency CABG was approximately $149 per PCI patient. In contrast, the most common complication was vascular (hemorrhage, transfusions, and/or surgical repairs), which occurred in 5.5% of patients and was associated with an incremental cost of approximately $4300 per occurrence, which translates into an estimated economic burden of $234 per PCI patient. Given that approximately 1 million PCI procedures are performed annually in the United States, these data suggest that the excess annual cost to society imposed by PCI-related vascular complications is approximately $230 million. The only other PCI-related complication with

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Table 1
Incidence, Incremental Cost, Per-Patient Cost, and Incremental Length of Stay for Selected PCI Complications Based on Analysis of 2002 Medicare Data (N = 335,477)

| Complication | Incidence (%) | Incremental Cost ($) | Per Patient Cost ($) | Incremental LOS (days) |
|---|---|---|---|---|
| Death | 1.90 | 4456 | 85 | −1.5 |
| Emergency coronary bypass surgery | 0.55 | 27,108 | 149 | +6.6 |
| Stroke | 0.16 | 7856 | 13 | +3.3 |
| Acute renal failure | 2.27 | 13,443 | 305 | +5.7 |
| Vascular complication | 5.47 | 4278 | 234 | +1.8 |
| Any complication | 9.48 | 8540 | 810 | +3.1 |

Incremental cost estimated and LOS based on propensity-matched analysis of patients with and without each specific complication. All estimated incremental cost and LOS values are significantly ($P < .001$) different from zero. PCI, percutaneous coronary intervention; LOS, length of stay. Adapted from Kugelmass AD et al.[16]

an overall economic burden approaching that of vascular complications was acute renal failure with an incremental cost of $13,443 per event and an estimated economic burden of $305 per PCI patient. Periprocedural MI was not an independent predictor of cost in the Medicare analysis. However, administrative data may underreport the incidence of this complication because markers of myonecrosis are not routinely checked after otherwise uncomplicated PCI at many institutions.

## Economic Evaluation of Bivalirudin in Percutaneous Coronary Intervention

Taken together, the available data suggest that an anticoagulation strategy that reduced the risk of periprocedural bleeding complications without compromising the anti-ischemic benefits of standard anticoagulation regimens could offer the potential for substantial hospital cost savings. Based on data from the Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, the direct thrombin inhibitor bivalirudin would appear to be such a candidate.[17] In REPLACE-2, 6010 patients undergoing planned, nonemergent PCI were randomized to receive either the standard anticoagulation regimen of low-dose heparin and routine GP IIb/IIIa inhibition or the novel regimen of bivalirudin with provisional glycoprotein IIb/IIIa inhibition. The main findings of REPLACE-2 were that compared with standard anticoagulation, the experimental regimen of bivalirudin and provisional GP IIb/IIIa inhibition was associated with similar rates of ischemic complications (6.6% vs 5.8%, $P = .43$) and a highly significant 42% reduction in the incidence of major bleeding complications (2.4% vs 4.1%, $P < .001$) (Figure 1).[17] Further details of these clinical comparisons are provided by Lee and Makkar elsewhere in this volume.[18]

In addition to these standard clinical comparisons, we have reported the results of a prospective economic evaluation that was performed alongside the REPLACE-2 trial.[5] Because of differences in hospital cost structures as well as practice patterns in the United States and other countries, the economic evaluation was restricted to the 4651 patients enrolled at US study centers. 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. A secondary analysis was restricted to the costs for the initial hospitalization alone—a perspective that is immediately relevant to most hospital administrators, because hospital care in the United States is generally reimbursed on an episode-of-care basis. The economic analysis used a combination of resource-based costing (for anticoagulants and other catheterization laboratory resources), hospital billing data (for ancillary hospital costs), and the Medicare fee schedule (for physician costs). Importantly, because billing data do not represent true costs, hospital charges were converted to costs for each patient by multiplying itemized charges by the hospital and cost-center specific cost-to-charge ratio derived from each hospital's Medicare cost report.[19] Anticoagulant costs for the analysis

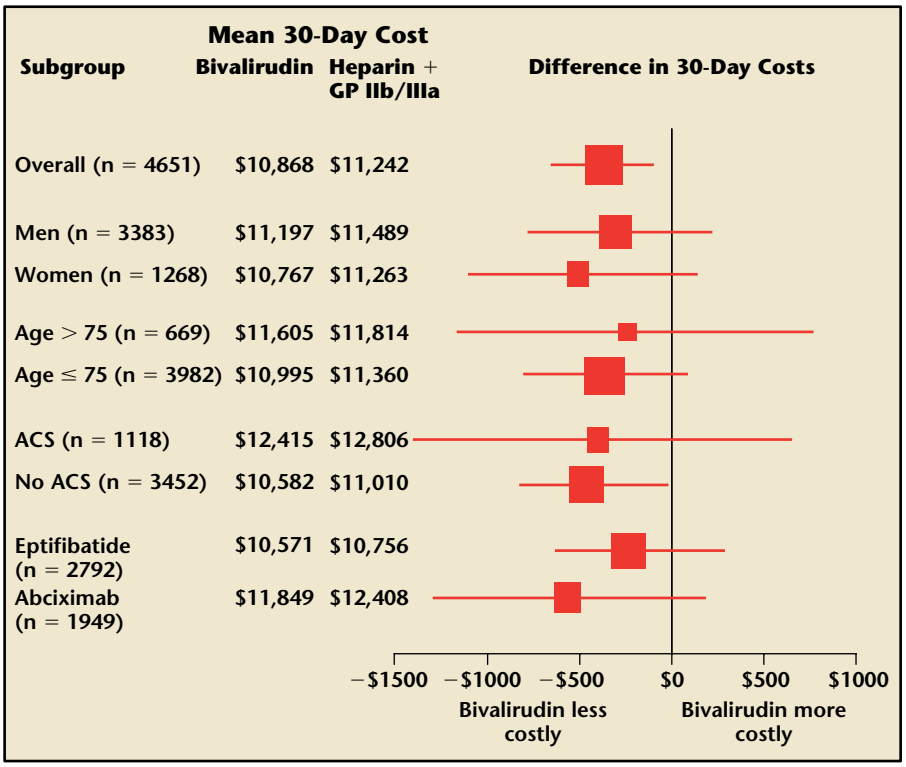


**Figure 1.** *Cost differences in the REPLACE-2 trial stratified by prespecified patient characteristics. The graph indicates the mean difference in costs between individuals in the 2 treatment arms (squares) along with the 95% confidence intervals (lines). There was no evidence of heterogeneity of treatment effects across any of the subgroups (P value for interaction > .05). GP, glycoprotein; ACS, acute coronary syndrome. Reprinted with permission from Cohen DJ et al.*[5]

were based on calculated bolus and infusion volumes (assuming any unused drug would be discarded) and average wholesale prices for each drug in 2003 (abciximab: $450 per vial, eptifibatide $54 per bolus vial and $169 per infusion vial, and bivalirudin $335 per vial).

Clinical outcomes for the US patients in REPLACE-2 were generally comparable to those observed in the overall clinical trial. 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. Primarily as a result of lower anticoagulation costs, mean procedural costs were significantly lower for patients in the bivalirudin group than for the heparin plus GP IIb/IIIa inhibitor group ($4606 vs $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 (Table 2). During the time from hospital discharge until the end of the 30-day study period, resource utilization and clinical outcomes were similar for the 2 groups ($488 vs $441, $P = .62$). 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 (95% CI, $61 to $688, $P < .001$).

Separate analyses of subgroups of patients found that cost savings were observed independent of gender, an age threshold of 75, and type of presentation (unstable angina/recent MI vs other presentations). 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.

## Mechanism of Cost Savings With Bivalirudin

In addition to the direct comparison of costs and clinical outcomes between the 2 treatment groups, the REPLACE-2 economic study provided an opportunity to assess the contributions of various patient factors and procedural complications to hospital cost in a contemporary PCI population. Table 3 displays the independent predictors of initial hospital cost for the REPLACE-2 population. Repeat revascularization procedures (in-hospital CABG, repeat PCI) were the strongest correlates of in-hospital cost. Among procedural complications, major bleeding, thrombocytopenia, and large periprocedural MI (CKMB > 10x upper limit of normal) had the greatest independent impact on cost, whereas small-to-moderate post-procedure MI and minor bleeding had lesser impacts. Several baseline patient characteristics including the need for multivessel PCI, acute coronary syndrome presentation, and a history of congestive cardiac failure were also associated with higher initial hospital costs.

When we considered both the incremental cost associated with each complication as well as its frequency, we found that adverse outcomes accounted for $907 of the initial hospital cost for the heparin and

Table 2
Initial Hospital Resource Utilization and Cost

| Parameter | Bivalirudin Group (n = 2319) | Heparin + GP IIb/IIIa group (n = 2332) | *P* Value |
|---|---|---|---|
| Bivalirudin use | | | |
| Number of vials | 1.35 ± 0.89 | 0 ± 0 | < .001 |
| > 1 vial used | 26.9% | 0% | < .001 |
| Provisional GP IIb/IIIa used | 7.7% | 0% | < .001 |
| Procedural costs | | | |
| All anticoagulants | $530 ± $445 | $932 ± $545 | < .001 |
| Bivalirudin | $453 ± $299 | $0 ± $0 | < .001 |
| GP IIb/IIIa inhibitors | | | |
| Abciximab | $130 ± $432 | $1467 ± $466 | < .001 |
| Eptifibatide | $42 ± $156 | $580 ± $183 | < .001 |
| Devices | $2075 ± $1399 | $2024 ± $1257 | .38 |
| Supplies | $715 ± $238 | $709 ± $236 | .30 |
| Room/overhead | $1162 ± $496 | $1153 ± $482 | .61 |
| Personnel | $123 ± $56 | $122 ± $54 | .61 |
| Total for index procedure | $4606 ± $1916 [$4141] | $4941 ± $1793 [$4603] | < .001 |
| Initial hospitalization costs | | | |
| Index procedure | $4606 ± $1916 [$4141] | $4941 ± $1,793 [$4603] | < .001 |
| Repeat procedures | $81 ± $547 [$0] | $80 ± $593 [$0] | .83 |
| Hospital room/ancillary | $3655 ± $5295 [$2263] | $3725 ± $5586 [$2374] | .39 |
| MD fees | $2220 ± $810 [$2042] | $2221 ± $825 [$2042] | .41 |
| Total for hospitalization | $10,561 ± $6267 [$9136] | $10,966 ± $6524 [$9616] | < .001 |

Standard deviations and [medians].
GP, glycoprotein. Adapted from Cohen DJ et al.[5]

GP IIb/IIIa group of $10,966 (8% of total hospital cost) (Table 3). The complications with the largest individual contributions to hospital cost included major bleeding, in-hospital CABG, minor bleeding, and thrombocytopenia. Comparison of event-related costs between the bivalirudin and heparin and GP IIb/IIIa groups indicated that reductions in major bleeding accounted for $107 per patient in hospital cost savings with bivalirudin, while reductions in thrombocytopenia and minor bleeding accounted for savings of $47 and $52 per patient, respectively.

These findings demonstrate that in the REPLACE-2 trial, the observed reduction in initial hospital costs with bivalirudin was driven by 2 main factors: the anticoagulants themselves and peri-procedural complications. Approximately 80% of the reduction in in-hospital costs occurred during the index revascularization procedure due to the lower acquisition cost of bivalirudin compared with parenteral GP IIb/IIIa inhibitors. Importantly, these savings were observed despite the fact that approximately 7% of patients assigned to bivalirudin received a provisional GP IIb/IIIa inhibitor at the time of PCI. The remaining 20% of hospital cost savings associated with bivalirudin were related to differences in rates of ischemic and hemorrhagic complications. Although bivalirudin was associated with marginally higher rates of in-hospital bypass surgery and non-fatal MI, the excess costs of these events were more than offset by savings associated with lower rates of major bleeding, minor bleeding, and thrombocytopenia.

## Additional Insights: Impact of Complications on the Cost of Percutaneous Coronary Intervention

In addition to quantifying the extent of cost savings associated with use of bivalirudin, this study adds importantly to our understanding of those factors that determine the cost of contemporary PCI. On a "per-event" basis, the most costly complications were the need for unplanned bypass surgery or repeat PCI before hospital discharge. On the other hand, when the frequency of complications is also considered, the most costly complications on a "per-patient" basis were major bleeding (attributable cost $342 per patient in the heparin

Table 3
Independent Predictors of In-Hospital Costs in the REPLACE-2 Trial

| Factor | Estimated Cost* ($) | Incidence in Hep + GP IIb/IIIa Group (%) | Incidence in Bivalirudin Group (%) | Attributable Cost in Hep + GP IIb/IIIa Group ($) | Net Cost Difference Associated With Bivalirudin ($) |
|---|---|---|---|---|---|
| Events | | | | | |
| In-hospital CABG | 29,506 | 0.56 | 0.86 | 165 | 87 |
| Repeat PCI | 8187 | 0.77 | 0.82 | 63 | 4 |
| Major bleed | 6300 | 4.46 | 2.76† | 281 | (107)† |
| Thrombocytopenia | 5842 | 1.50 | 0.69† | 88 | (47)† |
| MI (CK-MB > 10x) | 4084 | 1.54 | 1.64 | 63 | 4 |
| Diagnostic cath | 2446 | 2.66 | 2.98 | 64 | 8 |
| MI (CK-MB 5-10x) | 2233 | 1.76 | 2.72† | 39 | 21† |
| MI (CK-MB 3-5x) | 1165 | 2.83 | 2.67 | 33 | (2) |
| Minor bleed | 396 | 28.13 | 15.05† | 111 | (52)† |
| Patient characteristics | | | | | |
| Multivessel PCI | 1710 | 14.60 | 17.30† | 206 | 46† |
| ACS | 1534 | 23.10 | 22.70 | 354 | (6) |
| H/O CHF | 1165 | 6.60 | 7.30 | 77 | 8 |
| Total for events | | | | 907 | (84) |

*Estimated cost of each complication derived from linear regression model of initial hospital costs (model $R^2 = 0.46$). All coefficients were significant at the $P < .05$ level.
†Difference in incidence between groups statistically significant ($P < .05$).
REPLACE, Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events; Hep, heparin; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; CHF, congestive heart failure; CK, creatinine kinase; GP, glycoprotein; MI, myocardial infarction.
Adapted from Cohen DJ et al.[5]

and GP IIb/IIIa group), minor bleeding ($151 per patient), and in-hospital bypass surgery ($150 per patient). Although the definition of major bleeding used in the REPLACE-2 trial was somewhat more liberal than that used in previous trials, the substantial cost of major bleeding on both a per-event and per-patient basis confirms that this definition has both clinical and economic relevance in contemporary practice.

Previous studies have demonstrated the important impact of both ischemic and bleeding complications on hospital cost for PCI patients. Although the REPLACE-2 findings are thus qualitatively similar to many previous studies, the current study is the first to directly examine hospital costs and their determinants in a large population of patients undergoing contemporary PCI with stent implantation. Compared with previous studies from the balloon angioplasty era, the contribution of ischemic complications to in-hospital costs of PCI has fallen dramatically. For example, in the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial, complications increased initial hospital costs by approximately $2000 per patient in the control group, of which ischemic complications accounted for approximately 80%.[20] In contrast, in REPLACE-2, the aggregate cost of complications was approximately $1000 per patient, of which ischemic events accounted for less than 40%. These findings reflect a shift in the predominant mode of ischemic complications from abrupt closure requiring repeat revascularization to nonfatal MI—many of which are clinically silent. As a result, more than 60% of complication-related costs are now associated with hemorrhagic events and related outcomes (eg, thrombocytopenia). Also noteworthy is the substantial cost associated with even minor bleeding complications. Although these events are associated with only a modest increase in costs on a per-event basis, the fact that more than 25% of all patients treated with the heparin and GP IIb/IIIa inhibition experienced a minor bleed led to substantial excess costs in the overall population.

## Study Limitations and Future Directions

Although the randomized clinical trial is currently the gold standard for unbiased comparison of alternative treatment strategies, in some cases a double-blind design (such as REPLACE-2) may introduce its own biases. In the case of the REPLACE-2 trial, it is likely that the study design led to underestimation of the extent of cost savings that could be achieved in standard practice with bivalirudin. For example, it is possible that the design of the REPLACE-2 trial artificially increased hospital costs for the bivalirudin group. The mean infusion duration for bivalirudin was 44 minutes, compared with 12 hours for abciximab and 18 hours for eptifibatide. Nonetheless, as a double-blind trial, all patients in the bivalirudin group received 12 to 18 hours of a placebo infusion, thus eliminating an important opportunity to streamline care and reduce cost. Outpatient PCI is rarely performed in the United States today, in part due to the need for extended infusions of antiplatelet agents as well as lower reimbursement levels compared with inpatient procedures. Given its brief infusion duration and enhanced safety profile, bivalirudin with provisional GP IIb/IIIa inhibition might lead to substantial additional savings in the future by facilitating PCI in the outpatient setting.

Finally, it is important to recognize that the REPLACE-2 trial applies predominantly to patients at low to moderate risk of ischemic complications by virtue of its inclusion and exclusion criteria. In particular, patients with "hot" unstable angina who required ongoing pretreatment with a GP IIb/IIIa inhibitor were excluded, as were patients undergoing primary PCI for ST elevation MI. The use of bivalirudin in these populations is currently under investigation in the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) and the Harmonizing Outcomes with RevascularIZatiON and Stents in AMI study (HORIZON-AMI) trials, both of which include prospective economic evaluations.[21-23]

*It is possible that the design of the REPLACE-2 trial artificially increased hospital costs for the bivalirudin group.*

## Summary

As the number of coronary angioplasty procedures has increased, so has the complexity of adjuvant antiplatelet and antithrombotic combinations. This has resulted in fewer ischemia-related complications due to post-procedural thrombosis or re-occlusion but has increased the frequency of bleeding complications with 1 in 4 patients encountering minor bleeding on combinations of heparin with GP IIb/IIIa inhibitors. Bleeding complications result in increased in-hospital resource use and cost and predict an increased mortality rate during follow-up. Bivalirudin obviates heparin and routine GP IIb/IIIa inhibitors with similar clinical efficacy but significantly reduces bleeding rates. In addition to comparably lower acquisition costs, the cost of care is further reduced by avoiding bleeds. Whereas these benefits have been demonstrated in low-risk patients undergoing coronary angioplasty, studies in the higher risk setting of patients with acute coronary syndromes with and without ST elevation and PCI with stenting are in progress. ■

### References


1. American Heart Association. *Heart Disease and Stroke Statistics—2005 Annual Update*. Dallas, TX: American Heart Association; 2005.
2. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
3. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet*. 1998;352:87-92.
4. Steinhubl SR, Berger PB, Mann JT 3rd, et al., for the CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-2420.
5. Cohen DJ, Lincoff AM, Lavelle TA, et al. Economic evaluation of bivalirudin with provisional glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein IIb/IIIa


### Main Points

- It costs an average of $11,784 to treat an episode of bleeding that requires transfusion, while repeat percutaneous coronary intervention adds an average of $4667 to the cost of treatment.
- More than 60% of complication-related costs are now associated with hemorrhagic events and related outcomes (eg, thrombocytopenia).
- In low- to moderate-risk procedures, the use of bivalirudin with provisional glycoprotein IIb/IIIa inhibitor resulted in a significant reduction in the frequency of both major and minor bleeding complications, and substantial cost savings to both hospitals and the healthcare system.

inhibition for percutaneous coronary intervention. *J Am Coll Cardiol*. 2004;44:1792-1800.
6. Cohen DJ, O'Shea JC, Pacchiana CM, et al. In-hospital costs of coronary stent implantation with and without eptifibatide (the ESPRIT trial). Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin. *Am J Cardiol*. 2002;89:61-64.
7. Heiat A, Mattera JA, Henry GA, et al. Trends in cost of percutaneous transluminal coronary angioplasty. *Am J Manag Care*. 1998;4:1667-1674.
8. Lincoff AM, Mark DB, Tcheng JE, et al. Economic assessment of platelet glycoprotein IIb/IIIa receptor blockade with abciximab and low-dose heparin during percutaneous coronary revascularization: results from the EPILOG randomized trial. Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade. *Circulation*. 2000;102:2923-2929.
9. PRICE Investigators. Comparative 30-day economic and clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor use during elective percutaneous coronary intervention: Praire ReoPro versus Integrilin Cost Evaluation (PRICE) trial. *Am Heart J*. 2001;141:402-409.
10. Peterson ED, Cowper PA, DeLong ER, et al. Acute and long-term cost implications of coronary stenting. *J Am Coll Cardiol*. 1999;33:1610-1618.
11. Cohen DJ, Bakhai A, Shi C, et al. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (SIRIUS) trial. *Circulation*. 2004;110:508-514.
12. Greenberg D, Bakhai A, Cohen DJ. Can we afford to eliminate restenosis? Can we afford not to? *J Am Coll Cardiol*. 2004;43:513-518.
13. Moscucci M. Frequency and costs of ischemic and bleeding complications after percutaneous coronary interventions: rationale for new antithrombotic agents. *J Invasive Cardiol*. 2002;14:55B-64B.
14. Ellis SG, Miller DP, Brown KJ, et al. In-hospital costs of percutaneous coronary revascularization. Critical determinants and implications. *Circulation*. 1995;92:741-747.
15. Lauer MA, Karweit JA, Cascade EF, et al. Practice patterns and outcomes of percutaneous coronary interventions in the United States: 1995 to 1997. *Am J Cardiol*. 2002;89:924-929.
16. Kugelmass AD, Cohen DJ, Brown PP, et al. Hospital resources consumed in treating complications associated with percutaneous coronary interventions. *Am J Cardiol*. 2006;97:322-327.
17. Lincoff AM, Bittl JA, Harrington RA, et al., for the REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.
18. Lee MS, Makkar RR. Bivalirudin in acute coronary syndromes and percutaneous coronary intervention. *Rev Cardiovasc Med*. 2006;7:S27-S34.
19. Taira DA, Seto TB, Siegrist R, et al. Comparison of analytic approaches for the economic evaluation of new technologies alongside multicenter clinical trials. *Am Heart J*. 2003;145:452-458.
20. Mark DB, Talley JD, Topol EJ, et al., for the EPIC Investigators. Economic assessment of platelet glycoprotein IIb/IIIa inhibition for prevention of ischemic complications of high-risk coronary angioplasty. *Circulation*. 1996;94:629-635.
21. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: study design and rationale. *Am Heart J*. 2004;148:764-775.
22. ACUITY Trial. Available at: http://www.medscape.com/viewarticle/529634. Accessed April 14, 2006.
23. Angiomax Monograph. Available at: www.themedicinescompany.com/pdf/Product%20Monograph%20ANG-PMN-011-04.pdf. Accessed April 13, 2006.