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Short DAPT duration after ACS – not for the faint of heart

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Current guidelines recommend a minimum of 12 months of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor following an acute coronary syndrome (ACS)[1]. Furthermore, the extension of DAPT therapy beyond 12 months has been demonstrated to reduce cardiovascular events at the cost of increased bleeding[2]. Due to the elevated ischaemic risk in ACS patients, the benefit of extended DAPT duration appears to be more favourable in ACS patients compared to stable coronary syndromes[3]. Whether newer stent designs could lower ischaemic risk sufficiently to tip the scales in favour of shorter DAPT durations remains uncertain.

Critical appraisal of recent trials seeking to evaluate abbreviated DAPT duration among ACS patients treated with newer stents is paramount **(Table 1)**. The SMART-DATE trial compared 12 months or longer of DAPT to six months in ACS patients, and met statistical non-inferiority in the primary composite ischaemic endpoint but observed an increase in myocardial infarction (MI) with abbreviated DAPT[4]. The DAPT-STEMI trial compared six versus 12 months of DAPT in patients with ST-elevation MI (STEMI) and demonstrated non-inferiority in the composite bleeding and ischaemic endpoints[5]. It was relatively underpowered to examine ischaemic endpoints alone. The generalisability of these trials is complicated by the heterogeneity in patient and procedural characteristics.

In this issue of EuroIntervention, De Luca et al present the results of the REDUCE trial, a prospective, open label, multicentre study of 1,496 ACS patients randomised during their index hospitalisation to three or 12 months of DAPT[6].

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Similar to several prior non-inferiority studies testing short DAPT durations, the trial used a composite endpoint that combined both ischaemic and bleeding events, two inversely related outcomes, to meet a wide non-inferiority margin. Although non-inferiority was technically achieved, the authors rightly exercised caution in their interpretation of the results. The treatment arms had equivalent treatment regimens for the first three months after randomisation, and the primary endpoint was heavily influenced by target vessel revascularisation – an endpoint not expected to differ based on DAPT duration. Both of these factors further lowered the already low bar to achieve non-inferiority.

More concerning were the safety signals that appeared to emerge in the trial. The three-month DAPT group had twice the rate of stent thrombosis and a 60% higher cardiac mortality rate at one year. The landmark analyses beginning at three months clearly show these events beginning to diverge after discontinuation of DAPT in the short duration group. Similar signals of harm observed in the SMART-DATE trial should give clinicians pause for thought before entertaining an abbreviated DAPT regimen in ACS patients.

These safety signals should not be seen as a surprise. The occurrence of ACS should be seen as identifying a high-risk patient, and not just a high-risk lesion. In the DAPT study, the largest placebo controlled randomised trial of DAPT duration conducted to date, the reduction in MI from long-term DAPT therapy was driven as much through reducing MIs in non-stented regions as through reducing stent-related events[2]. The development of more potent $P2Y_{12}$ inhibitors only potentiates the secondary benefits of DAPT which, in turn, may favour longer DAPT duration, especially given the prothrombotic substrate of ACS patients. There is no free lunch to be gained through shorter DAPT durations – one must be prepared to accept higher ischaemic events with shortened DAPT duration.

These ischaemic implications must be weighed against bleeding risk. REDUCE, like other shorter DAPT duration trials, failed to demonstrate an expected significantly higher bleeding risk with longer DAPT[4,5]. This highlights either the underpowered nature of these trials or the overall low incidence of both bleeding and ischaemic events in trial-enrolled patients that questions the studies'

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Table 1. A systematic approach to critically appraising clinical trials evaluating DAPT duration.

Critical appraisal of DAPT duration randomised clinical trials	
1. Did randomisation occur at index procedure or after treatment arms diverged?	Randomisation at index procedure leads to a period of overlap during which different treatment regimens are identical. This overlap biases hazard ratios towards the null and favours non-inferiority. Landmark analysis beginning at the time of treatment divergence may be more informative.
2. Is the primary endpoint a composite endpoint of ischaemic and bleeding events?	Composite endpoints should ideally include components that are of equal importance and are expected to move in a similar direction with treatment. Composites that include components expected to move in opposite directions will favour non-inferiority but may obfuscate the risks and benefits of different DAPT durations.
3. Was the non-inferiority margin a fixed absolute or relative value?	The interpretation of non-inferiority using fixed absolute margins may be problematic when event rates are different than expected. Lower than expected event rates will lower the bar for establishing non-inferiority.
4. Do the confidence intervals for ischaemic endpoints include the possibility of substantial harm?	Studies that achieve non-inferiority may still include the possibility of harm from shorter DAPT durations. In particular, the upper 95% confidence limits for the risk ratio increases in stent thrombosis and MI will best determine how well the trial has assessed the ischaemic risks of shorter DAPT duration.
5. Does the study demonstrate an increased bleeding risk with longer DAPT?	Studies that fail to demonstrate an increased bleeding risk with longer DAPT durations are probably underpowered to detect differences in ischaemic endpoints.

ability to detect a signal for harm. Importantly, those patients at highest risk of bleeding who may derive the greatest benefit from shorter DAPT were excluded from this and other studies.

Collectively, De Luca et al add to the growing evidence base that DAPT duration should be guided by an individualised assessment of risk. The DAPT score is one example of a clinical tool that integrates patient and procedural characteristics to provide an uncoupled assessment of both bleeding and ischaemic risk, especially among ACS patients[7,8]. The question remains if it, or another similarly derived risk stratification tool, could help to identify those patients in whom less intensive antiplatelet regimens may be favoured.

Despite advances in stent technology and antiplatelet agents, the current data evaluating shorter DAPT durations are not reassuring. Some subsets of patients at particularly high risk of bleeding in excess of the ischaemic risk may benefit from shorter or less intensive DAPT regimens. Until adequately powered randomised controlled trials demonstrate a clinically meaningful identification of those patients, we should continue to adhere to the current guideline-recommended 12-month minimum DAPT duration following ACS.

Conflict of interest statement

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