The cost-effectiveness of the use of clopidogrel in acute coronary syndromes in five countries based upon the CURE study


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, compared with placebo, in the treatment of acute coronary syndromes (ACS).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a total of 12,562 patients recruited from December 1998 to September 2000 at 482 centres from 28 countries. Patients were eligible if they were hospitalised within 24 hours of onset of symptoms indicative of ACS, and they did not have significant ST segment elevation.

Setting
The setting was secondary and tertiary care. The economic study was carried out in the UK, USA, Sweden, France and Canada.

Dates to which data relate
The effectiveness data and resource use data were from the CURE study, which was carried out from December 1998 to 2001 and was published in 2001 (see 'Other Publications of Related Interest' below for bibliographic details). The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

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
It was unclear from this paper whether power calculations were performed to determine the sample size. A total of 12,562 patients were recruited from December 1998 to September 2000 at 482 centres from 28 countries. Among them were 737 patients from the UK, 462 from the USA, 360 from France, 260 from Sweden and 1,761 from Canada. The patients were randomised to receive either clopidogrel (loading dose of 300 mg followed by 75 mg/day) or a placebo for an average period of 9 months. Details of the patients in each group were not reported.
Study design
The study was a randomised controlled trial that was carried out in 482 centres from 28 countries. The duration of follow-up was an average period of 9 months.

Analysis of effectiveness
It was not stated whether the analysis of the clinical study was conducted on the basis of intention to treat or treatment completers only. The primary health outcomes used were:

the rate of the first primary outcomes,

the rate of refractory ischaemia in hospital,

the rate of heart failure, and

the risk of bleeds.

Effectiveness results
The clopidogrel group demonstrated a lower rate of the first primary outcomes (9.3% versus 11.4%, relative risk 0.80, p<0.001). It also demonstrated lower rates of refractory ischaemia in hospital (1.4% versus 2.0%, relative risk 0.68; p=0.01), and heart failure (3.7% versus 4.4%, relative risk 0.82; p=0.03). All components of the primary outcome showed similar trends in favour of clopidogrel.

Major bleeds were significantly more common in the clopidogrel group (3.7% versus 2.7%, relative risk 1.38; p=0.001). However, the difference in life-threatening bleeds was not statistically significant (2.2% versus 1.8%, relative risk 1.21; p=0.13).

There was a significant increase in the risk of minor bleeds (5.1% versus 2.4%, relative risk 2.12; p<0.001).

The use of thrombolytic therapy (1.1% versus 2.0%, relative risk 0.57; p=0.001) and glycoprotein IIb/IIIa receptor inhibitors (5.9% versus 7.2%, relative risk 0.82; p=0.003) was significantly reduced in the clopidogrel group.

Clinical conclusions
Clopidogrel is more effective than placebo.

Measure of benefits used in the economic analysis
The measure of benefits used was the event avoided (i.e. cardiovascular death, myocardial infarction or stroke prevented).

Direct costs
The direct costs included direct medical care costs for hospitalisation and drugs. The direct costs associated with outpatient visits and testing were not included. The health care costs consisted of two components. More specifically, health care services or resource use as measured in the clinical trial, and unit costs for health care services used in the different countries. Local unit costs were used for each country and resource use information was from the CURE study. Discounting was not performed. The price year was 2001.

Statistical analysis of costs
A bootstrap analysis was used to calculate the standard errors and 95% confidence intervals (CIs) for the difference in average costs. The bias corrected and accelerated method was used to obtain CIs for the average costs.
Indirect Costs
The indirect costs were not included.

Currency
UK pounds sterling (£), US dollars ($), Swedish kronor (SEK), Canadian dollars (Can$), and Euros (Euro) for France.

Sensitivity analysis
Although a sensitivity analysis was not carried out, the authors assessed the incremental cost-differences and incremental cost-effectiveness ratios for sub-groups of patients (low, intermediate and high risk) and for different durations of therapy (30 days, and 3, 6 and 9 months).

Estimated benefits used in the economic analysis
The absolute risk reduction for the occurrence of any primary outcome (including multiple events) was 2.0%.

Cost results
The total costs were significantly higher with clopidogrel than with placebo in all countries, except Canada. The difference was:

208 (95% CI: 119 - 297) per patient in the UK,

$451 (95% CI: 58 - 845) per patient in the USA,

SEK 2,571 (95% CI: 728 - 4,412) per patient in Sweden,

Euro 325 (95% CI: 85 - 565) per patient in France, and

Can$161 (95% CI: -181 - 506) per patient in Canada.

Synthesis of costs and benefits
The costs and benefits were combined by calculating the incremental cost-effectiveness ratio (ICERs).

For 9 months' follow-up, the ICER per event avoided with clopidogrel was 10,366 (95% CI: 4,411 - 42,981) in the UK, $22,484 (95% CI: 1,826 - 97,354) in the USA, SEK 127,951 (95% CI: 26,212 - 461,424) in Sweden, Euro 16,186 (95% CI: 3,311 - 72,368) in France, and Can$7,973 (95% CI: -9,401 - 54,235) in Canada.

The ICER for treatment with clopidogrel for 6 months was 4,860 in the UK, $8,425 in the USA, SEK 54,952 in Sweden, Euro 6,150 in France, and a dominant strategy (i.e. better results with lower costs) over placebo in Canada.

The ICER for treatment with clopidogrel for 3 months was 1,491 in the UK, $3,211 in the USA, SEK 22,180 in Sweden, Euro 2,169 in France, and a dominant strategy in Canada.

The ICERs for treatment with clopidogrel for 30 days showed that clopidogrel was a dominant strategy in all five countries.

The authors found no significant heterogeneity among the three sub-groups. During 30 days' follow-up, treatment with clopidogrel was a dominant strategy (i.e. better clinical results with lower costs) in all five countries. It remained a dominant strategy during the 3 months' and 6 months' follow-up in Canada.

Authors' conclusions
The use of clopidogrel in the CURE study reduced hospitalisation costs, but the acquisition cost of clopidogrel created
an overall increase in direct health care costs over 9 months. Nevertheless, the cost-effectiveness was in a range comparable to that of other therapies currently used for acute coronary syndromes (ACS).

CRD COMMENTARY - Selection of comparators
An implicit justification was given for the choice of placebo as a comparator for the intervention drug. This allowed the active effect of the treatment to be evaluated.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a large, multi-centre, randomised controlled trial, which was appropriate for the study question. Since little detail on the study samples was given, it was unclear whether the study sample was representative of the study population and whether the patient groups were comparable at baseline.

Validity of estimate of measure of benefit
The event avoided was used as measure of benefit. This was taken from the effectiveness analysis.

Validity of estimate of costs
Although the authors reported that the costs were estimated from a societal perspective, direct costs associated with outpatient visits and testing were not included, nor were indirect costs due to loss of productivity. The authors suggested that, based on their experience, the omissions of these costs was unlikely to have affected their conclusions. The costs and the quantities were not reported separately, and no sensitivity analyses of the quantities and prices were performed. This may limit the interpretation of the study findings.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed. The authors reported some limitations in their study, such as the omission of some direct and indirect costs.

Implications of the study
The study suggested that, taking multiple factors into consideration, clopidogrel given for up to 12 months (mean 9 months) as currently recommended by the ACC, AHA and the ESC has an acceptable cost-effectiveness ratio in Western countries. Decisions about the duration of therapy need to be individualised on the basis of patient profile, the relative costs of various therapies, and the overall economic status of particular societies.

Source of funding
Sanofi-Synthelabo and Bristol-Myers Squibb sponsored the CURE study.

Bibliographic details

PubMedID
15580055

Other publications of related interest
The CURE Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme. Rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Angina, Unstable /drug therapy; Canada; Cost-Benefit Analysis; Europe; Health Care Costs; Hospitalization /economics; Humans; Myocardial Infarction /drug therapy; Platelet Aggregation Inhibitors /economics /therapeutic use; Randomized Controlled Trials as Topic; Ticlopidine /analogs & derivatives /economics /therapeutic use; United States

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