VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2024, Vol. 31, No. 3, 504–506
DOI: 10.5603/cj.98301

ISSN 1897–5593
eISSN 1898–018X

Optimal antiplatelet therapy in patients with acute coronary syndromes — a still unfulfilled need?

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The search for optimal antiplatelet treatment in patients after acute coronary syndrome (ACS) remains a burning issue in contemporary cardiology. It is believed that in most patients this optimization can be obtained by de-escalation of dual antiplatelet therapy (DAPT) aiming to reduce bleeding without increasing ischemic events. De-escalation of DAPT can be obtained by shortening its duration, reducing the dose of a potent P2Y12 receptor inhibitor, switching to clopidogrel, or abandoning aspirin. Recently, the investigators of the ELECTRA-SIRIO 2 trial published the rationale and design of their study in Cardiology Journal [1, 2]. This randomized, placebo-controlled trial evaluates 2 novel approaches of unguided attenuation of DAPT in ticagrelor-treated patients after ACS. The study is financed by the Polish Medical Research Agency (Project no. 2019/ABM/01/00009) and is currently enrolling patients in over 30 Polish cardiac centers, with a target population of 4500 patients. Since the inception of the trial and its launch the results of several studies exploring different DAPT step-down approaches have become available. But do the data they provide indicate the optimal antiplatelet treatment in patients after ACS?

Two randomized clinical trials (RCTs) published in The Lancet reported decreased bleeding rates and non-inferior antithrombotic efficacy with 2 different unguided DAPT de-escalation strategies [3, 4]. Hyo-Soo et al. compared reduced (5 mg) and standard (10 mg) prasugrel maintenance doses in an open-label, multicenter study conducted in invasively-treated ACS patients [3]. Among 2338 participants included in the study, DAPT with 5 mg prasugrel was not inferior to a standard dose in regard to a net primary endpoint composed of all-cause death, myocardial infarction (MI), stent thrombosis (ST), repeat revascularization, stroke, and bleeding events ≥ 2 Bleeding Academic Research Consortium (BARC) criteria (7.2% vs. 10.1%, $p_{\text{non-inferiority}} < 0.0001$, $p_{\text{equivalence}} = 0.012$). There was no increase in ischemic risk in the de-escalation group (HR 0.76; 95% CI 0.40–1.45; $p = 0.40$), while the risk of bleeding was significantly decreased compared with the conventional arm (HR 0.48; 95% CI 0.32–0.73; $p = 0.0007$) [3]. Another large-scale ($n = 2697$) study assessed a uniform unguided de-escalation of DAPT from ticagrelor to clopidogrel after MI [4]. The composite primary endpoint of cardiovascular death, MI, stroke, or type 2, 3, or 5 BARC bleeding occurred in 4.6% patients in the de-escalation group compared with 8.2% patients in the ticagrelor-based DAPT group ($p_{\text{non-inferiority}} < 0.001$; HR 0.55; 95% CI 0.40–0.76; $p_{\text{superiority}} = 0.0001$). The benefit seen with this strategy was mainly driven by reduction in BARC 2, 3, or 5 bleeding (3.0% vs. 5.6%, HR 0.52; 95% CI 0.35–0.77; $p = 0.0012$). Yet again, no increase in adverse ischemic events was observed in patients in the de-escalation arm (cardiovascular death, MI, or stroke: 2.1% vs. 3.1%, HR 0.69; 95% CI 0.42–1.14; $p = 0.15$) [4]. However, both trials were conducted in South Korea, which limits the direct application of these results into non-East Asian patients due to "East Asian paradox," characterized by more bleeding events and fewer thromboembolic complications occurring in this population on antiplatelet treatment [5].

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Received: 22.11.2023 Accepted: 29.05.2024 Early publication date: 24.06.2024

Additional data have also been made available in a series of state-of-the art meta-analyses. In an individual patient meta-analysis of 4 RCTs including 10,133 patients with ACS treated with PCI, Kang et al. reported reduction of both bleeding and ischemic events in patients undergoing DAPT de-escalation [6]. The rate of cardiac death, MI, and cerebrovascular events was 24% lower in patients assigned to the de-escalation strategy compared with the standard strategy (2.3% vs. 3.0%; HR 0.76; 95% CI 0.60–0.97). Bleeding events also occurred 30% less often in the de-escalation group (6.5% vs. 9.1%; HR 0.70; 95% CI 0.61–0.81) [6]. Similar reduction in bleeding (BARC ≥ 2 bleeding: HR 0.57, 95% CI 0.42–0.78) and ischemic events (cardiovascular mortality; MI; ST; stroke: HR 0.77; 95% CI 0.62–0.96) was reported in analogous meta-analysis, which included invasively-treated ACS patients undergoing de-escalation from a standard DAPT with a potent P2Y12 receptor inhibitor [7]. Interestingly, reduction in bleeding appears to be more prominent in the unguided than in the guided de-escalation approach [6]. This was also observed in a meta-analysis by Kuno et al., which comprised 19 RCTs with 69,746 ACS patients [8]. In this study, unguided de-escalation of DAPT was related to a significant reduction in major and minor bleeding compared with guided de-escalation (HR 0.48; 95% CI 0.33–0.72), regardless of guided strategy (platelet function tests or genotyping). At the same time, unguided de-escalation did not increase the rate of cardiovascular death, MI, or stroke (HR 0.82; 95% CI 0.53–1.28) [8]. Recently, Kuno and coworkers published another relevant meta-analysis including 32 RCTs with 103,497 ACS patients [9]. As well as guided and unguided DAPT de-escalation, the authors evaluated shortening of the standard DAPT below 6 months. According to the presented results, unguided de-escalation strategy was the safest and the most effective in reducing major adverse cardiovascular events and major or minor bleeding, while short DAPT followed by P2Y12 inhibitor was the best for major bleeding and all-cause death reduction [9]. Due to the fact the guided de-escalation is not superior to unguided strategies, it should not be routinely recommended, particularly since an unguided approach requires less resources and is more feasible.

The abovementioned results unambiguously support DAPT de-escalation in patients after ACS; however, they do not fill the evidence gap completely. What remains unknown is when and how to de-escalate. From a pathophysiological point of view, attenuation of antithrombotic treatment potency should occur as soon as the prothrombotic state related to ACS diminishes [1]. Such adjustment allows the provision of potent platelet blockade directly after ACS when the thrombotic burden is highest, while subsequent de-escalation is expected to conform to a decreasing risk of cardiovascular complications, simultaneously limiting excessive bleeding resulting from disproportionate platelet inhibition. The ELECTRA-SIRIO 2 trial attempts to address these issues, as it evaluates a two-step de-escalation with ticagrelor maintenance dose reduction to 60 mg b.i.d. at one month after ACS, followed by discontinuation of aspirin with a subsequent monotherapy with reduced dose of ticagrelor starting 3 months after ACS [2]. Nevertheless, future RCTs should attempt to precisely define ACS patients without persistent high thrombotic risk who are appropriate for DAPT de-escalation.

Conflict of interest: Piotr Adamski received lecture fees from AstraZeneca.

Funding: None.

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