Acute coronary syndromes: further evidence on duration of dual antiplatelet therapy after drug-eluting stent implantation

A randomised controlled trial (RCT) found that continuing dual antiplatelet therapy beyond 12 months after drug-eluting stent implantation statistically significantly reduced the risk of stent thrombosis, and major cardiovascular (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. A meta-analysis of RCTs in people with various CV disorders, that included this RCT, compared dual antiplatelet therapy for at least 6 months with aspirin alone against dual antiplatelet therapy for less than 6 months. The meta-analysis did not find a statistically significant increase in all-cause, CV or non-CV mortality between the interventions. However, it is difficult to draw conclusions from the meta-analysis about the effect of extended dual antiplatelet therapy beyond 12 months after stent implantation. These studies are 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, 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 is a treatment option 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-Interruption1 (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).

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

Two further studies considering the duration of dual antiplatelet therapy have been published recently2,3. The Dual Antiplatelet Therapy (DAPT) study was an RCT in which 9961 people, who had been taking dual antiplatelet therapy for 12 months following insertion of a drug-eluting stent, were randomised to either continue taking a thienopyridine (clopidogrel or prasugrel) plus aspirin, or to take placebo plus aspirin, for a further 18 months2. People who had had a major adverse CV or cerebrovascular event, repeat revascularisation, moderate or severe bleeding, or who had not adhered to their thienopyridine at 12 months were excluded.

Compared with switching to aspirin monotherapy at month 12 and taking it for a further 18 months, continued dual antiplatelet therapy statistically significantly reduced the incidence of the primary efficacy endpoints at 30 months. Definite or probable stent thrombosis was reduced (0.4% versus 1.4%, hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.17 to 0.48, p<0.001), as were major CV and cerebrovascular events (death, MI, or stroke; 4.3% versus 5.9%, HR 0.71, 95% CI 0.59 to 0.85, p<0.001). In particular, the rate of MI was reduced in the group who continued dual antiplatelet therapy (2.1% versus 4.1%, HR 0.47, 95% CI 0.37 to 0.61, p<0.001). However, continuing dual antiplatelet therapy beyond 12 months was associated with an increase in the primary safety endpoint of moderate or severe bleeding at 30 months (2.5% versus 1.6%, HR 1.61, 95% CI 1.21 to 2.16, p=0.001) and continuing dual antiplatelet therapy was not found to be non-inferior to placebo plus aspirin for this endpoint. Severe or fatal bleeding were uncommon and did not differ between groups. In addition, an unexpected increase in death from any cause was seen in those who continued dual
antiplatelet therapy compared with aspirin monotherapy, although the statistical significance was borderline (2.0% versus 1.5%, HR 1.36, 95% CI 1.00 to 1.85, p=0.05). This seemed to be due to an increase in non-CV death (1.0% versus 0.5%, HR 2.23, 95% CI 1.32 to 3.78, p=0.002)².

In view of the unexpected increase in non-CV death with continued dual antiplatelet therapy, a systematic review and meta-analysis of 14 RCTs, including the DAPT study², assessed the effect of extended duration of dual antiplatelet therapy on mortality in 69,644 people who had various CV disorders³. In this study, dual antiplatelet therapy with aspirin and a thienopyridine for at least 6 months was compared with aspirin alone or dual antiplatelet therapy for less than 6 months. Follow-up between studies ranged from 12 months to a median of around 43 months and the difference in duration of dual antiplatelet therapy between groups in each study ranged from 6 months to a median of around 43 months. PCI had been carried out in 9 of the 14 RCTs, although it is not clear how many people had drug-eluting stents. Clopidogrel was the thienopyridine used in most studies, but in 2 studies some people took prasugrel.

Extended duration dual antiplatelet therapy for at least 6 months, compared with aspirin alone or dual antiplatelet therapy for less than 6 months, was not associated with an increase in all-cause mortality (5.8% versus 5.7%, HR 1.01, 95% CI 0.96 to 1.07; 14 RCTs), CV mortality (4.2% versus 4.1%, HR 1.01, 95% CI 0.93 to 1.12; 12 RCTs, n=66,269) or non-CV mortality (1.7% versus 1.7%, HR 1.03, 95% CI 0.90 to 1.26; 11 RCTs, n=65,418)³. These findings were consistent before and after inclusion of the DAPT study² and when the analysis was restricted to the 10 RCTs (n=42,616) of people who had coronary artery disease.

A limitation of the DAPT study² is that participants may have had a lower risk of stenosis or bleeding because it only included people who had been adherent to treatment and who did not have a major adverse CV or cerebrovascular event, or moderate or severe bleeding, in the first year. Also, it is not known whether the effects of dual antiplatelet therapy would be the same following insertion of different types of drug-eluting stents, or using different antiplatelets. The meta-analysis³ is limited by the fact that it included a variety of different populations and it was unable to consider the effect of specific patient characteristics on the association of dual antiplatelet therapy with mortality. In addition, it compared different durations of antiplatelet therapy and each trial might have assessed CV death slightly differently.

**Commentary**

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It is well established that dual antiplatelet therapy (DAPT) affords clinical outcome benefit both as a medical treatment after acute coronary syndromes (ACS) and after insertion of coronary artery stents, now most commonly drug-eluting (DES). The absence, or early cessation, of DAPT after DES is associated with development of stent thrombosis (ST) which has a mortality of between 10-40%⁴. The administration of DAPT, however, is inevitably also associated with elevated bleeding risk.

There is a wealth of observational and randomised trial data suggesting that with the most modern iterations of DES, the risk of ST has declined. Further, a series of randomised trials comparing “longer” versus “shorter” DAPT regimens have consistently indicated that there is no advantage to longer duration DAPT in terms of reduction of ischaemic outcomes, including ST, but that there is often a higher bleeding risk⁵. These trials are consistent, however, only in this main message, and in one other way: that they were not powered to look at the difference in ST specifically. Otherwise the trials are heterogeneous in regard to factors that have an important bearing on their interpretation in
the setting of real world clinical practice. These factors include: nature of presentation of patients (stable or ACS); duration of DAPT (3/6/12/24 month comparisons); type of DES employed; components of combined primary endpoint (death/ST/stroke/MI/target vessel failure/bleeding variously included). Given the consistency of their message, however, interventional cardiologists have recently been considering reducing the default duration of DAPT for some patients with the most modern DES. In most cases, particularly when the DES was deployed in the context of ACS, DAPT is used for 12 months. Perhaps surprisingly, the basis for this default regimen is not particularly robust.

In the context of this background, the results from the DAPT trial\(^2\) have introduced a new uncertainty into clinical practice. Prolonged DAPT for 30 months after the DES were inserted produces a significantly lower rate of ischaemic complications, including ST, compared with standard 12 months DAPT followed by 18 months of aspirin alone, but at the expense of increased moderate and severe bleeding. However, although the difference in all-cause mortality was not significant between the groups, the rate of non-CV death in the prolonged DAPT group was double that observed in those given 12 months DAPT (1.0% versus 0.5%; \(p=0.002\)). Whilst the latter observation could be explained away by the play of chance, or dismissed as involving only a small percentage of patients, when taken together with the elevated bleeding risk, the absolute numbers at risk if such a 30 month strategy were universally adopted is very large. This issue requires more scrutiny before we can justify changing to 30 months DAPT for all people who have had a DES inserted. Whilst the meta-analysis by Elmariah et al\(^3\) is reassuring about the mortality difference, further large analyses are to be published imminently and may shine a stronger light on this area of concern. In addition, as highlighted in an accompanying commentary to these studies, 6 of the 10 RCTs of people with coronary artery disease included in the meta-analysis compared 12 months of dual antiplatelet therapy with a shorter duration of dual antiplatelet therapy or aspirin monotherapy\(^6\). Also, although in 9 RCTs, PCI had been carried out, it is not clear how many people had drug-eluting stents. Therefore, it is difficult to draw conclusions from the meta-analysis about the specific and pure effect of extended dual antiplatelet therapy beyond 12 months after drug-eluting stent implantation.

Given the current uncertainties generated by the discrepant data that we have available, it seems that the most sensible approach is to continue with our current policy of DAPT for 12 months after DES, which is consistent with current NICE guidance, and await the next instalments in the evidence accumulating in this field. On balance, the negative findings in the DAPT trial (bleeding and death) outweigh the benefit identified in terms of reduced ST when considering a wholesale strategy switch towards extended duration DAPT. In an ideal world, RCTs powered to look at rates of ST would be carried out in homogeneous groups with discrete stable and ACS presentations and consistent P2Y12 inhibitors. In the meantime, we should await further detailed data about the optimal duration of DAPT and also the results from the GLOBAL LEADERS trial, randomising people who have had a DES to DAPT for a year followed by aspirin alone versus DAPT for 1 month followed by ticagrelor alone for 23 months, which looks at this clinical challenge from a whole new perspective.

**Study sponsorship**

DAPT\(^2\) was supported by Abbott, Boston Scientific, Cordis, and Medtronic, Bristol-Myers Squibb-Sanofi Pharmaceuticals Partnership, Eli Lilly, and Daiichi Sankyo, and by a grant from the Department of Health and Human Services (US). There was no funding source for the meta-analysis\(^3\); sponsorship details for the individual studies are not stated.

**References**


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