Myocardial infarction: risks and benefits of extended dual antiplatelet therapy

NICE guidance recommends offering dual antiplatelet therapy (DAPT) for up to 12 months after a myocardial infarction (MI), with aspirin monotherapy thereafter. A meta-analysis of 6 randomised controlled trials has examined the merits of extending DAPT beyond 12 months in people with stable ischaemic heart disease who have had an MI. The meta-analysis concludes that extending DAPT by a further 30 months on average (instead of switching to aspirin monotherapy) statistically significantly reduces the risk of major cardiovascular events but also increases the risk of major bleeding, with no statistically significant differences in the risk of death from cardiovascular or non-cardiovascular causes. The cost-effectiveness of extended-duration DAPT was not evaluated. Healthcare professionals should continue to follow NICE guidance regarding DAPT duration; decisions about adopting a longer duration should follow an informed discussion about the potential benefits and risks that takes into account the individual person’s clinical circumstances, values and preferences. The Cates Plots included in this commentary may help facilitate shared decision-making.

Overview and current advice

Myocardial infarction (MI) is usually caused by blockage of a coronary artery. MIs are traditionally divided into 2 types according to the changes they produce on electrocardiogram (ECG):

- ST-segment elevation myocardial infarction (STEMI), which is generally caused by complete and persisting blockage of the artery
- non-ST-segment elevation myocardial infarction (NSTEMI), reflecting partial or intermittent blockage of the artery.

STEMI is usually treated immediately with reperfusion therapy (thrombolysis or percutaneous coronary intervention [PCI] with insertion of a stent to keep the artery open). Immediate treatment for NSTEMI aims to prevent progression to total occlusion of the artery and may include coronary revascularisation, either by means of PCI or coronary artery bypass graft.

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 drug-eluting stent (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 unstable angina, NSTEMI, or STEMI that cardiologists intend to treat with PCI: see NICE technology appraisal 236.

In addition, NICE guidance on secondary prevention of MI recommends offering clopidogrel in addition to aspirin for at least 1 month and considering continuing it for up to 12 months in people who have had a STEMI and medical management, with or without a fibrinolytic agent.

A NICE Medicines Evidence Commentary (published in October 2014) discussed an open-label randomised controlled trial (RCT), ARCTIC- Interruption (n=1259), which 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 (CV) 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 study had several limitations (see the Medicines Evidence Commentary for details).

A second NICE Medicines Evidence Commentary (published in April 2015) discussed a double-blind RCT, the Dual Antiplatelet Therapy (DAPT) study, in which people who had received a DES and treatment with aspirin plus either clopidogrel or prasugrel for 12 months were randomised to receive a further 18 months' treatment with aspirin plus clopidogrel or prasugrel, or aspirin plus placebo. The longer duration of DAPT statistically significantly reduced the risk of stent thrombosis and major CV and cerebrovascular events at 30 months, compared with switching to aspirin monotherapy. However, continuing dual antiplatelet therapy was associated with a statistically significant increase in the combined risk of moderate or severe bleeding and an unexpected increase in non-CV death.

The NICE Pathway: myocardial infarction secondary prevention brings together all related NICE guidance and associated products on this condition in a set of interactive topic-based diagrams.

**New evidence**

A systematic review and meta-analysis has examined the risks and benefits of extended DAPT in people with a prior MI. It used data from 6 RCTs (including the DAPT study and ARCTIC- Interruption RCTs described above); total n=33,435. A single trial, PEGASUS-TIMI 54, contributed 63% of this pooled population. Nearly half (49%) of people had had a STEMI and 84% had undergone PCI. All the RCTs randomised people to receive either aspirin monotherapy or DAPT (aspirin plus clopidogrel, prasugrel or ticagrelor) for an extended period of time (mean 30 months, range 17–36 months), after an initial 1 year of DAPT. Three studies (n=28,584, 85% of the pooled population) were double blind; the remainder were unmasked open-label studies with blinded endpoint adjudication. Mean follow-up was 31 months (i.e. beyond the average period of extended DAPT). The authors state that, excepting unblinded study design, all studies were judged to be of high quality.

The primary outcome was major adverse CV events (MACE); a composite of CV death, non-fatal MI and non-fatal stroke. Secondary endpoints included the individual components of the primary outcome, death from any cause, non-CV death, major bleeding events (as defined in each trial) and (where relevant) stent thrombosis.

Extended DAPT reduced the risk of MACE compared with aspirin alone; risk ratio (RR) 0.78 (95% confidence interval [CI] 0.67 to 0.90); p=0.001. There were also statistically significant reductions in risk of CV death, MI, stroke and (where relevant) late stent thrombosis. Extended DAPT caused an increased risk of major bleeding compared with aspirin alone; RR 1.73 (95% CI 1.19 to 2.50), p=0.004. Rates of intracranial haemorrhage and fatal bleeds were not statistically significantly different in the 2
study groups, but these events were uncommon. There were no statistically significant differences in rates of non-CV death or all-cause mortality.

The meta-analysis included data at a study level only (rather than individual patient data) and those data often came from subgroups of RCTs. This increases the possibility that patient characteristics were not randomly distributed. The meta-analysis combined data from different types of patients, not all of whom had stents and, among those people who did have stents, it is not clear how many of these were DES and how many were bare-metal stents. RCT designs and intended primary outcomes differed and the studies were published between 2006 and 2015. It is likely that treatment plans, including concomitant treatments, differed among them reflecting contemporary practice; certainly, different antiplatelet drugs were used, and at different doses, for different durations. In at least some studies, only people who had not had a major bleed or MACE in the initial period of DAPT were eligible to participate. The authors did sensitivity analyses for MACE by sequential removal of individual trials (which yielded very similar RRs, except when the DAPT study was removed); and by defined subgroups such as the antiplatelet drugs used (but not dose or duration) and PCI or no PCI (but not type of stent), which did not suggest a statistically significant effect of these characteristics. However, no sensitivity analyses were reported for the risk of major bleeding. The cost–effectiveness of extended-duration DAPT was not evaluated.

Commentary

Commentary provided by Mr Sotiris Antoniou, Consultant Pharmacist, Cardiovascular Medicine, Barts Health NHS Trust

The term ‘acute coronary syndrome’ (ACS) encompasses STEMI, NSTEMI and unstable angina. DAPT with aspirin plus a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) is the current standard of care for patients with ACS who are treated either conservatively (medical management) or with mechanical reperfusion (PCI). The data support a decision to consider extending the duration of DAPT on an individual case-by-case basis taking into account the individual risk of future events and risk of bleeding. It is important to recognise that many of the studies excluded patients on concomitant long term anticoagulation and those with recent major surgery, prior intracranial haemorrhage, recent active bleed or bleeding diathesis. Therefore, the inclusion and exclusion criteria specified will not be entirely reflective of ‘real world’ people presenting with ACS.

More recently, the European Society of Cardiology (ESC) NSTEMI guidelines acknowledge the findings of recently published clinical trials in which the safety and efficacy of both short term and extended durations of DAPT have been investigated. The guideline does not make a definitive recommendation but suggests that treatment duration can be shortened (3-6 months) or extended (up to 30 months) in selected patients if required.

The adoption of currently available tools to assess ischaemic and bleeding risk may be helpful to appropriately risk stratify patients and identify those who would be suitable for and benefit most from extended-duration DAPT. The use of such tools could support clinical justification and rationale for such a strategy to the patients. Examples used in current practice are GRACE for ischaemic risk (as recommended within NICE UA/NSTEMI guidelines) and CRUSADE for the assessment of major bleeding.

Commentary provided by the Medicines and Prescribing Programme, NICE

Healthcare professionals should continue to follow NICE guidance regarding DAPT duration (see Overview and current advice); decisions about adopting a longer duration should follow an informed discussion about the potential benefits and risks that takes into account the individual person’s clinical circumstances, values and preferences.
The study authors calculated a number needed to treat (NNT) to prevent 1 MACE and a number needed to harm (NNH) for 1 major bleeding event. However, they did this from the total number of observed events as though they all came from 1 trial, and the study authors’ calculated NNT and NNH do not reflect the weighted pooled RR. It is not advisable to use this ‘treat as 1 trial’ approach for the rates of events in a meta-analysis, since it can give rise to misleading results and even, in extreme cases, appear to reverse the true direction of effect (due to Simpson’s paradox). It would be better to apply the pooled RR to the summed event rate in the control group (control event rate, CER), which gives an estimation of the baseline risk of the population, to calculate the absolute risk difference and NNT or NNH. Calculated thus, for a mean 30 months (range 17–36 months) of DAPT in addition to an initial 1 year of DAPT, the NNT for MACE over 31 months follow-up is 61 (95% CI 41 to 134). The NNH for major bleeding over that time is 125 (95% CI 61 to 481). To apply these results to the care of an individual person these figures would need to be adjusted for individual patients to take account of their individual baseline risk; for example, if the person’s baseline risk of major bleeding were estimated to be about double the mean risk in this meta-analysis (1.1%), the NNH would be halved. If their baseline risk of MACE were estimated to be about half the mean risk in this meta-analysis (7.5%), the NNT would be doubled. Tools are available to assist this risk assessment – see the Commentary by Antoniou.

As an alternative to NNTs and NNHs, and in keeping with the recommendation in NICE’s guideline on patient experience in adult NHS services to use a common denominator when discussing risk and benefits, these average benefits and harms can be expressed visually as Cates plots, which may facilitate shared decision-making. As with NNTs and NNHs, the numbers need to be adjusted to take account of the person’s individual baseline risks. As part of the discussion with the person, a healthcare professional might use a form of words similar to the following, pausing as needs be to check the person’s understanding or to answer questions:

“You have been taking 2 antiplatelet medicines, aspirin and [name of second antiplatelet] for a year now after your heart attack, to reduce the chance of you having another heart attack or having a stroke. There’s a choice now: you could either carry on taking the 2 medicines for longer, or you could switch to just taking aspirin on its own. Together, we have to weigh up the pros and cons of each of those options and what you feel about them, and I’d like to show you some diagrams that might help you decide.

“Imagine there were 1000 people like you, who have all had a heart attack and have already taken the 2 medicines for 1 year. This diagram shows the 1000 people:
Effect on risk of heart attack, stroke or dying from heart problems

*If all 1000 people now stop taking [name of second antiplatelet] and just take aspirin on its own, over the next 2½ years, and on average, 75 people would have a heart attack or stroke or die from heart problems (the red and yellow faces), but that means that 925 people would not (the green faces).*

*If all 1000 people decided to keep on taking aspirin and [name of second antiplatelet] for 2½ years, over that time and on average:

- 925 of them would not develop those problems, just as if they had changed to just taking aspirin on its own (the green faces)
- 59 people would still develop those problems, even though they kept on taking aspirin and [name of second antiplatelet] (the red faces)
- 16 people would be saved from developing those problems, because they kept on taking aspirin and [name of second antiplatelet] instead of just taking aspirin on its own (the yellow faces).*

*We can’t say if you would be 1 of the 16 people who benefit from keeping on taking [name of second antiplatelet] and aspirin, or 1 of the 984 people for whom doing so makes no difference to what would have happened if they had just taken aspirin on its own. We also don’t know what will happen after those 2½ years.*

*So, staying on [name of second antiplatelet] and aspirin has some benefits compared to taking aspirin on its own, but it also increases your risk of major bleeding [the nature and consequences of major bleeding may need to be explained to the person]. Let’s think about those same 1000 people, and look at this second diagram:*
Harms: major bleeding

“If all 1000 people decided to stop taking [name of second antiplatelet] and just take aspirin on its own, over the next 2½ years, and on average, 11 people would have a major bleed (the red faces), but that means that 989 people would not (the green faces and the green faces with a red cross).

“If all 1000 people decided to keep on taking aspirin and [name of second antiplatelet] for 2½ years, over that time

- 981 of them would not have a major bleed, just as if they had changed to just taking aspirin on its own (the green faces).
- 11 people would have a major bleed, but they would have done even if they had stopped taking [name of second antiplatelet] (the red faces)
- 8 people would have a major bleed because they kept on taking aspirin and [name of second antiplatelet] instead of just taking aspirin on its own (the green faces with a red cross).

“We can’t say if you would be 1 of the 8 people who have a major bleed because they keep on taking [name of second antiplatelet] and aspirin, or 1 of the 992 people for whom doing so makes no difference to what would have happened if they had just taken aspirin on its own. We also don’t know what will happen after those 2½ years.”

The healthcare professional could then seek to establish how the person feels about those options, and the relative importance they attach to avoiding cardiovascular events or major bleeds. The healthcare professional should make clear that they accept that the person may have different views from them about the balance of risks, benefits and consequences of treatments, and that the person has the right to decide whether to continue DAPT or aspirin monotherapy (as long as they have the capacity to make an informed decision and have been given and understand the information needed to do this).
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References

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