Non-ST-elevation acute coronary syndromes (NSTE-ACS): antiplatelets

A meta-analysis of 4 randomised controlled trials suggests that, when analysed together, prasugrel and ticagrelor are more effective than clopidogrel in reducing major cardiovascular events in people with NSTE-ACS, but are more likely to cause major bleeding. The meta-analysis also suggests differences between prasugrel and ticagrelor with regard to their efficacy and safety relative to clopidogrel, but shortcomings in the study limit the conclusions that can be drawn. Clopidogrel, prasugrel and ticagrelor are all recommended in NICE guidance as options for use in people with NSTE-ACS, in specified circumstances (see the NICE Pathway: acute coronary syndromes). When deciding on which antiplatelet to prescribe, discuss with the person the benefits and risks of each option to allow a shared decision to be agreed.

Overview and current advice

The term 'acute coronary syndromes' encompasses a range of conditions from unstable angina to ST-segment-elevation myocardial infarction (STEMI). Non-ST-elevation acute coronary syndromes (NSTE-ACS) include unstable angina and non-ST-elevation MI (NSTEMI) but exclude STEMI. If untreated, the prognosis is poor and mortality is high, particularly in people who have had myocardial damage. Management includes antiplatelet and antithrombin therapy and, often, coronary angiography with follow-on percutaneous coronary intervention (PCI) if indicated.

Initial treatment is with aspirin, started as soon as possible and continued indefinitely (unless contraindicated by bleeding risk or aspirin hypersensitivity) and usually in combination with another antiplatelet for up to 1 year. Other components of care are described in the NICE Pathway: acute coronary syndromes, which brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

There are 3 options within NICE guidance regarding choice of antiplatelet drug to add to aspirin: clopidogrel (see the NICE guideline on unstable angina and NSTEMI, published March 2010), prasugrel (for people undergoing PCI, see NICE technology appraisal guidance 317, published July 2014) or ticagrelor (see NICE technology appraisal guidance 236, published October 2011). Several
factors will influence the choice of treatment; especially the person’s risk of bleeding but also, for example, the fact that bivalirudin is licensed only for use with aspirin and clopidogrel, not with other antiplatelet drugs. In addition, European Society of Cardiology (ESC) guidelines in myocardial revascularisation (published August 2014) state that because clopidogrel is a prodrug with a slower onset of action and a larger variability in oral bioavailability, prasugrel or ticagrelor – which are faster-acting antiplatelet agents – are recommended in preference to clopidogrel for use in people with acute coronary syndromes undergoing PCI.

New evidence

Researchers conducted a meta-analysis to compare prasugrel and ticagrelor with clopidogrel in NSTE-ACS (Bavishi C et al. 2015). The meta-analysis included data relating to 31,470 patients (mean age 65 years) from 4 randomised controlled trials (RCTs). Approximately half the patients received clopidogrel and the others received prasugrel (n=9707) or ticagrelor (n=6244). Data for prasugrel came from 2 large RCTs of similar size (TRILOGY–ACS and TRITON–TIMI 38, contributing data from 9326 and 10,074 participants respectively), whereas the majority of data for ticagrelor came from 1 large RCT (PLATO, contributing data from 11,080 participants) supplemented by a second RCT about a tenth the size of the others (DISPERSE–2, n=990). Duration of follow-up varied from 12 weeks (DISPERSE–2) to 30 months (TRILOGY ACS). Follow up in TRITON–TIMI 38 was 15 months and 12 months in PLATO. The analysis, which used a random effects model, looked at the effects of prasugrel and ticagrelor agents together and separately compared with clopidogrel.

For the primary efficacy outcome, major adverse cardiovascular events (MACE) – that is, myocardial infarction (MI), stroke or death from cardiovascular causes – prasugrel and ticagrelor analysed together were statistically significantly superior to clopidogrel (relative risk [RR] 0.87, 95% confidence interval [CI] 0.80 to 0.95, p=0.002 overall). However, when they were considered individually, ticagrelor showed a statistically significant reduction in risk (RR 0.83, 95% CI 0.75 to 0.93, p=0.001) but prasugrel did not (RR 0.89, 95% CI 0.76 to 1.04 p=0.13). A similar result was found for the risk of MI alone (RR 0.86, 95% CI 0.75 to 0.98, p=0.03 for ticagrelor and 0.86, 95% CI 0.69 to 1.07, p=0.17 for prasugrel). Neither prasugrel nor ticagrelor produced a statistically significant difference in the risk of stroke or risk of death from cardiovascular causes alone, compared with clopidogrel. There was also no statistically significant difference in the risk of death from any cause, although none of the RCTs was adequately powered to evaluate this outcome.

The risks of major bleeding unrelated to coronary artery bypass grafting (non-CABG major bleeding) were found to be increased by prasugrel and ticagrelor analysed together compared with clopidogrel: RR 1.27, 95% CI 1.07 to 1.50 p=0.007. This was also the case for the composite of major and minor bleeding: RR 1.20, 95% CI 1.02 to 1.42, p=0.03. Ticagrelor did not show a statistically significantly increased risk of either bleeding outcome compared with clopidogrel: (RR 1.14, 95% CI 0.74 to 1.75, p=0.55 and 1.07, 95% CI 0.97 to 1.18, p=0.18 respectively). However, prasugrel statistically significantly increased the risk of both bleeding outcomes (RR 1.32, 95% CI 1.05 to 1.67, p=0.02 and 1.38, 95% CI 1.17 to 1.63 p=0.0002 respectively).

Commentary

Commentary provided by the Medicines and Prescribing Centre

The results of this meta-analysis appear to show that, in people with NSTE-ACS, ticagrelor reduces the risk of MACE (specifically MI) compared with clopidogrel but does not increase the risk of bleeding, whereas prasugrel does not reduce the risk of MACE but increases the risk of bleeding. However, the authors acknowledge several shortcomings of their meta-analysis and these limit the conclusions that can be drawn.
Firstly, patient-level data were not available so the analysis could not be adjusted to take account of factors such as severity of presentation, revascularisation strategy, dose of antiplatelet and use of other medicines, all of which might have affected the results. Secondly, the duration of follow-up varied from 12 weeks (DISPERSE–2) to 30 months (TRILOGY ACS); thus it is likely that short-, mid- and long-term risks were being assimilated. The 2 studies of similar size and follow-up (TRITON–TIMI 38 for prasugrel, 15 months, n=10,074; and PLATO for ticagrelor, 12 months, n=11,080) both showed almost identical statistically significant reductions in risk of MACE (RR 0.82, 95% CI 0.73 to 0.92 and 0.83, 95% CI 0.75 to 0.93, respectively) and increases in risk of non-CABG major bleeding (RR 1.40, 95% CI 1.05 to 1.87 and 1.36, 95% CI 1.06 to 1.76, respectively) compared with clopidogrel.

Clopidogrel, prasugrel and ticagrelor are all recommended in NICE guidance as options for use in people with NSTE-ACS, in specified circumstances (see the NICE Pathway: acute coronary syndromes). The authors of the meta-analysis suggest that use of prasugrel or ticagrelor should take account of an individual patient’s ischaemic and bleeding risk and this seems sensible advice. Where the person wishes to be involved in the decision, the risks and benefits of each option should be described in terms they can understand to enable a shared decision to be agreed.

**Study sponsorship**

No sponsorship for the meta-analysis was stated.

**References**


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