Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation

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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 use of clopidogrel given for up to one year in patients with acute coronary syndromes (ACS), but without ST-segment elevation. The regimen examined was a loading dose of 300 mg followed by 75 mg/day.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who had been hospitalised within 24 hours of onset of symptoms indicative of ACS, and who did not have significant ST-segment elevation.

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

Dates to which data relate
The effectiveness and resource use data were gathered from December 1998 to September 2000. Other data were derived from studies published from 2002 to 2004. The price year was not explicitly reported.

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 the clinical trial had been published and details were given elsewhere (Yusuf et al. 2001, see ‘Other Publications of Related Interest’ below for bibliographic details). An overall sample of 12,562 patients was enrolled into the trial. There were 6,259 patients (39% women) in the clopidogrel group and 6,303 patients (38% women) in the placebo group. In both groups the mean age of the patients was 64 (+/- 11) years.
Study design
This was a prospective, double-blind, randomised clinical trial that was carried out at 482 centres in 28 countries. The length of follow-up was 12 months. It appears that no patient has been lost to follow-up. Clopidogrel was given for 9 months. No other details about the study design were given.

Analysis of effectiveness
All of the patients included in the study sample were used for the analysis of effectiveness. The primary outcome measure used in the current study was a composite measure of all-cause death, myocardial infarction (MI), or stroke. The secondary outcome measures were:

the rates of all-cause death, MI and stroke;

the rates of major, life-threatening, and major plus life-threatening bleeding; and

the rate of minor bleeding.

At study entry, the patient groups were comparable in terms of the demographics and history of MI, diabetes, or hypertension.

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

The rates of composite outcome measure were 9.3% and 11.4%, respectively, (p<0.0001).

The rates of all-cause death were 5.8% and 6.2%, respectively, (p=0.2779).

The rates of MI were 5.2% and 6.7%, respectively, (p=0.0004).

The rates of stroke were 1.2% and 1.4%, respectively, (p=0.3532).

The rates of bleeding were 3.70% and 2.70%, respectively, (p=0.0015).

The rates of major bleeding were 1.5% and 0.9%, respectively, (p=0.002).

The rates of life-threatening bleeding were 2.1% and 1.7%, respectively, (p=0.10).

The rates of major plus life-threatening bleeding were 0.1% and 0.1%, respectively, (p=1.00).

The rates of minor bleeding were 5.1% and 2.4%, respectively, (p<0.0001).

Clinical conclusions
The effectiveness analysis showed that clopidogrel was associated with fewer fatal and nonfatal cardiovascular events, especially due to the reduction in MIs. However, significantly more major and minor bleeding episodes were observed in clopidogrel-treated patients.

Measure of benefits used in the economic analysis
The summary benefit measure used was life expectancy. This was estimated from two independent sources, the Framingham Heart Study and the Saskatchewan Health database. These sources provided gender- and age-specific estimates of life years lost due to events, which were then applied to the CURE trial patient population. Mean survival beyond the end of the trial was estimated by integrating the survival curves, adjusted for various patient characteristics, including experience of specific subsequent ischaemic 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 life-years gained (LYG).

**Direct costs**
The perspective of the third-party payer appears to have been used. The economic evaluation included the costs for hospitalisations (including diagnostic tests, therapeutic procedures and medications) and the cost of clopidogrel. Ambulatory care, including outpatient diagnostic procedures and testing, was not recorded and was thus excluded from the current analysis. Similarly, the use of medication other than the study drugs was not included because it was comparable across the patient groups. Non-cardiovascular follow-up hospitalisations were not considered because of their negligible impact on the total costs. The quantities of resources used were provided and the costs were presented as macro-categories for most items.

Resource use was estimated from data derived from the CURE trial. Each hospitalisation was assigned a diagnosis-related group (DRG), as used in Medicare programmes in the USA, by coders who were blinded to the treatment group. 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 estimate was generated by applying MEDSTAT costs to patients in the CURE trial who were younger than 65 years and Medicare costs to those older than 65 years. The authors noted that MEDSTAT estimates included professional costs, which for Medicare were calculated as a percentage of the hospital costs by DRG. The costs beyond the trial period were estimated as the average per capita participant Medicare reimbursement. The price year was not reported. 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 economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
A bootstrap method was used to estimate 95% confidence intervals (CIs) for both the costs and LYG. Univariate sensitivity analyses were also 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.

**Estimated benefits used in the economic analysis**
The LYG with clopidogrel over placebo were 0.0699 (95% CI: -0.0077 - 0.1440) when using the Framingham estimates and 0.0682 (95% CI: 0.0122 - 0.1190) when using Saskatchewan estimates. The difference was mainly due to the reduction in the risk of death and stroke with clopidogrel.

**Cost results**
In-trial costs exclusive of clopidogrel were comparable between the groups, irrespective of the source of the costs.

When clopidogrel costs were included, in-trial costs were $13,019 with clopidogrel and $12,578 with placebo (difference $442, 95% CI: 62 - 820) when using Medicare rates. The in-trial costs were $17,924 (clopidogrel) and
$17,586 (placebo), respectively, (difference $338, 95% CI: -165 - 827) when using MEDSTAT rates, and $15,357 and $15,014 (difference $343, 95% CI: -90 - 784) when using blended Medicare/MEDSTAT rates.

The results for several sub-groups resembled those for the total population.

**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.

When the analysis was restricted to in-trial costs, depending on the source of the costs, the ICER ranged from $4,833 to $6,318 when using the Framingham estimates and from $4,953 to $6,475 when using the Saskatchewan estimates.

When the direct costs beyond the trial period were included, depending on the source of the costs, the ICER ranged from $7,654 to $9,144 when using the Framingham estimates and from $7,833 to $9,343 when using the Saskatchewan estimates.

The ICERs were always higher when the Medicare costs were used.

The ICERs were below the threshold of $50,000 per LYG in 90% of cases when using the Framingham estimates and in 95% of cases when using the Saskatchewan estimates.

The results for most of the sub-groups were similar to the overall estimate. The exception was for women, for whom the ICER was higher because of a trend towards more non-cardiovascular deaths in the clopidogrel arm ($70,396 per LYG when using the Framingham database or $115,194 per LYG when using the Saskatchewan database).

The sensitivity analysis showed that if the estimated gain in life expectancy was only half of that projected, using the blended costing approach and Framingham life expectancy estimates, the ICER would be $9,820 (with 91.9% of bootstrap samples <$50,000/LYG), while on the basis of Saskatchewan data, it would be $10,065 (with 96.7% <$50,000/LYG). If the life expectancy gain was just 20% of that projected, the ICER would be $24,549 (with 77.7% <$50,000/LYG) on the basis of Framingham estimates, and $25,161 (with 81.8% <$50,000/LYG) based on Saskatchewan estimates.

If utility was less than 1.0 but equal for both arms, the incremental cost per quality-adjusted life-year (QALY) gained would be higher than the cost per LYG estimate. If utility was 0.80 in both arms, then the incremental cost per QALY gained using Framingham life expectancy and Medicare costs would be $7,898. If costs in added years of life were also included, the incremental cost per QALY gained would be $11,430.

**Authors' conclusions**

Platelet inhibition with clopidogrel in patients for up to one year after presentation with an acute coronary syndrome was cost-effective.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparator (placebo) was appropriate because aspirin therapy alone represented a standard treatment option for patients with symptoms indicative of ACS. This comparison was based on a large, randomised controlled trial. You should decide whether they are valid comparators in your own setting.

**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 validity of the study. However, some details of the study, such as the large sample of patients, the randomised design and the baseline comparability, ensure the robustness of the clinical information used in the analysis. The authors stated that the sub-group analysis was
underpowered, thus caution is required when interpreting these results. The elements mentioned here tend to enhance the validity of the clinical analysis.

Validity of estimate of measure of benefit
The summary benefit measure was appropriate as it reflected the most important dimension of health, namely the impact on mortality. The authors noted that the use of external databases to estimate expected survival may represent a limitation of the study. Discounting was applied, as suggested by US guidelines. The authors stated that quality of life estimates were not available, thus QALYs were only calculated in the sensitivity analysis and were based on assumptions.

Validity of estimate of costs
The authors did not state explicitly which perspective was adopted in the study. However, since the costs were mainly derived from reimbursement rates, the perspective of a third-party payer appears to have been used. Private cost estimates were also used, and blended estimates were reported together with totally private or totally public rates. The authors justified the exclusion of some categories of costs, mainly because of the lack of statistical difference between the groups. The unit costs and resource use were provided for most items, although a detailed breakdown of the costs was not given for those items that were presented as macro-categories. The source of the data was reported and most resource use information came from the clinical trial, thus using patient-level data. The price year was not explicitly stated, which limits the possibility of performing reflation exercises in other settings.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. The analysis actually focused on the US context but, as the authors noted that the CURE trial was a multinational study, treatment patterns used in the current economic evaluation might not reflect accurately the US setting. Some sensitivity analyses were carried out, which enhanced in part the external validity of the study.

Implications of the study
The study results supported the use of clopidogrel in patients with symptoms indicative of ACS and who did not have significant ST-segment elevation.

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Other publications of related interest


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