New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: a meta-analysis


CRD summary
The review concluded that new P2Y12 inhibitors decreased all-cause mortality and major ischaemic events after percutaneous coronary intervention compared with clopidogrel, but increased major and minor bleeding. Bleeding was not significantly increased for ST-segment elevation myocardial infarction patients. Uncertain study quality and grouping of different P2Y12 inhibitors together made the reliability of the authors’ conclusions unclear.

Authors’ objectives
To compare the efficacy and safety of new P2Y12 inhibitors versus clopidogrel after percutaneous coronary intervention.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1980 to January 2010 for publications in any language; search terms were reported. The bibliography of each retrieved article and relevant reviews, editorials and letters were handsearched. Full text articles, sub-studies and meeting abstracts were included.

Study selection
Randomised placebo-controlled trials (RCTs) that compared P2Y12 antagonists versus clopidogrel in percutaneous coronary intervention (PCI) patients were eligible for inclusion. All types of PCI were considered and included primary PCI (≤24 hours of symptom onset) and secondary PCI (>24 hours after symptom onset). Eligible studies had to include coronary patients where at least 70% of patients received PCI. The reference treatment had to be clopidogrel or (for short half-life intravenous P2Y12 inhibitors) placebo before clopidogrel administration. Studies had to provide data on both mortality and bleeding. The primary efficacy outcome was all-cause mortality. The primary safety outcome was thrombolysis in myocardial infarction bleeding (TIMI) non-coronary artery bypass graft major bleeding. Relevant outcomes were defined usually using definitions from the trials concerned. Relevant outcomes included the ischaemic events of cardiovascular death, myocardial infarction, stent thrombosis, stroke, major adverse cardiac events (MACE) and TIMI minor bleeding.

More than half of the studies compared new oral P2Y12 antagonists with clopidogrel. Two studies compared new intravenous P2Y12 inhibitors with an intravenous placebo with pre-PCI clopidogrel treatment. One study compared a new intravenous P2Y12 inhibitor with an intravenous placebo with post-PCI clopidogrel treatment. Half of the studies were phase II studies and half were phase III.

P2Y12 inhibitors included prasugrel (three studies and one additional sub-study, loading dose 60mg, maintenance dose 10mg in all three studies with alternatives of loading dose 60mg, maintenance dose 15mg or loading dose 40mg and maintenance dose 7.5mg in one study), cangrelor (two studies and one additional sub-study, 30µg/kg bolus then 4µg/kg/min for two to four hours), ticagrelor (two studies and two additional sub-studies, loading dose 180mg and maintenance dose 90mg twice daily) and elinogrel (one study; bolus range 10mg to 60mg). The loading dose of clopidogrel ranged from 300mg to 600mg and, where reported, long-term dosage was 75mg.

Ninety-four per cent of patients had acute coronary syndrome and 84% underwent PCI (range 42% to 100%). Patients included those with stable coronary artery disease, ST-segment elevation myocardial infarction (STEMI), non-STEMI, non-STEMI acute coronary syndrome and unstable angina. Sub-studies focused mostly on STEMI patients.

Follow-up ranged from 15 days to 15 months.

Three independent reviewers performed study selection.
Assessment of study quality
Criteria assessed included blinding, control for confounders, measurement of exposure and completeness of follow-up. No formal scoring system was used. Study quality was assessed by three reviewers independently.

Data extraction
Numbers of events were extracted and used to calculate odds ratios (OR) with 95% confidence intervals (CI). The percentage and type of PCI was extracted. Intention-to-treat (ITT) data were extracted. One small study reported major and minor TIMI bleeding combined. Three independent reviewers performed data extraction.

Methods of synthesis
Odds ratios and 95% CIs were pooled using an ITT analysis and a random-effects model (heterogeneity was expected). Results were confirmed using a fixed-effect model to avoid giving smaller studies too much weight. Analyses were performed for all patients, PCI patients (any PCI) and PCI for STEMI patients. Primary and secondary PCI patients were included for STEMI patients. An additional meta-analysis was performed for primary PCI STEMI patients alone. Between-study heterogeneity was determined using the Cochran Q (where p<0.1 indicated significant heterogeneity) and I^2. Publication bias was assessed visually using funnel plots. Sensitivity analyses omitted the largest study and cangrelor studies (an intravenous agent with a short half-life).

Results of the review
Eight studies were identified (n=48,469, range 70 to 18,624 from the table; the authors stated the total as n=48,599.) All were randomised double-blind controlled trials, three of which were phase 2 studies. There were four subgroup analyses of larger studies (n=25,366).

**Global analysis (eight RCTs):** New P2Y_{12} inhibitors versus clopidogrel significantly reduced death (OR 0.83, 95% CI 0.75 to 0.92), cardiovascular death (OR 0.82, 95% CI 0.72 to 0.92), MACE (OR 0.86, 95% CI 0.80 to 0.93), myocardial infarction, stent thrombosis and target vessel revascularisation. There was no significant difference for stroke. There was a significant increase for P2Y_{12} inhibitors versus clopidogrel for TIMI major bleeding (OR 1.21, 95% CI 1.05 to 1.40) and TIMI major or minor bleeding (OR 1.15, 95% CI 1.01 to 1.31). There was no significant heterogeneity for these analyses. Results were confirmed in a fixed-effect model.

**PCI-treated patients (any PCI) (six studies):** New P2Y_{12} inhibitors versus clopidogrel significantly reduced death (OR 0.85, 95% CI 0.75 to 0.96), cardiovascular death (OR 0.84, 95% CI 0.72 to 0.96), MACE (OR 0.87, 95% CI 0.79 to 0.95) and stent thrombosis (OR 0.60, 95% CI 0.44 to 0.81). There was no significant difference for stroke. A relative decrease in myocardial infarction (OR 0.86, 95% CI 0.74 to 1.01) was of marginal significance. There was a significant increase for P2Y_{12} inhibitors versus clopidogrel for TIMI major bleeding (OR 01.23, 95% CI 1.04 to 1.46) and TIMI major or minor bleeding (OR 1.25, 95% CI 1.11 to 1.40). Results were confirmed in a fixed-effect model. Sensitivity analysis after removal of the largest study produced similar results. Results for myocardial infarction and TIMI major bleeding were not significant. The result was still significant for TIMI major or minor bleeding.

**STEMI patients treated by PCI (four studies):** New P2Y_{12} inhibitors versus clopidogrel significantly reduced death (OR 0.78, 95% CI 0.66 to 0.92), cardiovascular death (OR 0.81, 95% CI 0.67 to 0.97), MACE (OR 0.82, 95% CI 0.73 to 0.92), stent thrombosis (OR 0.66, 95% CI 0.53 to 0.83; three studies) and myocardial infarction (OR 0.81, 95% CI 0.69 to 0.95). There was a significant increase in stroke for P2Y_{12} inhibitors versus clopidogrel (OR 1.48, 95% CI 1.07 to 2.07), but no significant difference between groups for TIMI major bleeding or TIMI major or minor bleeding (three studies). Results of sensitivity analysis after removal of the largest study were similar for most outcomes and still significant for death, MACE and stent thrombosis. Results were no longer significant for cardiovascular death, myocardial infarction and stroke. Sensitivity analysis restricted to primary PCI patients confirmed all results.

For all analyses similar results were obtained when cangrelor studies were removed from the analysis. Additional data
were available in the online version of the article.

There was no evidence of publication bias (funnel plots not presented).

Authors' conclusions
New P2Y\textsubscript{12} inhibitors decreased all-cause mortality and major ischaemic events after PCI compared with clopidogrel. The risk/benefit ratio was particularly favourable in PCI for STEMI patients in whom there was no significant increase in major bleeding compared to clopidogrel.

CRD commentary
The review addressed a well-defined question in terms of interventions, study design and relevant outcomes. One study inclusion criterion was that at least 70\% of participants should receive PCI, yet the authors reported lower percentages of patients who received PCI in three included studies. Relevant databases were searched in any language. It appeared that unpublished studies were not considered. Publication bias was assessed and none was found. Suitable criteria were used to assess study quality, but minimal details were reported. Efforts were made to reduce error and bias throughout the review process. No methods for resolving differences between reviewers were reported. Relevant study details were reported, but no details were given of patient age and gender or loss to follow-up.

Statistical heterogeneity was assessed and little heterogeneity was reported for the initial analyses of all patients. The statistical method used for meta-analysis seemed appropriate. Suitable sensitivity analyses were carried out and provided the basis for some recommendations for practice. Six authors received research grants and/or lecture or consultancy fees from various pharmaceutical companies and other organisations.

The review was generally well performed and the overall number of patients in the studies was large. The authors reported some study limitations that related particularly to grouping different P2Y\textsubscript{12} inhibitors together in the analysis, hence the reliability of the conclusions was not entirely clear.

Implications of the review for practice and research
Practice: The authors stated that new P2Y\textsubscript{12} inhibitors had a good safety profile in STEMI patients. There was a risk of excessive bleeding with the new agents for PCI in any patient.

Research: The authors did not state any implications for research.

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