Impact of clopidogrel loading dose on clinical outcome in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis


CRD summary
This review concluded that high clopidogrel doses (600mg) reduced the rate of major adverse cardiovascular events without increasing the incidence of major bleeding events in patients undergoing percutaneous coronary intervention one month after the start of therapy. Although these conclusions accurately reflect the results of the review, their reliability may be limited by concerns about publication bias and review methodology.

Authors' objectives
To compare the efficacy and safety of standard (300 mg) versus high (600 mg) loading dose of clopidogrel in patients undergoing percutaneous coronary intervention at one month after start of therapy.

Searching
MEDLINE, EMBASE, the Cochrane Central Database of Controlled Trials (CENTRAL) and Web of Science were searched without language restrictions up to March 2009. Search terms were reported. References of identified studies were checked.

Study selection
Randomised controlled trials (RCTs) or non-randomised controlled studies that reported on the use of clopidogrel loading doses in patients undergoing percutaneous coronary intervention were eligible for inclusion; follow-up at one month was required. Studies had to report the rate of major adverse coronary events or rate of bleeding events and the duration of follow-up. Non-randomised studies were required to report adjusted estimates of effect.

Studies included patients with ST-elevation and non-ST elevation myocardial infarction undergoing percutaneous coronary intervention; one study enrolled patients with acute coronary syndrome. Varying definitions of outcomes were employed.

The authors did not state how many reviewers selected the papers for inclusion.

Assessment of study quality
The studies were assessed for quality using the criteria of generation of randomisation sequence, allocation concealment, blinding, blinded outcome assessment, use of intention to treat (ITT), and incomplete outcome data assessment.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to permit the calculation of risk ratios (RRs) with 95% confidence intervals (CIs); where non-randomised studies reported odds ratios, these were converted to risk ratios. Adjusted hazard ratios were accepted as risk ratios.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled risk ratios with 95% confidence intervals were calculated using fixed-effect and random-effects models of meta-analysis. Heterogeneity was assessed using $X^2$ and $I^2$.

Sensitivity analyses were used to explore the impact of randomised versus non-randomised studies and low-risk versus
high-risk of bias in randomised studies. An interaction test was performed to assess the impact of each of these study
types on treatment effect. Numbers needed to treat (NNT) were calculated in some instances. The subgroup of trials
including patients presenting with acute coronary syndrome was also assessed.

Publication bias was assessed using the Egger regression test and visual inspection of funnel plots.

Results of the review
Seven studies (n=25,383 patients) were included in the review, of which five were RCTs. Four RCTs were judged to be
at low risk of bias. Follow-up in all trials was 30 days.

Major adverse coronary events: There was a statistically significant lower incidence of major adverse coronary events
in patients treated with 600mg loading dose of clopidogrel compared with those receiving 300mg loading dose in the
fixed-effect analysis (RR 0.78, 95% CI 0.69 to 0.88; $I^2=43\%$) and the random-effects analysis (RR 0.66, 95% CI 0.52
to 0.84; $I^2=43\%$). Results of sensitivity analyses were also reported. The test of interaction revealed no impact of study
design on treatment effect.

Myocardial infarction and death composite outcome: There was a statistically significant reduction in the composite
outcome (RR 0.52, 95% CI 0.29 to 0.99; $I^2=52\%$; random-effects model).

Major bleeding events: There was no statistically significant difference between the 600mg and 300mg clopidogrel dose
groups for the incidence of major bleeding events (RR 0.91, 95% CI 0.73 to 1.15; $I^2=0\%$; random-effects model); this
was replicated in the fixed-effect model. Excluding the largest study from the analysis did not change the non-
significant result.

The authors stated that the funnel plots were not ideally shaped.

Authors' conclusions
Intensified clopidogrel loading with 600mg reduced the rate of major adverse cardiovascular events without increasing
the incidence of major bleeding events in patients undergoing percutaneous coronary intervention during one month
follow-up.

CRD commentary
The review question and inclusion criteria were clear. The authors searched several relevant databases without language
restrictions, reducing the chances of selection bias or omission of relevant studies. Assessment of publication bias using
funnel plot assessment was problematic with so few included studies, but the authors considered that publication bias
might be indicated by their analysis; results of the Egger regression test were not reported. The authors did not report
using methods designed to reduce reviewer bias and error at any stage of the review process.

The assessment of study quality used appropriate criteria; the results of the assessment were used to inform the
synthesis, although there was very limited reporting of the process. There was little information reported on population
characteristics. The synthesis appeared appropriate. Reasonable steps were taken to explore the impact of pooling RCTs
and non-randomised studies. The authors' conclusions reflected the clear results from studies including a large number
of patients.

Although the authors' conclusions accurately reflect the results of the review, their reliability may be limited by
concerns about publication bias and review methodology, including the limited reporting of the quality appraisal.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need for studies to investigate the net benefit of higher clopidogrel dose
regimens compared with novel platelet inhibitors in patients undergoing percutaneous coronary intervention.
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.