Comparative cost-effectiveness of anticoagulation with bivalirudin or heparin with and without a glycoprotein IIb/IIIa-receptor inhibitor in patients undergoing percutaneous coronary intervention in Sweden: a decision-analytic model
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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 examined two anticoagulant strategies for the prevention of periprocedural complications in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). Use of bivalirudin was compared with a strategy in which 50% of patients receive heparin alone and the remaining 50% of patients receive heparin combined with a glycoprotein IIb/IIIa-receptor inhibitor (GPI) such as abciximab. Bivalirudin was given as a 250-mg vial, heparin as a 25,000-IU vial and abciximab as a 10-mg vial.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with CAD undergoing PCI. The typical patient had a mean age of 63 years and a mean weight of 78 kg to reflect Swedish populations with CAD undergoing PCI. The proportion of men was 75%.

Setting
The setting was a hospital. The economic study was carried out in Sweden.

Dates to which data relate
The effectiveness data and most resource use data were derived from studies published between 1998 and 2006. The price year was 2006.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
The authors stated that a model was used. However, they might have been referring to the conventional cost-effectiveness framework since they reported no information about a decision model.

Outcomes assessed in the review
The outcomes estimated from the literature were life expectancy after PCI and the probabilities of five complications
associated with PCI. Such complications were death, Q-wave myocardial infarction (MI), urgent revascularisation (UR), major bleeding and minor bleeding. The risk of death was adjusted to reflect the difference in mortality between heparin monotherapy and heparin plus a GPI. Life expectancy was differentiated according to the complication of interest, using specific hazard ratios for death.

**Study designs and other criteria for inclusion in the review**
The primary studies appear to have been identified selectively rather than through a systematic review of the literature. The probabilities of complications were derived from three randomised clinical trials (RCTs). Specifically, the second Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2), the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), and the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT). In particular, data for bivalirudin were taken from REPLACE-2, data for heparin monotherapy were obtained from pooling the results of ESPRIT and EPISTENT, and data for heparin plus GPI were obtained by pooling the results of all three trials. The sample size for each trial was reported. The adjusted risk of death was derived from a meta-analysis involving a total of 20,137 patients. Life expectancy was derived from Swedish life tables. The hazard ratios for death were derived from a 1-year follow-up study based on data from the REPLACE-2.

**Sources searched to identify primary studies**
Not relevant.

**Criteria used to ensure the validity of primary studies**
The use of data from RCTs with large sample sizes and a meta-analysis ensures the validity of the primary data.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Six primary studies provided the data.

**Methods of combining primary studies**
The primary studies of heparin monotherapy (2 studies) and heparin plus GPI (3 studies) were combined by calculating pooled estimates of clinical data.

**Investigation of differences between primary studies**
The authors stated that drug dosages were comparable across the primary studies. No other investigations were made to assess the comparability of patient populations and other characteristics of the primary studies. No test of heterogeneity was carried out.

**Results of the review**
The adjusted probability of death was 0.4340 with heparin monotherapy, 0.2994 with heparin + GPI, and 0.2344 with bivalirudin.

The probability of Q-wave MI was 0.0333 with heparin monotherapy, 0.0112 with heparin + GPI, and 0.0040 with bivalirudin.

The rate of UR was 0.0147 with heparin monotherapy, 0.0120 with heparin + GPI, and 0.0118 with bivalirudin.
The rate of major bleeding was 1.2002 with heparin, 1.0533 with heparin + GPI, and 0.6348 with bivalirudin.

The rate of minor bleeding was 1.7458 with heparin monotherapy, 2.9533 with heparin + GPI, and 1.3030 with bivalirudin.

The hazard risk of death within 30 days in patients receiving heparin plus a GPI compared with those receiving heparin monotherapy was 0.69 (95% confidence interval, CI: 0.53 to 0.90).

The hazard risks of death for patients experiencing an MI, UR or a major bleeding event compared with the general population were 2.86, 3.08 and 2.58, respectively, (p<0.05 for all events).

The life expectancy of a patients undergoing PCI was 16.8 years.

The life expectancy adjusted according to the complication of interest was 16.2 years after MI, 16.1 years after UR, and 16.3 years after major and minor bleeding events.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of life-years gained (LYG). This was derived according to the occurrence of complications and the estimated life expectancy following each complication. The numbers of MI, UR, major and minor bleeding episodes, and deaths were also reported, although these were not combined with the costs.

**Direct costs**
The viewpoint of a hospital was taken in the analysis. This included the costs of medications and the costs of treating complications. The unit costs and the quantities of resources used were reported separately for some items. All resource use data were based on the treatment pattern from the REPLACE-2. The costs of medications were obtained from the Swedish Pharmacopoeia. The costs of complications were estimated on the basis of diagnosis-related groups from four Swedish hospitals. Discounting was not relevant as the costs were incurred during a short timeframe. The price year was 2006. All costs derived from previous years were updated to 2006 values using the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case, but stochastic distributions were assigned in the sensitivity analysis.

**Indirect Costs**
The indirect costs were not included in the economic analysis.

**Currency**
Swedish kroner (SEK).

**Sensitivity analysis**
A stochastic simulation was run by assigning probabilistic distributions to all economic and clinical data. The proportion of patients in the combination strategy who received a GPI was varied (from 0 to 100% in steps of 10%). A further analysis considered the scenario in which half of patients receiving a GPI were administered abciximab and the other half received epifibatide (a less costly GPI) in order to reflect actual treatment patterns in some hospitals. Finally, an alternative scenario considered both Q-wave and non-Q-wave MIs (non-Q-wave MIs were not considered in the base-case analysis).

**Estimated benefits used in the economic analysis**
In a hypothetical cohort of 1,000 patients, the number of LYG with bivalirudin over the alternative strategy (50% heparin monotherapy and 50% heparin + GPI) was 19.8 (95% CI: 19.5 to 19.9). The number of LYG was 20.7 when bivalirudin was compared with a scenario in which 40% of patients received heparin monotherapy and 60% of patients received heparin combination therapy.

The mean number of patients experiencing complications was also lower with bivalirudin than with the alternative strategy. In a hypothetical cohort of 1,000 patients, the use of bivalirudin was associated with 18.2 fewer MIs, 1.6 fewer URs, 4.9 fewer major bleeding episodes, 10.4 fewer minor bleeding episodes and 1.3 fewer deaths compared with a strategy of 50% heparin and 50% heparin plus GPI.

Cost results
In a hypothetical cohort of 1,000 patients, the expected total costs per patient were SEK 6,472 with bivalirudin and SEK 7,773 with the alternative strategy (50% heparin monotherapy and 50% heparin + GPI).

The cost-difference was SEK 1,301 (95% CI: 1,367 to 1,229) in favour of bivalirudin.

The cost-savings amounted to SEK 338 (95% CI: 265 to 412) when bivalirudin was compared with a scenario in which 40% of patients received heparin monotherapy and 60% of patients received heparin combination therapy.

The cost-savings amounted to SEK 5,733 in a scenario when all patients in the comparison group were treated with the combination therapy.

In the comparison between bivalirudin and heparin monotherapy (0% of patients received GPI), bivalirudin was more expensive.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated in order to combine the costs and benefits of the alternative strategies.

The incremental analysis revealed that bivalirudin was the dominant strategy (both more effective and less expensive) in the base-case (50% heparin monotherapy and 50% heparin plus GPI) and when at least 40% of patients received GPI together with heparin.

For lower proportions of patients receiving GPI, the incremental cost per LYG with bivalirudin was SEK 24,814 (95% CI: 21,775 to 28,197) for 30% of patients receiving GPI, SEK 62,989 (95% CI: 59,786 to 66,276) for 20%, and SEK 98,348 (95% CI: 95,165 to 101,588) for 10%.

The sensitivity analysis revealed that the use of eptifibatide reduced the overall treatment costs in the comparison group and, therefore, slightly worsened the cost-effectiveness of bivalirudin. A similar conclusion was achieved when non-Q-wave MIs were considered. However, in most scenarios, either bivalirudin remained the dominant strategy or the cost-effectiveness of bivalirudin remained within a range generally considered acceptable in Sweden.

Authors' conclusions
A switch from heparin plus glycoprotein IIb/IIIa-receptor inhibitor (GPI; i.e. abciximab) to bivalirudin would improve life expectancy and reduce health care costs in patients undergoing percutaneous coronary intervention (PCI) in Sweden. The conclusions of the analysis also held in alternative scenarios that reflected the variability in treatment patterns with respect to use of GPI alongside heparin.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear and the authors justified their selection of the therapies under examination. Several scenarios were considered, assuming different proportions of patients receiving combination therapy with heparin and GPI. Further, the partial use of an alternative, less costly GPI (eptifibatide) was considered in
the sensitivity analysis. Finally, information on drug dosages was given. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The methods and conduct of a systematic review of the literature were not reported, so it is possible that the primary studies might have been identified selectively in order to include the most recent and valid sources of data. The use of clinical trials with a large sample size ensured a high internal validity on account of their randomised design. Similarly robust were the data retrieved from the meta-analysis. The authors did not explicitly address the issue of heterogeneity amongst the primary studies, reporting only that the drug dosages were comparable. In particular, comparability in relation to patient populations was not discussed which would appear to be an important issue. The authors performed extensive sensitivity analyses in order to deal with the uncertainty surrounding some model inputs.

**Validity of estimate of measure of benefit**
The summary benefit measure was appropriate as expected survival represents a key end point of the therapies examined in the study. Moreover, life-years can be compared with the benefits of other health care interventions. However, the authors did not consider the impact of the interventions on quality of life, which may be an important aspect of health for patients with CAD.

**Validity of estimate of costs**
The analysis was consistent with the perspective chosen in the economic analysis. The categories of costs included in the study were reported, but a detailed breakdown of cost items was not provided. Given the accounting system adopted in the hospital (i.e. diagnosis-related groups), most costs associated with complications were presented as macro-categories. However, the unit costs and resource use were reported separately for medications. The sources of the costs were reported for all items, while resource use was derived from one RCT in order to reflect actual treatment pattern. However, the impact of changes in costs and resources was evaluated in the sensitivity analysis, in which both statistical distributions were assigned and alternative estimates were considered. The price year was reported, which will assist with reflation exercises in other time periods.

**Other issues**
The authors did not compare their findings with those from other studies. Concerning the issue of the generalisability of the study results to other settings, the authors stated that the current findings could be extrapolated to other health care systems since the results were presented for alternative scenarios that reflected different treatment patterns. The study referred to patients undergoing PCI and this was reflected in the authors’ conclusions. The results of both the base-case and the sensitivity analysis were extensively reported. The authors noted that clinically important bleeding events might have been missed due to the definition of bleeding that was adopted in order to make the data comparable across the primary studies. Thus, the findings of this study might have been conservative for the bivalirudin strategy which is likely to reduce bleeding events. The authors pointed out that the characteristics of the hypothetical cohort considered in the study should reflect a typical European patient population. They stated that, although there were small differences between patient characteristics (age and gender) included in their analysis and the patient populations of the clinical trials used for efficacy data, these differences were unlikely to have affected the comparison between alternatives.

**Implications of the study**
The study results support the use of bivalirudin as an anticoagulant agent for patients undergoing PCI due to CAD.

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