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


CRD summary
This update review suggested that clopidogrel was effective for reducing adverse cardiovascular events in patients with non-ST-elevation acute coronary syndrome. There was insufficient evidence to enable conclusions to be drawn on treatment duration and a rebound effect on withdrawal of treatment. This was a generally well-conducted review and the authors’ conclusions appear to reflect the limited evidence available.

Authors' objectives
To update a previously published systematic review that investigated the clinical and cost-effectiveness of clopidogrel in combination with aspirin for the treatment of patients with non-ST elevation acute coronary syndrome (NSTE-ACS); including an investigation of the optimal treatment duration and effects of withdrawal of clopidogrel.

Searching
Ten electronic databases, including MEDLINE, EMBASE, BIOSIS Previews and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions. The main search was conducted between 2003 and February 2007. A separate search was conducted without date restrictions for studies that related to withdrawal.

Study selection
Randomised controlled trials (RCTs) that compared safety and efficacy of clopidogrel in combination with aspirin versus either placebo plus aspirin or aspirin alone in patients with NSTE-ACS (unstable angina or non-ST-elevation myocardial infarction (NSTEMI)) were eligible for inclusion. The primary outcomes of interest were non-fatal myocardial infarction, ischaemic heart disease without myocardial infarction, death and bleeding complications. Secondary outcomes included refractory ischaemia, severe ischaemia, heart failure, revascularisation, unstable angina and other vascular or adverse events. Studies administered similar initial and daily doses of clopidogrel. Aspirin doses in the control arm differed.

Any comparator trial that investigated duration of treatment was eligible if it directly compared outcomes for different clopidogrel treatment durations in patients with NSTE-ACS. Where data on these patients were not available, patients who had undergone a percutaneous coronary intervention, suffered stroke, peripheral artery disease (PAD) or ST-elevation myocardial infarction (STEMI) were also eligible. The primary and secondary outcomes of interest were similar to studies of safety and efficacy. Studies administered varying doses of clopidogrel (with or without aspirin) and ticlopidine. In studies of populations other than NSTE-ACS, many patients had undergone stent implantation.

For the outcome of treatment withdrawal, studies of any design in a wide range of patients were eligible. Studies could evaluate any thienopyridine (clopidogrel, ticlopidine or prasugrel) with or without aspirin if they reported changes in biomarkers as the primary outcome and occurrence/rates of adverse events post-withdrawal as the secondary outcome. Studies administered varying doses of clopidogrel (with or without aspirin) and ticlopidine. In studies of populations other than NSTE-ACS, many patients had undergone stent implantation.

Two reviewers independently screened potentially relevant studies for inclusion. Any disagreements were resolved by consensus or referral to a third reviewer.

Assessment of study quality
Two reviewers independently assessed quality of RCTs based on randomisation, allocation concealment, blinding, reporting of withdrawals, sample size and intention-to-treat analysis. Disagreements were resolved by consensus.

Data extraction
One reviewer performed data extraction and this was checked for accuracy by a second reviewer. Data on incidence of each outcome and number of patients who required hospitalisation were extracted, along with statistical analyses reported by individual studies (included relative risk (RR), absolute risk reduction and relative risk reduction). Attempts were made to obtain additional data on clinical effectiveness from authors of included studies. Discrepancies were resolved by consensus and referral to a third reviewer if necessary.

**Methods of synthesis**
Due to clinical heterogeneity, results were presented as a narrative synthesis and in tables.

**Results of the review**
**Safety and efficacy studies** (two RCTs, n=12,648, one study was rated as good quality): The two RCTs reported that clopidogrel in combination with aspirin was more effective than placebo plus aspirin. One RCT reported greater effectiveness in reduced risk of cardiovascular death, non-fatal myocardial infarction or stroke at 30 days (RR 0.79, 95% CI 0.67 to 0.92) and this continued up to 12 months (RR 0.82, 95% CI 0.70 to 0.95). The second RCT reported a greater reduction in non-fatal myocardial infarction, recurrent ischaemia and cardiovascular-related death (RR 0.56, 95% CI 0.28 to 1.13) and a reduction in the proportion of patients who required hospital admission (RR 0.67, 95% CI: 0.37 to 1.21), but these results were not statistically significant.

**Other studies**: Eleven RCTs, one retrospective cohort study (n=3,137), two observational cohorts, 11 case series, and 34 case reports (not possible to calculate the total number of patients included in these studies) were included in the review. One RCT that assessed duration of treatment and one RCT that assessed rebound were of good quality. There were no studies that assessed clopidogrel treatment durations in patients with NSTE-ACS. Findings on the rebound effect following withdrawal of clopidogrel in patients with NSTE-ACS were mixed and were reported in the review. Evidence from studies that investigated clopidogrel treatment durations and rebound effect in patients other than those with NSTE-ACS were reported in the review.

**Cost information**
An existing decision model was revised to estimate costs and cost-effectiveness of alternative durations of clopidogrel treatment in patients with NSTE-ACS. This concluded that at a threshold of £30,000, 12 months of treatment with clopidogrel appeared to be cost-effective in average patients (based on average across all patient risks considered) and high-risk patients (aged >70 years, presence of ST depression or diabetes) compared with shorter treatment durations. The incremental cost-effectiveness ratio (ICER) of 12 months duration ranged from £13,380 to £20,661 per additional quality of adjusted life year (QALY) gained across different scenarios. Treatment with clopidogrel beyond three months did not appear to be cost-effective in lower-risk patients (those without any of the risk factors).

**Authors' conclusions**
The evidence suggested that clopidogrel was effective in reducing adverse cardiovascular events in patients with NSTE-ACS. The greatest benefit was in the first three months. Evidence that related to effectiveness of different treatment durations of clopidogrel or the presence or absence of a rebound effect on withdrawal of treatment was insufficient to enable conclusions to be drawn.

**CRD commentary**
The review question was clear and was supported by clearly defined inclusion criteria. A comprehensive search of the literature was undertaken without language restrictions, which reduced potential for language bias. There was no apparent search for unpublished data, which meant that potentially relevant papers may have been missed. Each stage of the review process was undertaken in duplicate, which minimised potential for reviewer error and bias. The quality of RCTs was assessed appropriately, but the overall quality was poor as study methods were not reported clearly. A narrative synthesis was appropriate given the presence of clinical heterogeneity. The authors attempted to expand the limited evidence available by broadening the inclusion criteria. The available evidence was limited and the results for the safety and efficacy were mainly based on one large RCT. This was a generally well-conducted review and the authors' conclusions appeared to reflect the evidence available. However, the limited quantity and quality of evidence should be borne in mind when interpreting the conclusions.

**Implications of the review for practice and research**
Practice: The authors stated that there was evidence of some rebound effect following withdrawal of clopidogrel, but its clinical significance was unclear.

Research: The authors stated that a large well-conducted RCT was required to compare different durations of clopidogrel treatment in patients with NSTE-ACS to determine optimal treatment duration and address the potential rebound effect associated with clopidogrel withdrawal.

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