Long-term cost effectiveness of early and sustained dual oral antiplatelet therapy with clopidogrel given for up to one year after percutaneous coronary intervention: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) 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 use of clopidogrel prior to percutaneous coronary intervention (PCI) and for up to 1 year after PCI was studied. The regimen examined was a loading dose of 300 mg given 3 to 24 hours prior to PCI, followed by 1 year of therapy with clopidogrel 75 mg/day.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with coronary artery disease undergoing planned or probable PCI.

Setting
The setting was a hospital. The economic study was carried out in the USA and Canada.

Dates to which data relate
The effectiveness and resource use data were collected between June 1999 and April 2002. Other data were collected from studies published between 2000 and 2005. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the clinical study.

Study sample
There was limited information on the method of selecting the sample since details of the clinical trial had been published already (Steinhubl et al, 2002, see 'Other Publications of Related Interest' below for bibliographic details). A total of 2,116 patients were recruited from 99 centres across Canada and the USA. Of these, 1,053 were randomised to the clopidogrel group (29.3% women) and 1,063 to the placebo group (27.9% women). The mean age of both groups was 62 (+/- 11) years.
Study design
A prospective, multi-centre, randomised controlled trial was conducted across 99 sites. The duration of follow-up was 12 months. It would appear that no patient was lost to follow-up. No other details of the study design were provided in this paper, for full details the reader should refer to Steinhubl et al. (2002).

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary outcome measure used in the current study was a composite measure of cardiovascular death, nonfatal myocardial infarction (MI) or stroke. The secondary outcome measures were the rates of cardiovascular death, nonfatal MI and stroke, and the rates of major and minor bleeding. There was no difference between the groups in age, gender, MI (either at presentation or in the past), diabetes or hypertension.

Effectiveness results
The results are presented for the clopidogrel group versus the placebo group.

The rate of composite event was 8.5% versus 11.5%, (p=0.02).

The rate of cardiovascular death was 1.7% versus 2.3%, (p=0.45).

The rate of nonfatal MI was 6.6% versus 8.5%, (p=0.13).

The rate of stroke was 0.9% versus 1.1%, (p=0.68).

The rate of major bleeding was 8.8% versus 6.7%, (p=0.07).

The rate of minor bleeding was 5.3% compared with 5.6%, (p = 0.84).

Clinical conclusions
The effectiveness analysis showed that clopidogrel was associated with fewer fatal and nonfatal cardiovascular events. There were, however, more incidences of major bleeding among those receiving clopidogrel.

Measure of benefits used in the economic analysis
The outcome measure used was the number of life-years gained (LYG). This was estimated from two independent sources, the Framingham Heart Study and the Saskatchewan Health database. These sources provided estimates of life-years lost due to events (death, MI and stroke). The life-years lost were calculated by subtracting the mean survival given observed events in the trial, from the survival expected with no events. Mean survival was calculated by integrating the survival curves, adjusted for various patient characteristics, including experience of specific ischemic events. For patients who experienced multiple events of different types during the trial, lost life expectancy was estimated assuming a hierarchy of death, stroke and MI. It was further assumed that clopidogrel would be stopped at the end of the trial, thus there would be no reduction (or increase) in nonfatal events between the two arms. An annual discount rate of 3% was applied to future LYG.

Direct costs
The costs included in the analysis were the direct medical care costs for hospitalisation and the cost of clopidogrel and aspirin. The direct costs associated with ambulatory care and outpatient visits were not included since there was no information available from the CREDO trial. The impact of bleeding on cost was derived using CURE trial data as this was not available in the CREDO trial dataset. The cost of other medication was not included as medication use other than the study drug was not found to differ between the two groups. Resource use was collectively prospectively within the CREDO trial. Each hospitalisation was assigned a diagnosis-related group (DRG), as used in Medicare programmes.
in the USA. The costs for each DRG were estimated using average Medicare reimbursement rates. Such rates were obtained from the Medicare Part A data file and average private payer reimbursement rates derived from the MEDSTAT database. Consequently, a blended MEDSTAT-Medicare cost could be estimated. The price year was 2001. Some costs were incurred after the first year and were appropriately discounted at an annual rate of 3%.

**Statistical analysis of costs**
The costs were treated deterministically.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to examine the robustness of the base-case cost-effectiveness ratios to variations in life expectancy (reduction of 50% or 80%), costs (addition of costs associated with bleeding or those due to prolonged life expectancy) and quality-adjusted survival. The authors chose the alternative values used on the basis of evidence from other published studies.

**Estimated benefits used in the economic analysis**
Based on the Framingham model, patients in the clopidogrel group were estimated to have gained, on average, 0.1526 life-years (95% CI: 0.0263 to 0.2838) over those receiving the placebo. The Saskatchewan model resulted in an overall life expectancy gain of 0.1920 life-years (95% CI: 0.0539 to 0.3369) for those receiving clopidogrel compared with those receiving the placebo.

**Cost results**
The 1-year costs were higher for the clopidogrel group using all three costing methods.

The results are presented for the clopidogrel group versus the placebo group.

Medicare: $19,994 versus $19,431 (difference of $563, 95% CI: -483 to 1,642).

MEDSTAT: $23,394 versus $22,821 (difference of $573, 95% CI: -633 to 1,765).

Blend: $21,974 versus $21,310 (difference of $664, 95% CI: -461 to 1,784).

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio (ICER; i.e. the incremental cost per LYG) was calculated to combine the costs and benefits of clopidogrel versus placebo. Bootstrap methods (5000 iterations) were used to estimate the 95% CIs of the distribution of ICERs.

When the analysis was restricted to in-trial costs, depending on the source of the costs, the ICER ranged from $3,684 with MEDSTAT to $4,353 with blend when using the Framingham estimates.

When using the Saskatchewan estimates, the ICER ranged from $2,929 with MEDSTAT to $3,460 with blend.

The ICERs were below the threshold of $50,000 per LYG in over 97% of cases when using the Framingham estimates, and in over 98% of cases when using the Saskatchewan estimates.
Blending the effectiveness estimates from the Framingham and Saskatchewan data results in the three costing approaches yielding similar results, with over 90% of bootstrap-derived ICERs below $18,000.

The sensitivity analysis showed that if the estimated gain in life expectancy was only half of that projected, the ICER would be $8,706 (with 95.7% of bootstrap samples less than $50,000/LYG) when using the blended costing approach and Framingham life expectancy estimates, and $6,921 (with 97.9% less than $50,000/LYG) on the basis of Saskatchewan data. If the life expectancy gain was just 20% of that projected, the ICER would be $21,766 (with 82.7% less than $50,000/LYG) on the basis of Framingham estimates and $17,302 (with 89.3% less than $50,000/LYG) on the basis of Saskatchewan estimates.

The results of other sensitivity analyses were fully presented in the paper.

Authors’ conclusions
A loading strategy followed by 1 year of antiplatelet therapy with clopidogrel was highly cost-effective for patients undergoing percutaneous coronary intervention (PCI).

CRD COMMENTARY - Selection of comparators
The selection of the comparator was appropriate given the question being evaluated.

Validity of estimate of measure of effectiveness
The effectiveness data came from a prospective, randomised clinical trial, which was appropriate for the study question. Since the study had been published already, only key characteristics of the patient sample and study design were reported in the current publication. Thus, it was difficult to assess the internal validity of the study. However, some details of the study details that were presented, such as the large sample of patients, the randomised design and the baseline comparability, suggest that the clinical information is likely to be robust. However, to fully evaluate the validity of the clinical trial the reader will need to refer to the parent clinical paper (Steinhubl et al. 2002).

Validity of estimate of measure of benefit
The summary benefit measure (i.e. LYG) was appropriate. The authors stated that utility estimates were not available, thus quality-adjusted life-years (QALYs) could not be calculated directly from the patient level data. Therefore, QALYS were only discussed for illustrative purposes in the sensitivity analysis and all values were based on ‘what if’ type assumptions.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the study. However, since the costs were mainly derived from reimbursement rates and productivity losses were not included, the perspective of a third-party payer appears to have been used. The authors noted the lack of indirect costs as a limitation, and suggested that they would be higher among the placebo group because there were more events that could lead to more resource consumption and more time lost from work. They suggested, therefore, that not including indirect costs underestimated the cost-effectiveness of clopidogrel. Private cost estimates were also used, and blended estimates were reported together with totally private or totally public rates. The authors excluded some categories of costs because of a lack of available data and excluded others because of the lack of a statistical difference between the groups. The source of the data was reported and most resource use information came from the clinical trial, thus patient-level data were used. The price year was stated which will aid reflation exercises.

Other issues
The authors compared their findings with those from other studies. They did not, however, explicitly address the issue of the generalisability of the study results to other settings. The authors noted that US costs based on DRGs were applied to both American and Canadian patients and might not account for variation in resource use between the
different heath systems. The limitations of using external databases to estimate life expectancy were discussed, and it was noted that the uncertainty underlying life expectancy estimates from Saskatchewan and Framingham models was not accounted for in the analysis. Other sensitivity analyses were carried out, which enhanced in part the external validity of the study.

**Implications of the study**
The study supports the use of platelet inhibition with clopidogrel loading before PCI followed by therapy for 1 year.

**Source of funding**
None stated.

**Bibliographic details**

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**Other publications of related interest**


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**MeSH**
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