The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis

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Executive summary

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Executive summary

Background

Acute coronary syndrome (ACS) is a fissuring or rupturing of atheromatous plaques leading to occlusive thrombi in the arteries. Non-ST-elevation-ACS (NSTE-ACS) can be classified as unstable angina with undetectable markers but with electrocardiogram changes, or non-ST-elevation myocardial infarction (NSTEMI) where there is evidence of myocardial necrosis. Sixteen-year survival rates for men aged 50–59 years are 34% with a history of myocardial infarction (MI) and 53% with a history of angina, compared with 72% of those with no history of coronary disease. For patients with confirmed NSTE-ACS, UK guidelines recommend early treatment with antiplatelets, which are effective in preventing ischaemic vascular events in patients at increased risk. Guidance by the National Institute for Health and Clinical Excellence (NICE) in 2004 was based in part on a Technology Assessment Report undertaken by the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE), and published as a Health Technology Assessment (HTA) report (Main *et al*., 2004). The report presented the results of a systematic review assessing the clinical effectiveness and cost-effectiveness of clopidogrel in combination with aspirin for people with NSTE-ACS. Only one relevant trial was identified for inclusion in the systematic review [the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial]. For patients with NSTE-ACS at moderate to high risk of ischaemic events treated with clopidogrel, the NICE guidance recommended that it be given in combination with aspirin.

Objectives

The objective of this research project was to update the previous model, and formally assess the potential value and feasibility of further research to address the optimal duration of clopidogrel treatment using value of information (VOI) analysis and a Bayesian decision theoretic approach. In line with this we aimed to update the previous systematic review of the use of clopidogrel in combination with aspirin for patients with NSTE-ACS, investigating the optimal duration of treatment and effects of withdrawal from treatment.

Methods

We conducted a systematic review of the clinical effectiveness and cost-effectiveness literature. Ten electronic databases and internet resources were searched from 2003 to February 2007, including MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, CENTRAL and CINAHL. Randomised controlled trials (RCTs) of clopidogrel plus aspirin compared with aspirin alone were used to evaluate clinical effectiveness and safety. Inclusion criteria were broadened to include any comparator trial for duration of treatment studies, and any study design conducted in patients with NSTE-ACS, percutaneous coronary intervention (PCI), stroke, peripheral artery disease (PAD) or ST-elevation myocardial infarction (STEMI) for evidence of rebound (a reactivation of the condition or concentration of adverse events) on withdrawal of treatment. The primary outcomes for the evaluation of efficacy, safety and the duration of treatment were non-fatal MI, ischaemic heart disease (IHD) without MI, death and bleeding complications.

The systematic reviews were used to assist in updating the existing model in order to provide a more robust approach to evaluating the cost-effectiveness of alternative durations of clopidogrel. The previous work was also extended to include a formal assessment of the potential value of further research using VOI approaches. These approaches were applied to estimate the expected costs of decision uncertainty predicted by the model and the maximum value that can be placed on additional research aimed at reducing this uncertainty. The costs of decision uncertainty were quantified using the expected value of perfect information (EVPI). These were used to help identify the potential design and value of further research which could be undertaken in this area. Consideration was also given to the potential impact that the introduction of a generic version of clopidogrel may have on the VOI results.

Results

Two RCTs were included for the review of clinical effectiveness and safety. The only RCTs identified that evaluated different durations of

clopidogrel treatments were conducted in patients with stroke, PAD, STEMI or PCI. Two small RCTs and one uncontrolled retrospective cohort study were identified for the review of rebound after thienopyridine withdrawal in patients with medically-treated NSTE-ACS. When the criteria were broadened, five RCTs, two observational cohorts, nine case series and 33 case reports were identified in patients post-PCI, and two case series and two case reports were identified in patients with stroke, PAD or STEMI.

The CURE trial reported that the proportion of patients experiencing cardiovascular death, MI or stroke was lower in the clopidogrel group at 30 days [relative risk (RR) 0.79; 95% confidence interval (CI) 0.67–0.92) and from 30 days to 12 months (RR 0.82; 95% CI 0.70–0.95). Overall, clopidogrel seems to be effective in reducing adverse cardiovascular events in patients with NSTE-ACS at intermediate (RR 0.86; 95% CI 0.75–0.98) and high (RR 0.77; 95% CI 0.64–0.93) risk of ischaemic events, and there is evidence that clopidogrel increases the risk of bleeding when compared with aspirin in patients with intermediate risk of ischaemic events (RR 1.44; 95% CI 1.12–1.86). A post hoc analysis indicated that the treatment effect in the first 3 months may be greater than in later periods; however, this analysis comprised non-randomised comparisons. There were no direct comparisons of the effectiveness of different durations of clopidogrel treatment in patients with NSTE-ACS. The evidence available relating to the potential rebound effect on withdrawal of clopidogrel therapy in patients with NSTE-ACS was limited and provided no conclusive evidence of its presence or absence.

In terms of the cost-effectiveness of alternative durations of clopidogrel, the updated model reinforced the conclusions from the earlier analysis. That is, a policy of 12 months of clopidogrel for patients with NSTE-ACS appears to be cost-effective both in 'average' patients (i.e. based on the average across all patient risks considered) and in the subgroup of higher-risk patients (presence of any of the following: age > 70, presence of ST depression or diabetes), compared with shorter-term durations. The incremental cost-effectiveness ratio (ICER) of 12 months' duration ranged from £13,380 to £20,661 per additional quality-adjusted life-year (QALY) across the different scenarios considered. However, for lower-risk patients (absence of any of the risk factors) treatment with clopidogrel beyond 3 months does not appear to be cost-effective. The ICER of 12 months' treatment with clopidogrel varied between £49,436 and £58,691 per QALY. These conclusions appeared robust to alternative assumptions related to whether the relative effect of clopidogrel was assumed to remain constant over time or where the treatment effect in the first 3 months was assumed to be greater than in later periods.

Estimates of EVPI were markedly higher for the combined analysis of all patients (representing an average of the risks) and for analysis of high-risk patients alone, compared with those for lower-risk patients (ranging between £48.69 million and £108.4 million at a threshold of £30,000 per QALY). It was also acknowledged that more recent changes in routine clinical practice in the UK has shifted to the extent that the CURE trial itself (or the model presented here) may no longer considered to be representative of current practice for groups at high risk, and as such the EVPI results for this group of patients may be overstated.

At a threshold of £20,000–£30,000 per QALY, total EVPI ranged between £3.27 million and £20.38 million in the lower-risk group. Given that a trial is unlikely to be able to report until after the entry of generic clopidogrel, equivalent EVPI estimates for this scenario ranged between £10.8 million and £11.9 million. The expected value of partial perfect information (EVPPI) calculations demonstrated that approximately 40–45% of this value was related to the treatment effectiveness parameters for clopidogrel (i.e. those for which an RCT would be required).

Limitations and uncertainties

Our review was limited by the lack of available data. Although one additional trial was identified that provided information on the clinical effectiveness of clopidogrel in patients with NSTE-ACS, this trial was likely to be underpowered and reported limited results. Thus the CURE trial remains the primary source of data.

No studies directly compared different durations of clopidogrel treatment, and insufficient evidence was identified to adequately assess the clinical significance of any rebound effect after withdrawal of clopidogrel in these patients. Therefore, there is still a large degree of uncertainty surrounding both the optimal duration of clopidogrel treatment and the impact of withdrawal of clopidogrel treatment, which can only be addressed by further research.

The cost-effectiveness and VOI analyses are subject to a number of potential limitations. These relate not only to the limitations noted above pertaining

to the clinical effectiveness data, representing important assumptions and parameters of the model, but also to the uncertainty surrounding a range of other factors. Firstly, the issue of risk stratification is clearly an important consideration. However, it should be noted that the pragmatic approach to risk stratification applied in the decision model (due to limited patient numbers and information available from the epidemiological data used) dichotomised the population into two separate risk categories (higher- and lower-risk patients). This meant that consideration could not be given to a wider categorisation (i.e. including a third group to represent patients at intermediate risk). Similarly, these definitions are not directly comparable with other risk stratification approaches that have been applied elsewhere. Indeed, it should be recognised that the sample of patients included in the epidemiological data set were all hospitalised for NSTE-ACS and hence are likely to be more representative of patients at intermediate to high risk using conventional classifications. Thus, the interpretation of the results in low- and high-risk groups should be seen in this context. Secondly, changes in routine clinical practice (particularly for the high-risk group) may mean that the results presented here are more reliable for the lower-risk group. Finally, the results of the VOI demonstrate considerable variation in the potential value of further research. More importantly, the EVPI results present an upper bound to further research and hence do not provide both a necessary and a sufficient condition, even if the cost of trial fell below this amount. This is because a trial will resolve only a proportion of the uncertainty and, as such, the amount of uncertainty that is likely to be resolved would have to be assessed against the cost of the trial to ensure that any further research was considered an efficient use of resources.

Conclusions

- Clopidogrel combined with aspirin reduces adverse cardiovascular events in comparison with aspirin alone in patients with NSTE-ACS, but may increase the risk of bleeding.
- The optimal duration of clopidogrel treatment in patients with NSTE-ACS is uncertain and requires further research.
- There is some evidence that a rebound effect occurs following the withdrawal of thienopyridine treatment, but its clinical significance is uncertain.
- The results of the updated decision model suggest that durations of clopidogrel treatment beyond 3 months do not appear to be cost-effective in patients at lower risk. However, for an average-risk patient (and in higher-risk patients), 12 months of treatment with clopidogrel appear to be cost-effective.
- These conclusions appeared robust to alternative assumptions related to whether the treatment effect remained constant over a 12-month period or was assumed to decline after 3 months.
- There is considerable variation in the costs of uncertainty surrounding the different scenarios and populations considered. The validity of these may also be less reliable in the higher-risk groups owing to changes in clinical practice. The results in the lower-risk group suggested that the upper bound of the value of a future trial was between £10.8 million and £11.9 million (and of this total, approximately 40–45% related to parameters for which a randomised design would be essential).

Recommendations for research

An adequately powered, well-conducted RCT that directly compares different durations of clopidogrel treatment in patients with NSTE-ACS would ideally be required to provide more robust evidence in relation to the impact of clopidogrel withdrawal. The use of an RCT would minimise possible biases associated with establishing causality with any potential rebound effect and providing robust estimates of the relative effect of alternative durations of treatment, However, the design and cost of this trial need to be evaluated carefully in relation to the VOI estimates reported here and against other uses of NHS resources. In lower-risk groups, for which shorter durations of clopidogrel appear more cost-effective, it would seem unlikely that an adequately powered RCT would be considered to provide value for money owing to the significant cost that would be required to undertake such a study and the cost of the uncertainty that such a trial might resolve.

Publication

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/19/01. The contractual start date was in April 2007. The draft report began editorial review in May 2008 and was accepted for publication in December 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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