VIA MEDICA

INVITED REVIEW ARTICLE

A new approach to ticagrelor-based de-escalation of antiplatelet therapy after acute coronary syndrome. A rationale for a randomized, double-blind, placebo-controlled, investigator-initiated, multicenter clinical study

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Abstract

The risk of ischemic events gradually decreases after acute coronary syndrome (ACS), reaching a stable level after 1 month, while the risk of bleeding remains steady during the whole period of dual antiplatelet treatment (DAPT). Several de-escalation strategies of antiplatelet treatment aiming to enhance safety of DAPT without depriving it of its efficacy have been evaluated so far.

We hypothesized that reduction of the ticagrelor maintenance dose 1 month after ACS and its continuation until 12 months after ACS may improve adherence to antiplatelet treatment due to better tolerability compared with the standard dose of ticagrelor. Moreover, improved safety of treatment and preserved anti-ischemic benefit may also be expected with additional acetylsalicylic acid (ASA) withdrawal. To evaluate these hypotheses, we designed the Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome — a randomized clinical trial (ELECTRA-SIRIO 2), to assess the influence of ticagrelor dose reduction with or without continuation of ASA versus DAPT with standard dose ticagrelor in reducing clinically relevant bleeding and maintaining anti-ischemic efficacy in ACS patients.

The study was designed as a phase III, randomized, multicenter, double-blind, investigator-initiated clinical study with a 12-month follow-up (ClinicalTrials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). (Cardiol J 2021; 28, 4: 607–614)

Key words: acute coronary syndrome, ticagrelor, antiplatelet therapy, de-escalation, ELECTRA-SIRIO 2

Introduction

Elevated rates of ischemic events clustering during the first month after acute coronary syndrome (ACS) is reflective of elevated platelet reactivity during this period. The risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction (MI), and stroke, gradually decreases, reaching a stable level after 1 month, while the risk of bleeding is

mainly related to the type and dosage of antiplatelet drugs and remains steady during the whole period of dual antiplatelet treatment (DAPT). Therefore, in the earliest phase after ACS, the ischemic component should be especially targeted with potent antiplatelet strategies, whereas after the clinical stabilization occurs, de-escalation of the antiplatelet therapy may be justified [1–8]. Treatment with ticagrelor or prasugrel is recommended over clopidogrel due to better efficacy, albeit with more bleeding complications. These higher bleeding rates have provoked trials investigating de-escalation from ticagrelor or prasugrel to clopidogrel in the hope of reducing bleeding without increasing rates of thrombotic events [4, 5]. Several strategies aiming to enhance the safety of antiplatelet treatment without depriving it of its efficacy have been evaluated so far.

Replacing a potent P2Y12 receptor inhibitor (prasugrel or ticagrelor) with a weaker one (clopidogrel) was the first de-escalation strategy tested. In the TOPIC study downgrading of DAPT (from prasugrel or ticagrelor to clopidogrel) 1 month after ACS was associated with a net clinical benefit mainly driven by a significant reduction in bleeding complications, while the risk of recurrent ischemic events remained unchanged [9]. The limitations of this study, including small study sample size (645 patients), non-homogenous treatment at baseline and in the control arm (prasugrel or ticagrelor), and moderate adherence to the treatment, warrant cautious interpretation of these results. On the other hand, the SCOPE registry (n = 1363) reported switching from clopidogrel to novel P2Y12 receptor inhibitors to be safe, while a downgrade was an independent predictor of net adverse cerebrovascular events in patients with ACS [10]. The safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel were tested in the TROPICAL-ACS study (n = 2610) [11]. High platelet reactivity is associated with an increased risk of recurrent ischemic events, while the use of clopidogrel is burdened with high interindividual variability of the antiplatelet effect and the possibility of drug interactions [12]. Hence, platelet function testing was applied for guidance of de-escalation of antiplatelet treatment in this study. In the de-escalation group as much as 39% of patients required a switch-back to prasugrel due to insufficient platelet inhibition with clopidogrel defined as high platelet reactivity [11]. The primary endpoint, defined as net clinical benefit (cardiovascular death, MI, stroke, or bleeding grade 2 or higher according to Bleeding Academic Research

Consortium [BARC] criteria) 1 year after randomization, occurred in 7% of patients in the guided de-escalation group and in 9% of patients in the control group ($p_{non-inferiority}$ = 0.0004; hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.62–1.06, $p_{superiority}$ = 0.12). The prevalence of ischemic events (cardiovascular death, MI, and stroke) was 3% in both study arms, while the prevalence of BARC grade 2 or higher was 5% and 6%, respectively. Despite of the lack of significant differences in the whole study population, subgroup analyses revealed a net clinical benefit from guided de-escalation in ST-segment elevation MI patients, subjects ≤ 70 years of age, and those without diabetes. Summing up, this investigator-initiated, randomized, open-label, assessor-blinded, multicenter trial showed that platelet function testing-guided de-escalation from prasugrel to clopidogrel was non-inferior to standard treatment with prasugrel at 1 year after percutaneous coronary intervention (PCI) in terms of net clinical benefit in patients with ACS [11].

Kheiri et al. [13] conducted a meta-analysis (3 randomized clinical trials with 3391 patients) aimed at evaluating the clinical outcomes of antiplatelet de-escalation based on switching from prasugrel or ticagrelor to clopidogrel compared with continuation of DAPT with more potent P2Y12 receptor inhibitor in patients treated with PCI. The net clinical outcome (composite of bleeding or thrombotic events) was significantly reduced in the group switched to clopidogrel; however, no differences between the groups in a separate analysis for MACE, as well as for bleedings, were found [13].

Pharmacodynamic data show that reduction of ticagrelor bioavailability by one-third significantly decreases the antiplatelet effect of ticagrelor in patients with acute MI, but not in subjects without ACS [14–16]. More pronounced ticagrelor-induced platelet inhibition seen in a stable setting compared with MI reflects the excessive platelet activation occurring during the initial phase of ACS. Subsequently, the enhanced platelet reactivity and aggregation decrease over time when ACS patients become stable [17–22]. This observation was confirmed in a sub-study of the PEGASUS-TIMI 54 trial showing similar platelet inhibition with reduced (60 mg b.i.d) and standard (90 mg b.i.d) maintenance doses in stable patients more than 1 year after MI, despite one-third lower ticagrelor plasma concentrations in the lower dose arm [23–25]. Recently, we demonstrated in a randomized, pharmacodynamic trial that a reduced ticagrelor maintenance dose of 60 mg b.i.d. provides a comparable antiplatelet effect to the standard

90 mg b.i.d. dose in patients already 1 month post MI, when the disease proceeds to its stable phase. Importantly, no differences in the prevalence of on-ticagrelor high platelet reactivity between patients receiving the reduced and standard maintenance doses was observed in this trial [26, 27].

The number of studies reporting clinical outcomes in coronary artery disease patients receiving reduced maintenance dose of ticagrelor is limited; however, available results indicate that in a stable setting this strategy offers improved safety with preserved efficacy in the prevention of thrombotic events [7]. The PEGASUS-TIMI 54 study showed comparable clinical efficacy of two ticagrelor doses (90 mg b.i.d. and 60 mg b.i.d.) administered with acetylsalicylic acid (ASA); however, better tolerability of treatment with the lower dose was observed in stable patients 1 year after MI [23].

Another strategy to optimize antiplatelet treatment, by adjusting its potency to time-changing required platelet inhibition, has been validated in the TWILIGHT study [28]. The primary endpoint was the first occurrence of BARC type 2, 3, or 5 bleeding between randomization and 1 year in a time-to-event analysis. The key secondary endpoint was the first occurrence of death from any cause, nonfatal MI, or nonfatal stroke in a time-to-event analysis. The results of this randomized trial showed that in 7119 high-risk patients who had undergone PCI and were treated with ticagrelor 90 mg b.i.d. and ASA for 3 months, subsequent monotherapy with ticagrelor resulted in substantially fewer bleeding events than in the ticagrelor plus ASA arm (4.0% vs. 7.1%, respectively; HR 0.56; 95% CI 0.45–0.68; p < 0.001), without any ischemic harm over a period of 1 year; the key secondary endpoint occurred in 3.9% of patients in both study arms [28]. Even in high-risk patients after complex PCI, the DAPT downgrade to ticagrelor monotherapy was associated with lower incidence of bleeding without increased risk of ischemic events compared with continuation of DAPT [29, 30].

Khan et al. [31] performed a Bayesian network meta-analysis comparing early de-escalation of DAPT (1–3 months) to monotherapy with either P2Y12 inhibitor or ASA versus 12 months de-escalation of DAPT after PCI with drug-eluting stent. Among the 7 trials included (35,821 patients), 52.6% of patients presented with ACS. No significant differences in terms of ischemic endpoints among different DAPT strategies were found; however, early de-escalation of DAPT to monotherapy with a P2Y12 inhibitor instead of ASA might be a safer approach compared with 12 months of DAPT in patients treated with PCI [31].

Taking into account these data, we hypothesized that reduction of ticagrelor maintenance dose to 60 mg b.i.d. 1 month after ACS and its continuation until 12 months may improve adherence to antiplatelet treatment due to better tolerability compared with DAPT including standard dose ticagrelor. Moreover, based on the TWILIGHT study results [29], improved safety of treatment and preserved anti-ischemic benefit with additional ASA withdrawal may also be expected. To evaluate these hypotheses, we designed the Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome — a randomized clinical trial (ELECTRA-SIRIO 2), to assess the influence of ticagrelor dose reduction with or without continuation of ASA versus DAPT with standard-dose ticagrelor in reducing clinically relevant bleeding and maintaining anti-ischemic efficacy in ACS patients.

Current standard of treatment according to the guidelines

In ACS patients DAPT with a P2Y12 receptor inhibitor on top of ASA is recommended for 12 months to reduce platelet reactivity and adverse thrombotic events (class of recommendation I) [1, 2, 4]. However, in specific clinical scenarios the DAPT duration can be shortened (< 12 months), extended (> 12 months), or modified (switching DAPT, DAPT de-escalation), and these decisions depend on individual clinical judgement being driven by the patient's ischemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medications, and availability of drugs [2]. Early discontinuation of P2Y12 receptor inhibitor therapy 3 months after non-ST-elevation ACS should be considered in those who are at high bleeding risk (High Bleeding Risk according to Academic Bleeding Consortium — ABC-HBR criteria or ≥ 25 score in PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy — PRECISE-DAPT score) (class of recommendation IIa) [4]. Termination of treatment with ASA 3–6 months after ACS in patients treated with PCI with stent implantation should be considered, depending on the balance between bleeding and ischemic risk (class of recommendation IIa). Moreover, patients at very high bleeding risk, i.e. those who experienced bleeding episode within a month preceding the index ACS or those scheduled for surgical intervention in the

early future, may benefit from 1-month DAPT comprising ASA and clopidogrel, with the intention to continue monotherapy with clopidogrel afterwards (class of recommendation IIa) [4].

De-escalation of treatment with P2Y12 receptor inhibitor (e.g. switch from prasugrel or ticagrelor to clopidogrel) may be considered in patients after ACS deemed unsuitable for potent platelet inhibition. De-escalation may be unguided, based solely on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on the patient's risk profile and availability of respective assays (class of recommendation IIb) [4].

Dual antiplatelet treatment with ASA and P2Y12 receptor inhibitor (ticagrelor may be preferred over clopidogrel and prasugrel) or with a low dose of rivaroxaban is recommended in subjects without atrial fibrillation at high/moderate ischemic risk and low bleeding risk beyond 12 months post ACS (class of recommendation IIa/IIb) [4, 5].

Adherence to DAPT after ACS

Despite the numerous advantages of a potent antiplatelet treatment, this therapy is also burdened with non-negligible side effects, greatly related to bleeding. These adverse effects quite often require medical attention or lead to discontinuation of treatment. Of note, the rate of premature discontinuation of antiplatelet treatment in the landmark PLATO study was 23% of patients receiving ticagrelor and 22% treated with clopidogrel, which shows the magnitude of the problem [17]. Premature discontinuation of antiplatelet therapy, especially in invasively treated ACS patients, may lead to detrimental cardiovascular and thrombotic events, such as recurrent ACS or stent thrombosis [12, 17–21, 32, 33].

Premature discontinuation of treatment with ticagrelor in the PEGASUS-TIMI 54 was mostly driven by non-serious adverse events that occurred primarily early after randomization, and it was more common in patients receiving standard compared with reduced ticagrelor maintenance dose [23–25]. Thus, better adherence to treatment would be expected with low-dose ticagrelor in real-life practice.

The ELECTRA-SIRIO 2 study

The ELECTRA-SIRIO 2 study was designed as a phase III, randomized, multicenter, double-blind, placebo-controlled, investigator-initiated clinical study with a 12-month follow-up (Clinical-Trials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). The study is aimed to test two ticagrelor-based de-escalation strategies versus standard treatment.

During the first month after ACS subjects from all three arms will receive a standard DAPT with ticagrelor 90 mg b.i.d and 100 mg ASA once daily. Patients assigned to the control group will continue this standard treatment for a total of 12 months, while in both experimental arms after 1 month the maintenance dose of ticagrelor will be reduced to 60 mg b.i.d. Then, 3 months after ACS, treatment with ASA will be terminated in one of the experimental arms. The primary safety composite endpoint of this study is the first occurrence of type 2, 3, or 5 bleeding according to the BARC criteria, occurring during the first 12 months after ACS. The primary efficacy endpoint is the composite of time to death from any cause, first nonfatal MI, or first nonfatal stroke.

Special care will be applied with regard to adherence to the study treatment (tablet counting at follow-up visits and evaluation with use of the Adherence in Chronic Diseases Scale). The adherence to treatment is of vast importance because early termination of ticagrelor leaves the ACS patients in the monotherapy arm unprotected against ischemic consequences, such as recurrent ACS [34–40].

To increase adherence to treatment all patients will undergo continuous multilevel educational and motivational interventions according to the Multilevel Educational and Motivational Intervention in Patients After Myocardial Infarction (MEDMOTION) project, including assessment with the Readiness for Hospital Discharge after Myocardial Infarction Scale at the end of hospitalization, and with the Functioning in Chronic Illness Scale during follow-ups [41–48].

Summary

To date, de-escalation of antiplatelet therapy in ACS patients based on lowering the dose of ticagrelor with or without discontinuation of ASA has not been tested in a large randomized clinical trial.

Taking into account existing evidence, one would expect equal clinical efficacy of reduced and standard maintenance doses of ticagrelor already after 1 month post ACS based on their documented antiplatelet effects. The two antiplatelet de-escalation strategies proposed in the ELECTRA-SIRIO 2 study are expected to essentially decrease the incidence of clinically significant bleeding events

during the first year after ACS, without negative impact on the antithrombotic efficacy. In contrast to the platelet function testing-guided de-escalation strategy applied in the TROPICAL-ACS study [11], the strategy proposed in the ELECTRA-SIRIO 2 study does not require a platelet reactivity assessment, making this step-down approach more feasible for wide application in clinical practice.

Moreover, the quality of life in post-ACS patients on the tested regimen may increase due to lower incidence of dyspnea, an adverse effect typical for ticagrelor. This assumption is based on observations from the PEGASUS-TIMI 54 trial, where dyspnea occurred less frequently in patients who received the lower dose of ticagrelor compared with those treated with the standard dose (16% vs. 19%) [23–25]. Thus, a lower number of patients are expected to permanently and prematurely discontinue ticagrelor.

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