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EDITORIAL

DAPT de-escalation post-ACS: a new rule or just a new option? Lessons from the 4D-ACS trial

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The optimal management of dual antiplatelet therapy (DAPT) in patients presenting with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) remains a dynamic and evolving area of cardiovascular medicine. The key challenge lies in striking a delicate balance between ischaemic protection and the risk of bleeding complications[1]. The 4D-ACS trial contributes valuable insights to this ongoing evolution, advocating for an unguided, de-escalated approach to DAPT in ACS patients. This reflects the growing emphasis and evidence on individualised antiplatelet strategies, including de-escalation strategies[2].

In this issue of EuroIntervention, Jang et al present the results of the 4D-ACS study, conducted in South Korea, which randomised 656 ACS patients immediately post-PCI to either a short DAPT regimen – 1 month of aspirin plus 10 mg prasugrel followed by prasugrel monotherapy at a reduced dose of 5 mg – or to a standard 12-month DAPT regimen with aspirin and prasugrel 5 mg daily[3]. All patients received a polymer-free, biolimus-coated stent (BioFreedom Ultra [Biosensors]). At the 12-month follow-up, the primary endpoint – net adverse clinical events (NACE), a composite of death, myocardial infarction, stroke, target vessel revascularisation, and Bleeding Academic Research Consortium (BARC) 2-5 bleeding – occurred significantly less frequently in the short-DAPT group (4.9% vs 8.8%). This reduction met both non-inferiority and superiority criteria, with the benefit primarily driven by a substantial decrease in bleeding events: a 77% relative risk reduction in BARC 2-5 bleeding and an 87% reduction in major bleeding. In parallel, ischaemic event rates remained very low and comparable between the groups, with no stent thrombosis in either group.

This study adds to a growing body of evidence from previous de-escalation trials – TOPIC (ClinicalTrials.gov: NCT02099422), TROPICAL-ACS (NCT01959451), TALOS-AMI (NCT02018055), and HOST-REDUCE-POLYTECH-ACS (NCT02193971) – all of which have raised questions about the need for prolonged and intensive antiplatelet regimens in selected post-ACS patients. These earlier investigations demonstrated that while potent DAPT using full-dose potent $P2Y_{12}$ inhibitors provides early ischaemic benefit, including reduction of life-threatening events such as stent thrombosis, most of the bleeding complications emerge during the chronic maintenance phase[4,5]. This has led to the broader development of de-escalation strategies aimed at mitigating late-phase bleeding risks without compromising early ischaemic protection, with a "two-step" DAPT approach: a potent one for the early phase, followed by de-escalation.

Various de-escalation strategies have been explored: some trials, such as GLOBAL LEADERS (NCT01813435), TICO (NCT02494895), and TWILIGHT (NCT02270242), focused on dropping aspirin and continuing $P2Y_{12}$ inhibitor monotherapy; others, like HOST-REDUCE-POLYTECH-ACS and TALOS-AMI, opted to reduce the dose of the $P2Y_{12}$ inhibitor itself, while TOPIC and TROPICAL-ACS evaluated switching from potent agents to clopidogrel[2]. Yet, despite these advances, the optimal de-escalation strategy remains undefined. No head-to-head comparisons have conclusively established whether dose reduction, drug substitution, or aspirin withdrawal offers the best safety-efficacy profile. Future studies will be essential to address this important clinical question.

One notable feature that distinguishes 4D-ACS is its immediate post-PCI randomisation, omitting any run-in phase to assess early safety and tolerability. This differs from most of the earlier studies where randomisation was performed later. This design – similar to that of HOST-REDUCE-POLYTECH-ACS – favours simplicity and real-world applicability but could potentially overlook early intolerance or ischaemic recurrence that would otherwise necessitate therapeutic adjustments. This approach may also influence the trial's primary endpoint, given that both groups initially received the same treatment during the critical early phase.

Crucially, 4D-ACS reinforces an increasingly accepted paradigm: bleeding is not a trivial side effect but a clinically significant event associated with increased mortality. Reducing bleeding risk is now recognised as a core objective of post-PCI management, particularly in patients at high bleeding risk. In this context, de-escalation should be seen not merely as a compromise, but as a proactive strategy to prevent harm rather than reacting after complications arise. However, it is worth noting that the control group's BARC ≥3 bleeding rate (4.6%) was considerably higher than in other contemporary trials – such as HOST-REDUCE-POLYTECH-ACS (0.7%) and TALOS-AMI (2.3%) – despite similar Asian patient populations and antiplatelet regimens. This discrepancy raises questions about patient selection, procedural practices, and regional differences in bleeding risk, all of which could affect the generalisability of de-escalation strategies.

Another critical aspect is the distinction between guided and unguided de-escalation. While trials like TROPICAL-ACS and POPular Genetics (NCT01761786) have demonstrated the feasibility and safety of using platelet function testing or genetic profiling to guide de-escalation, 4D-ACS employed a purely unguided strategy – simple, pragmatic, and accessible to centres lacking specialised testing resources. The trial's positive results highlight the real-world applicability of this approach.

Nonetheless, caution is warranted when extrapolating these findings. All patients in 4D-ACS received the same stent platform (BioFreedom Ultra), and the study excluded individuals over 75 years of age or requiring oral anticoagulation – two high-risk groups commonly encountered in clinical practice. However, previous trials testing de-escalation used different stent platforms and reported similar findings, suggesting that de-escalation post-ACS is a valid option regardless of the stent platform used[2]. Furthermore, the trial population in 4D-ACS consisted of East Asian patients with a relatively low ischaemic risk profile, and more than one-third of enrolled patients had unstable angina rather than myocardial infarction. As such, the study may have been underpowered to detect differences in rare but critical ischaemic events such as stent thrombosis. These limitations underscore the need for further validation in broader and more diverse ACS populations, including those with complex coronary anatomy, high ischaemic risk, or prior thrombotic complications.

Ultimately, 4D-ACS does not dictate a new standard but rather expands the therapeutic toolbox – offering an attractive option for patients at increased bleeding risk. It supports the viability of a shorter DAPT course followed by low-dose prasugrel monotherapy as a means to minimise bleeding without compromising ischaemic safety. This trial further reinforces the transition from a rigid, uniform approach to a risk-adapted, dynamic, and patient-centred model of care. As Sir William Osler once said, "The good physician treats the disease; the great physician treats the patient who has the disease." With 4D-ACS, we move closer to the ideal of truly personalised antiplatelet therapy after ACS.

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Conflict of interest statement

T. Cuisset reports consulting fees and honoraria from Abbott, Boston Scientific, Edwards Lifesciences, Terumo, Medtronic, Inari, BMS-Pfizer, and MicroPort. G. Cayla reports consulting fees and honoraria from Abbott, Shockwave Medical, MicroPort, Biotronik, Edwards Lifesciences, BMS-Pfizer, and Medtronic.

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