Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Acute coronary syndromes: Duration of dual antiplatelet therapy after drug-eluting stent implantation

A randomised controlled trial reported that continuing dual antiplatelet therapy beyond a year after stent implantation did not statistically significantly reduce the risk of the combined outcome of death or cardiovascular events compared with continuing aspirin monotherapy. However, continuing dual antiplatelet therapy was associated with a statistically significant increase in the combined risk of major or minor bleeding. This is consistent with NICE guidance that recommends dual antiplatelet therapy as a treatment option for up to 12 months after stenting.

Overview and current advice:

Acute coronary syndrome refers to a group of symptoms associated with acute myocardial ischaemia with or without infarction. It encompasses a spectrum of disorders or syndromes including acute myocardial infarction (MI) and unstable angina pectoris. In ST-segment-elevation myocardial infarction (STEMI), there is usually total occlusion of the affected coronary artery. STEMI is treated immediately with reperfusion therapy (thrombolysis, or percutaneous coronary intervention [PCI] with insertion of a stent to keep the artery open). Acute coronary syndrome without STEMI is classified as either unstable angina or non-ST-segment-elevation MI (NSTEMI), the difference being primarily in the severity of myocardial ischaemia. Immediate treatment for these conditions aims to prevent progression to total occlusion of the artery and, for people at high risk of MI, may include coronary revascularisation, either by means of PCI or coronary artery bypass graft.

NICE technology appraisal 152 recommends drug-eluting stents (DES) in PCI in certain circumstances. DES are bare-metal stents coated with a drug, usually an immune suppressant to reduce inflammation, or an antimitotic agent to reduce cell proliferation. The use of both DES and bare-metal stents is associated with an increased risk of thrombosis.

Long-term management of acute coronary syndromes includes the use of aspirin in combination with clopidogrel, prasugrel or ticagrelor. NICE guidance on secondary prevention of MI recommends offering indefinite treatment with aspirin to everyone who has had an MI (unless they are allergic to
aspirin, in which case clopidogrel is an alternative, or they have an indication for anticoagulation). In addition to aspirin:

- clopidogrel for up to 12 months is a treatment option in people who have had a STEMI and received a bare-metal stent or DES, or who have had an NSTEMI regardless of treatment: see NICE guidance on secondary prevention of MI and on unstable angina and NSTEMI
- prasugrel for up to 12 months is a treatment option in adults with STEMI, unstable angina or NSTEMI, who are having primary or delayed PCI: see NICE technology appraisal 317
- ticagrelor for up to 12 months is a treatment option in adults with STEMI that cardiologists intend to treat with PCI, unstable angina or NSTEMI: see NICE technology appraisal 236

In addition, offering clopidogrel in addition to aspirin for at least 1 month and considering continuing it for up to 12 months is a treatment option in people who have had a STEMI and medical management, with or without a fibrinolytic agent.

The NICE Pathways: myocardial infarction secondary prevention and acute coronary syndromes bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams.

**New evidence**

An open-label randomised controlled trial (RCT), ARCTIC-Interruption, has compared the safety and efficacy of continuing dual antiplatelet therapy beyond 12 months or reverting to aspirin monotherapy in people with a DES.²

This was the second phase of the ARCTIC RCT: the first phase (ARCTIC-Monitoring) compared 2 different antiplatelet strategies over 1 year in 2440 people after coronary stenting with a DES at 38 centres in France.²³ Among other exclusion criteria, people having primary PCI for STEMI or people having chronic anticoagulation were excluded from ARCTIC. Participants were randomised to a strategy of platelet function testing with antiplatelet treatment adjustment or antiplatelet treatment without platelet function assessment.²³ No difference was found between these 2 groups on the primary outcome, a composite of death from any cause, MI, stroke or transient ischaemic attack, urgent coronary revascularisation or stent thrombosis.

After 1 year, patients who had not had a cardiovascular event or significant bleeding were invited to enrol in the second phase of the ARCTIC RCT, ARCTIC-Interruption.² Nearly half of all patients from ARCTIC-Monitoring were not randomised to this second phase, the main reason (in 57% of cases) being ‘physician’s decision’. A total of 1259 people were re-randomised to either interruption of dual antiplatelet treatment (aspirin 75 mg–100 mg daily continued as monotherapy, n=624) or continuation of dual antiplatelet therapy for a further 6 to 18 months (n=625). Dual antiplatelet therapy consisted of aspirin plus either clopidogrel (90% of the continuation patients, usually 75 mg daily) or prasugrel 10mg daily. At the last follow-up visit, 77% of people in the continuation group and 17% of the discontinuation group were receiving clopidogrel or prasugrel and more than 94% were receiving aspirin. The primary endpoint was the same as for the first phase of the study (see above). The main safety endpoint was major bleeding (using the PCI-specific STEEPLE definitions).

After a median follow-up of 17 months, there was no statistically significant difference in the primary outcome for aspirin monotherapy compared with continued dual antiplatelet therapy (around 4% in both groups, hazard ratio [HR] 1.17, 95% confidence interval [CI] 0.68 to 2.03, p=0.58). This was also the case for the main secondary outcome, a composite of stent thrombosis and urgent revascularisation (1.6% compared with 1.3% respectively, HR 1.30, 95% CI 0.51 to 3.30, p=0.58), as well as for individual components of the primary endpoint. The observed difference in the rates of
major bleeds was not statistically significant (0.16% in the aspirin group compared with 1.10% in the
dual antiplatelet group, HR 0.15, 95% CI 0.02 to 1.20, p=0.07). However, aspirin monotherapy was
associated with a statistically significant reduction in the combined risk of major or minor bleeding
compared with continued dual antiplatelet therapy (0.5% compared with 1.9%, HR 0.26, 95%
CI 0.07 to 0.91, p=0.04).

ARCTIC-Interruption included fewer participants than was planned and a separate power calculation
was not performed. The small number of events may have resulted in the study having insufficient
statistical power (that is, it may have been unable to establish ‘beyond reasonable doubt’ whether or
not observed differences in outcomes were true differences rather than arising from the play of
chance). In addition, the study authors note that no conclusion can be made for ‘high-risk patients’,
because people who were at high risk of thrombosis or bleeding were excluded from ARCTIC-
Interruption.

**Commentary**

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Dual antiplatelet therapy is normally prescribed for 12 months following the use of drug-eluting
coronary stents. Therapy comprises of aspirin 75 mg once daily and one of clopidogrel 75mg daily,
prasugrel 5mg or 10mg daily, or ticagrelor 90mg twice daily. The aim of treatment is to prevent acute
stent thrombosis, which can carry a high risk of sudden death. However, the risk of stent thrombosis
persists well beyond one year following stent implantation. This new study addresses whether
routine use of dual antiplatelet therapy beyond one year confers additional benefit for the patient. The
results demonstrate that routine use of dual antiplatelet therapy confers no additional benefit and may
be harmful by causing increased bleeding. The results are consistent with current NICE guidance and
therefore, should not change current UK practice.

The study specifically excluded patients deemed to be at high risk of stent thrombosis. This included
patients who had already experienced one episode of stent thrombosis and might also have included
patients with stenting of the left mainstem and patients in whom multiple stents had been used
(although these were not specified by the authors). Some specialists currently use lifelong dual
antiplatelet therapy for these high risk patients; no conclusions can be drawn from the current study
about optimal treatment for this group.

What is perhaps more important for UK practice is whether the duration of dual antiplatelet therapy
can safely be shortened to 6, or even 3, months. With an increasingly elderly population undergoing
PCI, the issues resulting from 12 months’ of dual antiplatelet therapy (major bleeding, excessive
bruising and the necessity to postpone elective surgery, such as hip or knee replacement) are
increasingly problematic. The trade-off between less frequent bleeding episodes and a possible
increase in stent thrombosis is being addressed in several ongoing studies (such as NCT00661206
and NCT00977938).

**Study sponsorship**

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References


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