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INVITED EDITORIAL

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De-escalation of antiplatelet therapy — an approach to improve safety and efficacy of treatment in patients after acute coronary syndrome

Dual antiplatelet treatment (DAPT) with aspirin and P2Y12 inhibitor - clopidogrel has been shown to reduce the risk of ischaemic events in patients after acute coronary syndrome (ACS) [1–3]. Further studies proved the superiority of ticagrelor and prasugrel over clopidogrel in this clinical setting [4–6]. It has been also demonstrated that prolongation of DAPT over one year with lower doses of P2Y12 inhibitor may further improve clinical outcome in patients with previous ACS [7]. At the same time significant improvement in the technology of stents and implantable scaffolds, including design, materials, and antiproliferative agents, occurred resulting in the reduction of thrombogenicity of these devices and allowing the safe shortening of DAPT if necessary [8]. Moreover, changes of platelet reactivity on treatment with P2Y12 inhibitors during the acute phase and the following stable period after ACS [9–18] is an additional factor to be considered. The complexity and ever-better understanding of the pathophysiology of ACS, as well as the ever-wider therapeutic possibilities, require a rethinking of the antiplatelet treatment strategy in this clinical setting.

According to the current guidelines, DAPT with a P2Y12 receptor inhibitor and aspirin is recommended for 12 months to reduce adverse thrombotic events [10, 12, 19, 20]. DAPT can be modified, its duration can be shortened or extended depending on the patient's ischaemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medications, and drugs availability [12]. Termination of treatment with aspirin after 3-6 months after PCI with stent implantation for ACS should be considered, depending on the balance between bleeding and ischaemic risk [19]. De-escalation of DAPT defined as replacing prasugrel or ticagrelor with clopidogrel may be considered in patients after ACS. 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 [19].

The recommendation regarding the de-escalation strategy based on switching a potent P2Y12 receptor inhibitor to clopidogrel is based on the TOPIC study and the TROPICAL-ACS study [19, 21, 22]. In the TOPIC study switching from prasugrel or ticagrelor to clopidogrel one month after ACS was associated with a net clinical benefit mainly driven by bleeding reduction with an unchanged risk of ischaemic events [21]. The TROPICAL-ACS study showed that de-escalation from prasugrel to clopidogrel guided by platelet function testing was non-inferior to standard treatment with prasugrel at 1 year after percutaneous coronary intervention in terms of net clinical benefit in patients with ACS. However, 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 HPR [22].

The TWILIGHT study tested another de-escalation strategy comparing DAPT with ticagrelor 90 mg b.i.d. and aspirin versus ticagrelor 90 mg b.i.d. alone was assessed [28]. Monotherapy with ticagrelor resulted in substantially less bleeding events than DAPT arm without ischaemic harm [23].

Recently a new antiplatelet de-escalation approach was proposed in the ELECTRA-SIRIO 2 study (Clinical-

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Trials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). The study was designed to evaluate the safety and efficacy of ticagrelor dose reduction with or without the continuation of aspirin versus DAPT with standard-dose ticagrelor in ACS patients. The strategy proposed in the ELECTRA-SIRIO 2 study does not require platelet reactivity testing, making de-escalation more feasible for a wide clinical application [24–28]. The study population will comprise 4,500 patients consecutively admitted to the study centres due to ACS, including patients with ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina [24]. The intention-to-treat analysis, i.e. with the inclusion of all patients according to the randomly assigned trial group, irrespective of the actual treatment received, is a widely used method in randomized clinical trials, therefore adherence to study medication is a pivotal issue. Poor adherence to the study treatment may lead to serious evaluation bias [29, 30]. The MEDMOTION project involving patients' education, motivation, reminding them to take medications and to attend consecutive medical appointments will be applied to improve adherence to study medication [31–50]. The project includes the diagnosis of study participants concerning their readiness for discharge from the hospital (the Readiness for Hospital Discharge after Myocardial Infarction Scale – RHD-MIS), the risk of non-adherence to the medication (the Adherence in Chronic Diseases Scale, ACDS), and the functioning in disease (the Functioning in Chronic Illness Scale, FCIS). A prespecified sub-analysis of the ELECTRA-SIRIO 2 trial is planned to evaluate the impact of the results of MEDMOTION diagnostic tools on the clinical outcomes [24, 51–59].

The ELECTRA-SIRIO 2 study testing a new approach to treatment de-escalation is expected to provide a new, safer, yet easy-to-apply antiplatelet treatment strategy in a patient after ACS.

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