Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials

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CRD summary
This review concluded that dabigatran was associated with an increased risk of myocardial infarction or acute coronary syndrome. Despite the large number of patients included in the review, concerns about the appropriateness of the synthesis and the potential for publication bias mean that the reliability of the authors' conclusion is unclear.

Authors' objectives
To evaluate the risk of myocardial infarction or acute coronary syndrome with the use of dabigatran.

Searching
PubMed, Scopus and Web of Science were searched up to May 2011. Search terms were reported; a full strategy for the PubMed search was available in a separate online appendix.

Study selection
Randomised controlled trials (RCTs) of dabigatran that reported myocardial infarction or acute coronary syndrome (confirmed unstable angina, myocardial infarction, and cardiac death) were eligible for inclusion. Overall mortality was a secondary outcome.

Included trials used warfarin, enoxaparin or placebo as the comparator; all were non-inferiority trials. Included trials assessed stroke prophylaxis in atrial fibrillation, the prevention of deep vein thrombosis during joint replacement surgery, or the incidence of bleeding in acute coronary syndrome. None of the trials had myocardial infarction or acute coronary syndrome as the primary outcome. Duration of trials ranged from three months to two years; treatment duration ranged from eight days to two years.

The authors did not state how many reviewers selected the studies for the review.

Assessment of study quality
Trials were assessed for quality using the Jadad scale, awarding up to 5 points for the criteria of randomisation, blinding and treatment of withdrawals and drop-outs. A score of 3 or more was considered to indicate high quality. Funding sources were also noted.

The authors did not state how many reviewers were involved in the assessment of validity.

Data extraction
Data on the number of patients with the composite primary outcome was extracted by one reviewer and checked by a second; differences were resolved through discussion. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. In trials with multiple arms, data from groups treated with different doses of dabigatran were combined, as were arms using different comparators, to give binary comparisons.

Methods of synthesis
A Mantel-Haenszel fixed-effect meta-analysis was used to calculate pooled odds ratios with 95% confidence intervals. Heterogeneity between trials was assessed using the Q statistic and $I^2$.

Sensitivity analyses were conducted using random-effects models and Peto and inverse variance approaches, and by calculating relative risks and risk differences. The impact of using the revised results of one trial were assessed, as was that of excluding short-term trials or a trial with a Jadad score of less than 3 points. Random-effects meta-regression was used to explore the relationship between baseline risk and the odds ratio for acute coronary events.

Publication bias was assessed using funnel plots and the Egger test.
Results of the review
Seven RCTs (n=30,514 patients) were included in the review. Six trials were considered to be high quality.

Dabigatran was associated with an increased risk of myocardial infarction or acute coronary syndrome (237 out of 20,000 patients or 1.19%) than control interventions/placebo (83 out of 10,514 patients or 0.79%; OR 1.33, 95% CI 1.03 to 1.71). Heterogeneity was low and there was consistency between analyses. Sensitivity analyses did not significantly alter the findings. There was no evidence of publication bias.

Overall mortality was significantly lower in the dabigatran (945 out of 19,555 patients or 4.83%) than in the control groups (524 out of 10,444 patients or 5.02%; OR 0.89, 95% CI 0.80 to 0.99).

Authors’ conclusions
Dabigatran was associated with an increased risk of myocardial infarction or acute coronary syndrome in a broad spectrum of patients when tested against different controls.

CRD commentary
The review question and inclusion criteria were clear although studies reporting only mortality appeared to be excluded. Three relevant databases were searched, but no attempts were reported to identify unpublished studies. This may have increased the risk of publication bias and, while a subsequent evaluation did not find evidence of it, the tests used to assess publication bias were unreliable as only a small number of studies were included. The authors reported using a method designed to reduce reviewer bias and error in the extraction of data, but not at other stages of the review process.

Although trial quality was assessed, the use of a composite score from a limited checklist was not very informative and the ability to use quality to inform the synthesis was consequently restricted. The synthesis used a number of methods and included attempts to assess and explore statistical heterogeneity, but the appropriateness of combining trials with a high degree of clinical heterogeneity was unclear, as was the rationale for some of the exploratory analyses. There was no stratification of analyses based on the indication for use of dabigatran.

The authors’ conclusion reflected the results of the review, which included trials comprising a large number of patients. Despite this, concerns over the pooling of clinically heterogeneous data, even for the assessment of adverse events, and the potential for publication bias mean that the reliability of the conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that clinicians should consider the potential for serious cardiovascular adverse effects with the use of dabigatran.

Research: The authors stated that the cardiac risk associated with dabigatran should be further investigated, particularly when used in populations at high risk of myocardial infarction or acute coronary syndrome.

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