Cost-effectiveness of clopidogrel in myocardial infarction with ST-segment elevation: a European model based on the CLARITY and COMMIT trials

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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 evaluated two treatment options for patients with ST-segment elevation myocardial infarction (STEMI). The options were clopidogrel in combination with acetylsalicylic acid (ASA) and ASA alone.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients with STEMI. Although the inclusion criteria were not reported, certain characteristics of the study population were presented. The characteristics of the study population were compared with those of the three large parent clinical trials used by the authors: the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial and the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), which were conducted in Sweden, Germany and France, and the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (Sabatine et al. 2005, Chen et al. 2005 and Yusuf et al. 2001, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The setting was secondary care. The economic study was carried out in France, Sweden and Germany.

Dates to which data relate
The effectiveness data were derived from studies published between 2001 and 2005. In addition, national data were taken from registers covering the period 1995 to 2005. The cost data were derived from sources published between 1999 and 2005. All costs were reported for the price year 2005.

Source of effectiveness data
The model parameters included:

- the risk of the combined end point of MI, stroke and cardiovascular death in month 1; and
- for the time period of 2 to 12 months, the risk reduction for treatment,
- the risk of the combined end point after no event,
- the risk for MI or stroke after no event,
the risk of death from non-cardiovascular causes after no event,

the risk of the combined end point after MI,

the risk of MI or stroke after MI, and

the risk of death from non-cardiovascular causes after MI.

Modelling
The authors constructed a combined decision tree and Markov model in order to model short- and long-term ischaemic events. The health states, time horizon, transition probabilities and several of the authors’ modelling assumptions were presented in full. Based on published data, the risks of events (MI, stroke, cardiovascular death and death from non-cardiovascular causes) during months 2 to 12, in patients who had an MI event, were estimated using logistic regression analysis. Mortality risks after the onset of events were modelled using Weibull survival regression. The results of the logistic regressions for risk calculations and the Weibull survival regressions were presented in full. The model was run separately for treatment effect data coming from the CLARITY and COMMIT trials.

Sources searched to identify primary studies
The baseline model parameters were derived from the three parent clinical trials: CLARITY, COMMIT and CURE (Sabatine et al. 2005, Chen et al. 2005 and Yusuf et al. 2001). The CLARITY and COMMIT trials were large multi-centre randomised, double-blind, placebo-controlled trials, while the CURE trial was a large randomised trial. Mortality data were derived from the Swedish Hospital and Death Registers. Weibull regression was then undertaken to ascertain the survival.

Methods used to judge relevance and validity, and for extracting data
The process used to identify the data was not reported. No inclusion criteria were explicitly stated. However, it appears that, at the time of the study, the two parent clinical trials (i.e. CLARITY and COMMIT) were the most recent large randomised trials to have investigated the effect of clopidogrel in STEMI patients. It was reported that, given the methodological differences (inclusion criteria, patient numbers and treatment schedules applied) between the two studies, the model was run separately for the two groups of trial results.

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years gained (LYG) and quality-adjusted life-years (QALYs). The LYG were obtained from the model, while the utilities were derived from a published cross-sectional study. All utility values were reported. The benefits were discounted at an annual rate of 3%.

Direct costs
The direct costs included in the analysis were clopidogrel (75-mg dose), the cost after nonfatal MI or stroke (including acute hospitalisation, inpatient and outpatient care and pharmaceuticals) incurred during month 1, months 2 to 12 and the second and subsequent years, and the cost of hospitalisation due to gastrointestinal bleeding. Summary costs per patient for each category were reported separately for each country. Resources use was not reported. The costs were mainly derived from published sources. The direct costs were appropriately discounted at an annual rate of 3% and were reported for the price year 2005.

Statistical analysis of costs
The quantities and the costs were treated deterministically in the base-case.

Indirect Costs
For Sweden, the summary mean category costs of productivity losses due to MI (month 1 and months 2 to 12) and stroke (month 1 and months 2 to 12, second and subsequent years after stroke) were reported.

**Currency**
Euros (EUR).

**Sensitivity analysis**
Various one-way sensitivity analyses were performed for each country (Germany, France and Sweden) separately. The parameters tested in the sensitivity analysis (treatment effects, costs and the discount factor) and the ranges over which they were varied were reported in full. Uncertainty in the model parameters was further tested using a second-order stochastic sensitivity analysis. A bootstrap technique with 1,000 replicates of the means was used to determine the distributions of the cost parameters, survival parameters and those risk parameters for the period of 2 to 12 months. One thousand simulations were performed and data were drawn randomly from their underlying distributions.

**Estimated benefits used in the economic analysis**
The incremental benefits (LYG) were reported.

For a patient cohort with the same characteristics and even rates of the CLARITY population, treatment with clopidogrel plus ASA up to 1 year compared with ASA alone resulted in 0.144 LYG in Sweden, 0.143 LYG in Germany and 0.145 LYG in France.

For a patient cohort with the same characteristics as the study population of the COMMIT study, the clopidogrel strategy resulted in 0.194 LYG in Sweden, 0.192 LYG in Germany and 0.195 LYG in France when compared with ASA alone.

Estimated QALYs were not reported.

**Cost results**
The incremental costs per patient were reported.

From the health care payer perspective and for a patient cohort with the same characteristics and event rates of the CLARITY population, the clopidogrel strategy compared with ASA alone resulted in cost-savings of EUR 111 in Sweden, in an incremental cost of EUR 13 in Germany, and in cost-savings of EUR 367 in France. For the same cohort of patients, when applying a societal perspective (direct and indirect costs), the cost-savings amounted to EUR 850 per patient compared with ASA alone.

From a health care payer perspective and for a patient cohort with the same characteristics as the study population of the COMMIT study, the clopidogrel strategy compared with ASA alone resulted in an incremental cost of EUR 538 in Sweden, EUR 798 in Germany and EUR 545 in France. For the same cohort of patients, when applying a societal perspective the incremental cost amounted to EUR 407 compared with ASA alone.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios (ICERs) were reported as the incremental costs per additional LYG.

For a patient cohort resembling that of the CLARITY study, the clopidogrel strategy was dominant from a health care payer’s perspective (Sweden, France) and from a societal perspective (Sweden). In Germany, the clopidogrel strategy resulted in an ICER of EUR 92/LYG. When QALYs were used as the measure of benefit, the clopidogrel strategy was dominant in France and resulted in ICERs of EUR 2,711 and EUR 94 per extra QALY gained in Sweden and Germany, respectively.

For a patient cohort resembling the COMMIT study, the clopidogrel strategy resulted in an ICER of EUR 2,100/LYG.
and EUR 2,772/LYG from the perspectives of the health care payer and society, respectively, in Sweden. In Germany and France, the clopidogrel strategy resulted in ICERs of EUR 4,144/LYG and EUR 2,786/LYG, respectively. When QALYs were used as the measure of benefit, the clopidogrel strategy resulted in an ICER of EUR 5,452/QALY gained in Germany, EUR 3,674 in France, and was dominant in Sweden.

The sensitivity analyses demonstrated that, in all three countries, the results were most sensitive to the cost of added LYGs and the exclusion of costs after the second year from the analysis.

The results of the stochastic analysis were presented using cost-effectiveness acceptability curves. Observed oscillations regarding the CLARITY trial, in the probability of being cost-effective at various thresholds of willingness-to-pay (WTP), were attributed to the uncertainty surrounding the impact of the strategy on survival in the CLARITY study. The stochastic analysis for Sweden demonstrated that, at the commonly applied WTP threshold of EUR 50,000 per QALY, the clopidogrel strategy was cost-effective in around 90% of the simulations (CLARITY cohort) and 84% when applying COMMIT results, indicating differences in certain end points between the two studies.

**Authors’ conclusions**
The treatment of patients with ST-segment elevation myocardial infarction (STEMI) with clopidogrel for up to 1 month and up to 1 year was cost-effective.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators was explicitly justified. ASA seems to have represented standard practice in the authors’ setting. You should decide if this comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
Basic estimates of effectiveness were derived from published research (the COMMIT, CLARITY and CURE trials). Data from the literature were combined in order to estimate the risk of events and to conduct survival analysis, using logistic regression and Weibull survival regression respectively. Although the authors did not report the search methods used to identify the included studies, the parameters were mainly derived from large multi-centre randomised, double-blind controlled trials, which potentially have a high level of internal validity. Some justification for the selection of these trials would have made the validation of this judgement simpler.

**Validity of estimate of measure of benefit**
The authors used LYG and QALYs as the measures of benefit in the economic analysis. The estimation of health benefit (LYG) was derived using a Markov model. The utilities were taken from a published cross-sectional study and no details of the valuation method were reported. All benefits were appropriately discounted.

**Validity of estimate of costs**
The analysis of the costs for the three countries was performed from the perspective of the health care payer, while the analysis for Sweden was also undertaken from a societal perspective. It is unclear whether all the relevant categories of costs were included in the analysis, as only summary costs were reported, hence making it impossible to know which aspects of costs were included. The costs were obtained from published sources, but it is not clear that adjustments for inflation were conducted. The unit costs and resource use were not reported separately, which will hinder the analysis being easily reworked for other settings. However, uncertainty surrounding the cost estimates was investigated in the sensitivity analysis. Discounting and the price year were reported.

**Other issues**
The authors compared their results with those from published studies and discussed variations in the results. Although the authors do not appear to have presented their results selectively, stochastic sensitivity analysis and cost-effectiveness acceptability curves were conducted only for Swedish data, owing to a lack of access to primary data. The authors’ conclusions appear to adequately reflect the scope of the analysis. The issue of the generalisability of the results was not directly addressed.

The authors reported a number of further limitations to their study. For example, there was limited data available on
STEMI patients, which meant that data had to be obtained and combined for general MI and on non-STEMI patient populations. However, evidence in the literature suggested that the long-term results were unlikely to have been affected. As the clinical outcomes were derived from published literature, they may not coincide with those from current clinical practice and updated medical treatment. In addition, the study population based on register data did not meet all the exclusion criteria of the two parent clinical studies, and this might have led to an underestimation of event risks and overall results.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice. They called for further research to estimate the long-term effects of clopidogrel in STEMI patients. An economic evaluation should also be carried out to account for the latest changes in the treatment of acute coronary syndrome.

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Other publications of related interest
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