Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes


CRD summary
The review found that the antithrombotic drugs prasugrel and ticagrelor seemed to have similar efficacy and safety for acute coronary syndrome and that both were superior to clopidogrel. Given limitations in the review process, the limited search, failure to report trial quality, the small number of included trials, and questionable use of indirect comparisons, these conclusions should be regarded with caution.

Authors' objectives
To compare prasugrel versus ticagrelor antithrombotic therapy for patients with acute coronary syndromes.

Searching
PubMed was searched in February 2010 with no language restriction. Search terms were reported. ClinicalTrials.gov was searched for further trials. References of primary studies, reviews, and the proceedings of the meetings of the American College of Cardiology, American Heart Association, European Society for Cardiology and Transcatheter Cardiovascular Therapeutics were checked.

Study selection
Randomised controlled trials (RCTs) that compared clopidogrel, prasugrel and/or ticagrelor in patients with acute coronary syndrome were eligible for inclusion. Trials were required to have at least one month follow-up and to use intention-to-treat analysis. Trials that included participants with stable coronary artery disease were excluded.

Primary outcomes were overall death and non-fatal myocardial infarction or non-fatal stroke (composite outcome) at the longest follow-up. The rate of major bleeding (defined using Thrombolysis in Myocardial Infarction criteria and not related to coronary artery bypass grafting) was the primary safety outcome. Secondary outcomes were overall death, cardiovascular death, myocardial infarction, stroke, definite or probable stent thrombosis (using Academic Research Consortium criteria), Thrombolysis in Myocardial Infarction (TIMI) major bleeding, TIMI major or minor bleeding, and drug discontinuation.

Participants in the included trials had a mean age of 61 to 63 years and were predominantly men (mean 62% to 64%). The rate of non-ST-elevation acute coronary syndrome ranged from 62% to 100%. Diabetes mellitus ranged from 23% to 25%. Participants with prior myocardial infarction ranged from 18% to 26%. Pretreatment with clopidogrel ranged from 27% and 46% (where reported). Glycoprotein IIb/IIIa inhibitor use ranged from 27% to 55%. From 42% to 99% of participants had percutaneous transluminal angioplasty; 1% to 10% had coronary artery bypass grafting.

Ticagrelor (90mg) was given twice daily for three or nine months (after an initial loading dose of 180mg in one trial). A Prasugrel (10mg) was given daily for 15 months after a loading dose (60mg). Both drugs were apparently given with aspirin. Clopidogrel (75mg) was given daily for three to 15 months after a loading dose of 300mg or 600mg. Data on time since drug discontinuation to surgery were poorly reported in the primary trials.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed trial quality. However, trials were required to use intention-to-treat analysis and rates of blinding were reported.

Data extraction
Odds ratios (ORs) and 95% confidence interval (CIs) were extracted or calculated from event rates in direct comparison groups. Data on participants in one trial (where participants received twice the dose of daily ticagrelor) were excluded from analysis. Primary trial authors were approached for additional data as required.
The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Trials of direct comparisons of prasugrel and ticagrelor versus clopidogrel were pooled using a fixed-effect model to calculate pooled odds ratios and 95% confidence intervals. Adjusted indirect comparison of the pooled estimates was conducted using published methods (Song 2003) to generate odds ratios that compared prasugrel with ticagrelor. Heterogeneity was investigated using $I^2$. Publication bias was not formally assessed due to the small number of included trials.

Results of the review
Three RCTs were included in the review including 33,222 patients (range 990 to 18,624), of whom 32,899 were included in analyses. All trials were double-blinded.

For all data pooled at 12 months, the combined prasugrel and ticagrelor groups had a significantly lower risks compared with clopidogrel for the composite outcome of overall death, non-fatal myocardial infarction or non-fatal stroke (OR 0.83, 95% CI 0.77 to 0.89; $I^2=0\%$), overall death (OR 0.83, 95% CI 0.74 to 0.93; $I^2=51\%$), non-fatal myocardial infarction (OR 0.79, 95% CI 0.73 to 0.86; $I^2=0\%$) and stent thrombosis (OR 0.61, 95% CI 0.51 to 0.74; $I^2=82\%$). Combined prasugrel and ticagrelor groups had a significantly higher risk of major bleeding unrelated to bypass surgery (OR 1.27, 95% CI 1.09 to 1.49; $I^2=0\%$), major or minor bleeding (OR 1.10, 95% CI 1.01 to 1.20; $I^2=82\%$) and drug discontinuation (OR 1.12, 95% CI 1.05 to 1.19; $I^2=0\%$). Rates of non-fatal stroke, any major bleeding, and major bleeding related to bypass surgery did not differ significantly between the groups.

In indirect comparisons between prasugrel and ticagrelor, there was no significant difference between the groups for any measures of effectiveness (death, non-fatal myocardial infarction and/or non-fatal stroke). Prasugrel was associated with a significantly lower risk of stent thrombosis (OR 0.64, 95% CI 0.43 to 0.93), but a higher risk of major bleeding (OR 1.43, 95% CI 1.10 to 1.86), major bleeding associated with bypass grafting (OR 4.30, 95% CI 1.74 to 10.64) and major or minor bleeding (OR 1.27, 95% CI 1.04 to 1.55). The groups did not differ significantly for rates of major bleeding not related to bypass surgery, minor bleeding or drug discontinuation.

Authors’ conclusions
Prasugrel and ticagrelor seemed to have similar efficacy and safety for acute coronary syndrome. Risk of stent thrombosis may be lower with prasugrel, but risk of bleeding may be higher. Both drugs were superior to clopidogrel.

CRD commentary
The objectives of the review were clear. The inclusion criteria were not reported in detail; it was unclear why a group of patients in one trial were omitted from analysis. The search was not restricted by language or publication status, but only one database of published studies was searched, so it was possible that some studies were missed. The review process was poorly reported, which made it difficult to judge whether steps were taken to minimise the risk of reviewer error and bias (such as having more than one reviewer independently conduct review processes). It was unclear whether trial quality was systematically assessed. The timing of outcome assessments was unclear. Appropriate methods were used to pool direct comparisons and assess heterogeneity, but where substantial heterogeneity was found ($I^2\geq82\%$ in four analyses), it was not addressed or discussed in the text. As the authors noted, the findings of indirect comparison meta-analyses can be largely hypothesis generating; they may be biased unless there is across-the-board comparability of trials. It was questionable whether the trials in the review were sufficiently similar to justify indirect comparison, in view of clinical and methodological differences between them (such as patient diagnosis, rate of percutaneous coronary intervention, duration of intervention) plus the high levels of statistical heterogeneity mentioned above. The authors noted that some data pertaining to bleeding risk was poorly reported in the primary trials.

In view of limitations in the review, including the limited search, failure to report trial quality, small number of trials and questionable use of indirect comparisons, the authors’ conclusions should be regarded with caution.

Implications of the review for practice and research
Practice: The authors stated that prasugrel or ticagrelor (plus aspirin) could be used instead of clopidogrel in patients...
with acute coronary syndrome without high risk of bleeding, although drug discontinuation for adverse effects was more likely with these drugs than with clopidogrel. Each type of treatment may have advantages in different clinical scenarios. Other implications for practice were stated in the review.

**Research:** The authors stated that further head-to-head randomised trials were needed in this area.

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