Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis

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CRD summary

The authors concluded that about one in five patients who undergo percutaneous coronary intervention with stenting are labelled ex vivo clopidogrel unresponsive and are at increased risk of poorer cardiovascular outcomes. Differences between the studies, lack of systematic reporting of study quality, and pooling of different study designs make it difficult to determine the reliability of these conclusions.

Authors' objectives

To determine the prevalence of clopidogrel nonresponsiveness and the effect of unresponsiveness on clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) with stenting.

Searching

MEDLINE, EMBASE, the Cochrane CENTRAL Register and Web of Science were searched from inception to October 2006; the search terms were reported. In addition, reference lists in relevant studies and reviews, editorials and letters were screened, and authors of identified studies were contacted for more data. Studies reported as abstracts were eligible. No language restrictions were applied.

Study selection

Study designs of evaluations included in the review

Inclusion criteria were not specified in terms of the study design. The included studies were randomised controlled trials (RCTs), prospective cohort studies and case-control studies.

Specific interventions included in the review

Studies that evaluated clopidogrel for the prevention of coronary events and described the laboratory method used to assess the effects of clopidogrel on platelets were eligible for inclusion. In the included studies, the loading dose of clopidogrel was either 300 or 600 mg; all studies used a 75-mg maintenance dose. Where reported, studies also used concomitant aspirin at doses ranging from 75 to 325 mg.

Participants included in the review

Studies of patients undergoing PCI with stenting were eligible for inclusion.

Outcomes assessed in the review

Studies that reported the prevalence of clopidogrel nonresponsiveness, the occurrence of stent thrombosis (sub-acute) or other ischaemic events were eligible for inclusion. In the included studies, the time from loading dose of clopidogrel to measurement of responsiveness varied from less than 24 hours to more than 7 days.

How were decisions on the relevance of primary studies made?

Two reviewers independently selected the studies. Any disagreements were resolved by consensus and discussion with a third reviewer.

Assessment of study quality

Two reviewers independently assessed validity using the following criteria: control for confounders, measurement of exposure, completeness of follow-up and blinding. Case-control studies were also assessed for matching and case definition. Any disagreements were resolved by consensus and discussion with a third reviewer.

Data extraction

Two reviewers independently extracted the data using a standardised form. Any disagreements were resolved by consensus and discussion with a third reviewer. For each study, the crude odds ratio (OR) and 95% confidence interval

(CI) were calculated to demonstrate the relationship between clopidogrel unresponsiveness and cardiovascular events.

Methods of synthesis

How were the studies combined?

The pooled prevalence of clopidogrel unresponsiveness was estimated with its 95% CI using a general linear non-parametric mixed model. Pooled ORs with 95% CIs were calculated for cardiovascular events. Positive and negative predictive values (PPV and NPV, respectively) were calculated to illustrate the risk of events or no events in patients with clopidogrel unresponsiveness.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. Studies of prevalence were stratified by the following factors: method used to measure unresponsiveness; time between clopidogrel loading and measurement; clopidogrel loading dose; and concomitant dose of aspirin. Analyses were performed with and without fixed-effects for these variables and with a random-effect for each study. Multivariate linear regression analysis was used to examine the influence of various factors on prevalence. Separate analyses were undertaken for stent thrombosis and a composite measure of all clinical ischaemic events.

Results of the review

Twenty-five studies (n=3,688) were included: 2 RCTs (n=482), 3 case-control studies (n=233) and 20 prospective cohort studies (n=2,973).

Prevalence of clopidogrel responsiveness (22 studies, n=2,574).

The pooled prevalence of clopidogrel responsiveness was 21% (95% CI: 17, 25).
Statistically significant heterogeneity was detected (I-squared 90.5%; p<0.0001).
A higher prevalence of nonresponsiveness was found when it was measured within 24 hours (36%, 95% CI: 28, 44) of the loading dose compared with 24 to 48 hours (13%, 95% CI: 5, 21), 2 to 7 days (10%, 95% CI: 2, 18) or later (0%, 95% CI: 0, 7). There was no difference in prevalence across different time period when only studies that used a 600-mg loading dose of clopidogrel were analysed. A lower adjusted prevalence of nonresponsiveness was found when the loading dose of clopidogrel was 600 mg (7%, 95% CI: 0, 15) compared with 300 mg (22%, 95% CI: 15% 29). The prevalence of nonresponsiveness was not associated with the measurement method or concomitant dose of aspirin.

Clinical outcomes (11 studies, n=2,319).

The pooled OR showed a significant increase in the risk of cardiovascular outcomes for patients with clopidogrel unresponsiveness (8.0, 95% CI: 3.4, 19.1), based on 8 studies with data available for pooling. Statistically significant heterogeneity was detected (I-squared 63%; p=0.009). In their discussion, the authors stated that almost all studies showed a positive relationship between unresponsiveness and the risk of cardiovascular events. The pooled PPV for nonresponsiveness was 34% and the NPV was 92%. There was no significant difference in the pooled OR for clopidogrel nonresponsive patients in the occurrence of stent thrombosis (3 studies, n=218), but the OR was significantly increased for a composite end point of cardiovascular events (OR 12.0, 95%: 5.9, 24.4; 4 studies, n=837); the PPV was 33% and the NPV 96%.

Authors' conclusions

Approximately one in five patients undergoing PCI with stenting are labelled ex vivo clopidogrel unresponsive and are at increased risk of poorer cardiovascular outcomes.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention and outcomes. Inclusion criteria were not defined for study design and this led to the inclusion of various study designs. Several relevant sources were searched and attempts were made to minimise language bias; no attempts were made to minimise publication bias. Validity was assessed using defined criteria but, although some methodological problems were shown in the data extraction tables, the results were not reported systematically or summarised in the text; this makes it

difficult to obtain an overall assessment of study quality. Methods were used to minimise reviewer error and bias in the study selection, validity assessment and data extraction processes. Statistical heterogeneity was assessed and potential sources of heterogeneity amongst the studies were examined. However, it may not have been appropriate to pool randomised and non-randomised studies. The evidence presented appears to support the authors' conclusions, but differences between the studies, lack of systematic reporting of study quality, and pooling of studies with different designs mean that the reliability of these conclusions cannot be determined.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated the need for future studies to determine the method and timing of measurement of clopidogrel unresponsiveness that will best identify patients at the highest risk, and a need to develop treatments for these high-risk patients. The finding that a 600-mg loading dose of clopidogrel will reduce the risk associated with clopidogrel unresponsiveness needs to be confirmed in larger studies.

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