Cost-effectiveness of clopidogrel plus aspirin for stroke prevention in patients with atrial fibrillation in whom warfarin is unsuitable

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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.

CRD summary
This study assessed the cost-effectiveness of clopidogrel plus aspirin, compared with aspirin alone, for the prevention of stroke in patients with uncomplicated atrial fibrillation. The authors concluded that clopidogrel plus aspirin appeared to be cost-effective for patients at a high risk of ischaemic stroke and a low risk of major bleeding. There were some limitations in the reporting and the methods, and the authors’ conclusions may not adequately reflect the uncertainty in the cost-effectiveness results.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of clopidogrel plus aspirin for the prevention of stroke in patients with uncomplicated atrial fibrillation, who were 65 years old, had a low risk of bleeding, and were unsuitable for warfarin. Patients had a Congestive heart failure, Hypertension, Age, Diabetes, and Stroke (CHADS\textsubscript{2}) score of two.

Interventions
Clopidogrel, 75mg per day, plus aspirin, 75mg to 100mg per day, was compared with aspirin alone.

Location/setting
USA/out-patient secondary care.

Methods
Analytical approach:
A Markov model was constructed of the ongoing risk of stroke, myocardial infarction and adverse events, over 35 years. The clinical data were from one trial. The authors stated that the perspective was that of Medicare, a US third-party payer.

Effectiveness data:
The key clinical outcomes included stroke, myocardial infarction, and the risk of major haemorrhage. The model included baseline clinical data on the risks of these outcomes for patients on aspirin, and the relative risks of these outcomes for patients on clopidogrel and aspirin. The relative risks and most of the baseline clinical data were from a randomised controlled trial (RCT); the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-A trial (Connolly, et al. see 'Other Publications of Related Interest' below for bibliographic details). Other sources included observational studies and the US Census Bureau. Assumptions were made for the increased risk of adverse events over time, and the increase in risk of death after a stroke.

Monetary benefit and utility valuations:
The utility values were estimated, for a range of states including healthy (on each treatment), neurologic events, bleeds, and myocardial infarction, using scores from published studies and economic models. The utility for being healthy on clopidogrel plus aspirin was assumed to be slightly lower than that on aspirin alone, due to having to take two drugs instead of one.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs). Future benefits were discounted at a rate of 3% per annum.

Cost data:
The direct costs included those of the drugs, and in-patient and out-patient care for a range of adverse events and complications (minor or severe stroke, reversible ischaemic neurologic event, intracranial bleed, gastrointestinal bleed, other major or minor bleed, myocardial infarction, or death). The drug costs were estimated, using their average wholesale prices, and the costs of complications and adverse events were from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization 2008 data set or published estimates. The costs of major extracranial haemorrhages were estimated from the diagnosis-related group costs of a gastrointestinal bleed. The costs were inflated to 2011 US $, using the Consumer Price Index for medical care. Future costs were discounted at a rate of 3% per annum.

Analysis of uncertainty:
One-way sensitivity analysis was performed on all the model parameters, with values varied across preset plausible ranges. The chance of each treatment being cost-effective, at different willingness-to-pay thresholds, was estimated using 10,000 Monte Carlo simulations. The authors assumed triangular distributions for each parameter, defined by the likeliest, low, and high values.

Results
Aspirin resulted in 9.01 QALYs at a cost of $79,093, while clopidogrel plus aspirin resulted in 9.37 QALYs at a cost of $88,798. The incremental cost-effectiveness ratio (ICER) was $26,958 per QALY gained.

The one-way sensitivity analysis showed that the ICER was most sensitive to varying the estimates for the CHADS2 score, the major bleeding risk on aspirin, the relative risk decrease in ischaemic stroke with clopidogrel, and the utility for clopidogrel plus aspirin. At a willingness-to-pay threshold of $50,000 per QALY gained, clopidogrel plus aspirin was no longer cost-effective when the CHADS2 score was less than one; the risk of major bleeding on aspirin was over 2.5% per patient-year; the relative risk decrease in ischaemic stroke on clopidogrel plus aspirin versus aspirin alone was less than 25%; or the utility of being healthy with atrial fibrillation on clopidogrel plus aspirin decreased to 0.95.

The likelihood of combined therapy being cost-effective was 55% at a willingness-to-pay threshold of $50,000 per QALY gained and 74% at a threshold of $100,000 per QALY gained.

Authors' conclusions
The authors concluded that clopidogrel plus aspirin appeared to be cost-effective, compared with aspirin alone, for stroke prevention in patients at a high risk of ischaemic stroke and a low risk of major bleeding. At a generic price for clopidogrel (likely to be available in the USA in 2012), combined treatment could be less costly and more effective than aspirin alone.

CRD commentary
Interventions:
The authors did not consider all the possible relevant interventions: rivaroxaban and dabigatran were mentioned as alternative drugs, approved by the Food and Drug Administration for stroke prevention. No clear justification was given for excluding these alternatives and the cost-effectiveness of any intervention depends on its comparators.

Effectiveness/benefits:
Few details of the RCT that provided the relative risk estimates were reported, making it difficult to assess if the data were appropriate and generalisable. This trial was clearly relevant, but the justification for choosing it was not reported and there might have been other relevant studies available in the literature. A literature search was reported for studies on anticoagulation. The model was comprehensive, incorporating a range of states, including adverse events. The relative risks and treatment appear to have been assumed to be constant for the 35-year time horizon. No details on the method of utility valuation and the values derived were reported.

Costs:
The cost items, estimates and sources were clearly reported and were relevant to the US Medicare perspective.
Discounting and the inflation of costs were clearly reported.

Analysis and results:
The model was clearly described, with a diagram provided. Assumptions on the structure of the model (the possible transitions) were clearly reported, but no justifications were given. The methods used to select the sources for the model inputs were not fully reported. The sensitivity analysis was well reported and the results were clearly presented, but the use of triangular distributions was inappropriate and the probabilistic sensitivity analysis might not accurately reflect the uncertainty in the results. The likeliest, low, and high values used to determine the triangular distributions were not reported and neither was the method used to determine them. The value ranges for the one-way sensitivity analysis were reported, alongside the main values, but the method used to derive the ranges was not stated.

Concluding remarks:
There were some limitations in the reporting and the methods. Not all the relevant interventions were considered; the justification for the choice of sources for the model inputs was unclear; and the authors' conclusions do not appear to adequately reflect the uncertainty in the cost-effectiveness results.

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Other publications of related interest

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