Economic evaluation of bivalirudin with provisional glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein IIb/IIIa inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared the use of percutaneous coronary intervention (PCI) using bivalirudin with provisional platelet glycoprotein (GP) IIb/IIIa inhibition, with that of heparin plus routine GP IIb/IIIa inhibition. Bivalirudin was administered as a 0.75 mg/kg bolus, followed by a 1.75 mg/kg per hour infusion for the duration of the PCI procedure. Heparin was administered as a 65 U/kg bolus.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients undergoing non-emergent PCI at treatment sites in the USA. Patients were eligible if they were undergoing PCI with an approved device. Key exclusion criteria included ongoing acute myocardial infarction (MI), recent receipt of one of the study drugs or low molecular weight heparin, or the need for concomitant warfarin therapy. Patients were also excluded if they had a platelet count less than 100,000, a serum creatinine level greater than 4.0 mg/dL., or were at increased risk of bleeding complications.

Setting
The study setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were collected from patients enrolled in the study between October 2001 and August 2002. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a single study, details of which were reported elsewhere (Lincoff et al., see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
The authors did not report whether the sample size was determined in the planning phase of the study. They also did not report any retrospective power calculations. A total of 6,100 patients undergoing non-emergent PCI were enrolled in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial. However, the economic analysis was confined to those patients enrolled at US treatment sites, with 4,651 patients enrolled. Out of these, 2,319 patients were allocated to the bivalirudin group and another 2,332 to the heparin+GP IIb/IIIa group. The mean age in each of the two groups was 63 (+/- 11) years. The proportion of males was 72.7% in the bivalirudin group and 72.8% in the heparin+GP IIb/IIIa group.

Study design
The study was a randomised controlled trial (RCT) that was carried out at different treatment sites across the USA. Randomisation was stratified by study site and by the operator's intent to use either abciximab or eptifibatide as the GP IIb/IIIa inhibitor. The groups were followed for 30 days after hospital discharge. The authors reported no loss to follow-up. The authors reported that the patients were randomised in a double-blind fashion.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes used were MI, major bleeding, minor bleeding, death and any repeat revascularisation. MI was defined as either the development of new pathologic Q waves, the elevation of creatine kinase-MB fraction (CKMB) to at least 3 times the upper limit of normal within 48 hours of PCI, or the elevation of CKMB to at least twice the upper limit of normal at any other time during follow-up. Major bleeding was defined as any intracranial or retroperitoneal haemorrhage, clinically overt blood loss resulting in a decrease in haemoglobin greater than 3 g/dL, any decrease in haemoglobin greater than 4 g/dL, or the transfusion of at least 2 U of packed red cells. Minor bleeding was defined as any other clinically overt blood loss that did not meet the criteria for major bleeding. The baseline characteristics of the two treatment groups were well-matched, except for a modest excess of patients who underwent multi-vessel PCI in the bivalirudin group (17.3% versus 14.6%; p=0.01).

Effectiveness results
During the initial hospitalisation, there was no significant difference in the combined incidence of death or MI between the bivalirudin and heparin+GP IIb/IIIa groups (7.3% versus 6.6%).

Bivalirudin plus provisional GP IIb/IIIa inhibition was associated with a significant and consistent reduction in bleeding complications compared with heparin plus routine GP IIb/IIIa inhibition. Protocol-defined major bleeding was reduced by 38% (2.8% versus 4.5%; p=0.002), minor bleeding was reduced by 46% (15.1% versus 28.1%; p<0.001), and thrombocytopenia (defined as any platelet count less than 100,000/microL) was reduced by 54% (0.7% versus 1.5%; p=0.01).

Between hospital discharge and the 30-day follow up, there were no significant differences in clinical outcomes between the two groups.

Clinical conclusions
The authors concluded that, consistent with the results of the overall trial, bivalirudin in combination with provisional GP IIb/IIIa inhibition led to similar in-hospital and 30-day clinical outcomes among patients undergoing contemporary PCI procedures compared with the standard anticoagulation regimen of heparin with routine GP IIb/IIIa inhibition. However, bivalirudin in combination with provisional GP IIb/IIIa inhibition was associated with a significant reduction in bleeding complications compared with heparin plus routine GP IIb/IIIa inhibition during in-hospital follow-up.

Measure of benefits used in the economic analysis
The authors did not derive a measure of health benefits. The analysis was therefore categorised as a cost-consequences study.
Direct costs
The total costs and resource use were reported separately. The direct costs included in the analysis were those to the health care system. These were the costs of initial and repeat procedures, hospitalisation, doctor fees, and complication costs. The costs of the study drugs were based on the current average wholesale prices. The costs of additional disposable equipment, overheads and depreciation for the cardiac catheterisation laboratory were estimated on the basis of the average cost per procedure in the authors’ setting, and were adjusted for actual procedure duration. All other hospital costs were determined using a top-down accounting method based on each hospital’s Medicare cost report. Billing data were obtained for 2,821 of 4,862 admissions during the 30-day study period. The hospital costs were determined by multiplying itemised hospital charges by the cost-centre-specific cost-to-charge ratio. For those admissions for which billing data were not available, non-procedural hospital costs were imputed on the basis of a linear regression model, which was developed using the hospital admissions for which complete billing information was available. Physicians’ fees for inpatient services, major cardiac procedures, and surgical procedures were based on the 2002 Medicare Fee Schedule. Discounting was irrelevant, as all the costs were incurred during a 30-day period, and was therefore not performed. The study reported the average costs. The price year was 2002.

Statistical analysis of costs
The costs were reported as mean values +/- standard deviations. To reduce the impact of high cost outliers on group means, the protocol specified that 30-day costs greater than the 99th percentile for each treatment group were assigned costs equal to the 99th percentile for the group. A multiple linear regression was performed to identify independent predictors of initial hospital costs. These include patient characteristics, ischaemic complications, repeat procedures, and bleeding complications.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The initial hospital costs were $10,561 (+/- 6,267) in the bivalirudin group and $10,966 (+/- 6,524) in the heparin+GP IIb/IIIb group. There was a difference of $405 per patient, (p<0.001).

The follow-up medical care costs were similar for the two groups, $448 (+/- 2,829) in the bivalirudin group and $441 (+/- 2,586) in the heparin+GP IIb/IIIb group.

The total cost was $10,868 (+/- 5,479) in the bivalirudin group and $11,242 (+/- 5,420) in the heparin+GP IIb/IIIb group. There was a difference of $374 per patient, (p<0.001).

The results of sub-group analyses according to gender, age and the presence of an acute coronary syndrome, failed to reveal any significant interactions between baseline patient characteristics and the magnitude of cost-savings seen with bivalirudin.
**Synthesis of costs and benefits**
The costs and benefits were not combined. The results of the multiple linear regression showed that repeat revascularisation procedures (in-hospital coronary artery bypass grafting, repeat PCI) were the strongest correlates of in-hospital cost. Among procedural complications, major bleeding, thrombocytopenia and large periprocedural MI (CKMB greater than 10 times the upper limit of normal) had the greatest independent impact on cost, whereas small-to-moderate post-procedural MI and minor bleeding had smaller impacts. Several baseline patient characteristics (e.g. need for multi-vessel PCI, acute coronary syndrome presentation, and history of congestive heart failure) were also associated with higher initial hospital costs.

**Authors' conclusions**
Compared with heparin plus routine glycoprotein (GP) IIb/IIIa inhibition, bivalirudin plus provisional GP IIb/IIIa inhibition resulted in similar acute ischaemic events and cost-savings of $374 to $405 per patient, depending on the analytic perspective.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the use of heparin plus routine GP IIb/IIIa inhibition. In the past decade, numerous clinical trials had demonstrated that this intervention led to substantial reductions in periprocedural ischaemic complications in comparison with unfractionated heparin alone. You should decide if this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a double-blind RCT. This was appropriate for the study question as well-conducted RCTs, such as this one, are considered the 'gold' standard when comparing different health interventions. The study sample appears to have been representative of the study population, with more than 4,000 patients being recruited, hence increasing the power of the study. The patient groups were generally shown to be comparable at analysis, with the exception that more patients in the bivalirudin group underwent multi-vessel PCI. The clinical analysis was undertaken on an intention to treat basis, and appropriate statistical techniques were used to test for any statistically significant differences between the two groups.

**Validity of estimate of measure of benefit**
The authors did not derive a measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

**Validity of estimate of costs**
Although the authors reported that the costs were estimated from a societal perspective, the indirect costs (e.g. productivity losses due to premature death and morbidity) were not included. The perspective actually adopted was that of the third-party payer. The analysis did not include the costs for outpatient medical services and medications and, therefore, the total cost of each intervention may have been overestimated. The costs and the quantities were reported separately, which will increase the generalisability of the authors' results to other settings. Resource use was derived from the single study, with appropriate statistical techniques being used to test for any significant differences between the two groups. The unit costs were derived from several sources, with the majority of costs being derived from Medicare charges. Although charges were used, the authors adjusted charges to the specific cost-to-charge ratio, so that these costs would more accurately depict the actual cost of providing an intervention. The authors performed a multiple linear regression to identify the predictors of initial hospital costs. Discounting was irrelevant, as all the costs were incurred during a short time, and was not performed. The price year was appropriately reported, which will aid any possible inflation exercises.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies, showing qualitatively similar results. However, the authors reported that their study was the first to directly examine hospital costs and their
determinants in a large population of patients. The issue of generalisability to other settings was addressed in the multiple regression analysis. The authors do not appear to have presented their results selectively, and their conclusions reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, the primary cost data were not collected on all study participants. Second, the timeframe encompassed in the analysis was relatively brief, although the authors reported that it was unlikely that longer-term follow-up would have improved the estimation of cost-differences. Third, the results of the economic analysis do not apply to patients with ongoing acute MI or high-risk acute coronary syndromes receiving GP IIb/IIIa inhibition, which were excluded by protocol. Finally, the authors reported that it is likely that they might have underestimated the extent of cost-savings that might ultimately be achieved by bivalirudin in contemporary PCI, as it is possible that the design of the REPLACE trial artificially increased the hospital costs for this group.

**Implications of the study**
The authors reported that there seemed little question that bivalirudin would be reasonably cost-effective compared with heparin. However, for patients at very low risk of ischaemic complications, it is unclear whether bivalirudin plus provisional GP IIb/IIIa inhibition would offer any economic or clinical advantages for them.

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**Other publications of related interest**


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