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Review Article

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De-Escalation of $P2Y_{12}$ Receptor Inhibitor Therapy after Acute Coronary Syndromes in Patients Undergoing Percutaneous Coronary Intervention

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Conflict of Interest
Dr. Sibbing reports personal fees from Eli Lilly, personal fees from Pfizer, personal fees from Roche Diagnostics, personal fees from Daiichi Sankyo, personal fees from Astra Zeneca, personal fees from Bayer, personal fees from MSD, personal fees from Sanofi, outside the submitted work.

ABSTRACT

Dual antiplatelet therapy (DAPT) — a combination of a $P2Y_{12}$ receptor inhibitor and aspirin — has revolutionized antithrombotic treatment. Potent $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor exhibit a strong and more consistent platelet inhibition when compared to clopidogrel. Therefore, ticagrelor and prasugrel significantly reduce ischemic events, but at an expense of an increased bleeding risk in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). These observations have engaged intensive clinical research in alternative DAPT regimens to achieve sufficient platelet inhibition with an acceptable bleeding risk. Our review focusses on $P2Y_{12}$ receptor therapy de-escalation defined as a switch from a potent antiplatelet agent (ticagrelor or prasugrel) to clopidogrel. Recently, both unguided (platelet function testing independent) and guided (platelet function testing dependent) DAPT de-escalation strategies have been investigated in different clinical studies and both switching strategies could be possible options to prevent bleeding complications without increasing ischemic risk. In light of the still limited data currently available, future large-scale trials should accumulate more data on various DAPT de-escalation regimens with both ticagrelor and prasugrel in unguided and guided de-escalation approaches. In the current review we aim at summarizing and discussing the current evidence on this still emerging topic in the field of antiplatelet treatment.

Keywords: Acute coronary syndrome; $P2Y_{12}$ Inhibitors; DAPT de-escalation

INTRODUCTION

Dual antiplatelet therapy (DAPT) — a combination of a $P2Y_{12}$ receptor inhibitor and aspirin — has revolutionized antithrombotic treatment options in an acute coronary syndrome (ACS) patients with and without invasive management.[1)2)] The accessibility of a variety of $P2Y_{12}$ inhibitors enabled physicians to switch these drugs in reflection of individual patient features including their bleeding and thrombotic risk after stent implantation. The potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor exhibit a strong and more consistent platelet inhibition when compared to clopidogrel. These pharmacologic properties resulted in a significant reduction in ischemic events, albeit at the expense of an increased bleeding risk in ACS

Author Contributions

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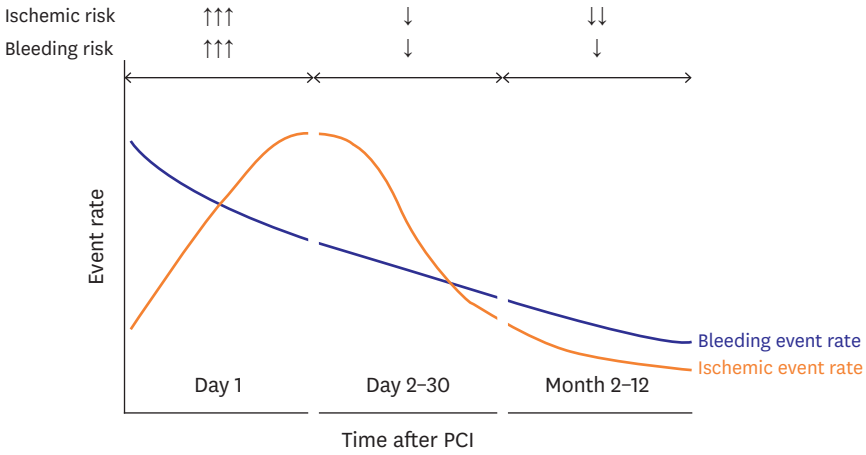

Figure 1. Timing of ischemic versus bleeding events after PCI. Ischemic and bleeding rates after PCI are displayed dependent on time. Whereas ischemic rates reach a plateau during the first month, bleeding rates steadily decline. In the second month, ischemic events substantially decrease resulting in an exuberant bleeding risk in the later phase post-PCI.
PCI = percutaneous coronary intervention.

patients undergoing percutaneous coronary intervention (PCI).[3-5] The challenge of preventing ischemic events with an acceptable bleeding risk of ACS patients by adapting $P2Y_{12}$ receptor inhibitor therapy is a field of intensive research.[2)6)] Switching between oral $P2Y_{12}$ inhibitors can either result in a stronger $P2Y_{12}$ receptor inhibition (e.g. clopidogrel to prasugrel or ticagrelor) or reduced $P2Y_{12}$ receptor inhibition (e.g. ticagrelor or prasugrel to clopidogrel). Those strategies are defined as DAPT escalation and de-escalation, respectively.[7)] In the pivotal phase III trials (PLATO, TRITON-TIMI 38) ticagrelor and prasugrel significantly reduced ischemic events especially in the early period after PCI when compared to clopidogrel.[3)4)8)] However, bleeding complications are an omnipresent issue during the entire maintenance phase of DAPT (**Figure 1**). In addition, switching to clopidogrel may have an economic advantage given the high treatment costs of ticagrelor and prasugrel.[7)] An unguided DAPT de-escalation approach is already adopted by many physicians when treating ACS patients after PCI[9)] but the limited data that is available is still conflicting.[9)10)] Moreover, the current clinical practice guidelines offer no clear recommendations on de-escalation of $P2Y_{12}$ inhibitors, leaving clinicians uninformed on how to manage these patients.[11)12)] Our review summarizes and explains the rationale as well as the current evidence on de-escalating $P2Y_{12}$ receptor inhibitor treatment, including both un-guided and guided treatment approaches.

GENERAL ASPECTS OF $P2Y_{12}$ RECEPTOR THERAPY DE-ESCALATION

Oral $P2Y_{12}$ receptor inhibitor treatment is a key element for secondary prevention of thrombotic events in ACS patients and especially for those patients with invasive management by means of PCI.[2)] For ACS patients the current clinical practice guidelines recommend a one-year treatment period with a potent $P2Y_{12}$ inhibitors combined with aspirin.[12-14)] Prasugrel and ticagrelor are superior to clopidogrel in preventing ischemic events[3)4)] due to a more immediate and intense platelet inhibition. In general, escalated DAPT is accompanied by a higher risk for bleeding events and those bleeds are very prominent during the maintenance phase of treatment (**Figure 1**).[3)4)15-18)] Therefore, identification of appropriate patients for DAPT de-escalation may prove useful for an optimized and more

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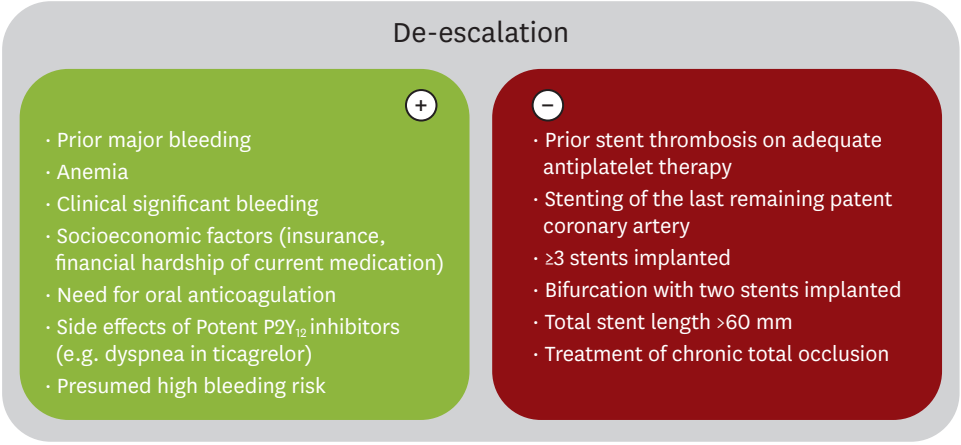

Figure 2. The Pros and Cons of DAPT de-escalation. Characteristics marked in red are variables that may favor a DAPT de-escalation approach and variables marked in blue could be considered as factors that argue against DAPT de-escalation as an alternative DAPT strategy after PCI. Part of the figure content and variables are adapted from the ESC 2017 DAPT guidelines[12].
DAPT = dual antiplatelet therapy, PCI = percutaneous coronary intervention.

personalized $P2Y_{12}$ receptor treatment after PCI. As outlined in **Figure 2** there are factors that favor and there are factors against a DAPT de-escalation approach. In clinical practice, there is a variety of possibilities to downgrade the potency of antiplatelet treatment over time and this may include a dose reduction of potent $P2Y_{12}$ receptor blockers,[19] a discontinuation of aspirin[12][20] and a possible shortening of the DAPT duration. Our review focuses on a true DAPT de-escalation defined as a switch from a potent $P2Y_{12}$ blocker such as prasugrel or ticagrelor to clopidogrel.[7] Indeed, many physicians already shorten the treatment duration with the potent drugs to the early weeks or months after the ACS event.[9][21-23] The main reasons for de-escalation in this setting are reduced costs and concerns of bleeding during prasugrel and ticagrelor treatment, respectively. In case of ticagrelor, side effects such as dyspnea represent an additional possibility for modifying the ongoing treatment.[3][24-26] Although there is general paucity of randomized data on de-escalating $P2Y_{12}$ blocker therapy (**Table 1**), 2 randomized controlled trials have provided first and promising results on the efficacy and safety of such a biologically plausible treatment regimen. Whereas the timing of optimal platelet inhibition after acute coronary syndrome (TOPIC)[27] trial investigated an unguided DAPT strategy that included both ticagrelor and prasugrel, Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndrome (TROPICAL-ACS)[28][29] used platelet function testing to guide DAPT de-escalation from the potent $P2Y_{12}$ inhibitor prasugrel to clopidogrel.

UNGUIDED DUAL ANTIPLATELET THERAPY DE-ESCALATION

Observational data suggests an in-hospital de-escalation rate of 5–14% and a post-hospital switching rate of 5–8%.[30] For instance, Treatment With Adenosine Diphosphate (ADP) Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE ACS), a large multicenter, longitudinal registry in 12,365 ACS patients captured data on post discharge switching in patients with acute myocardial infarction.[30] Among patients discharged on prasugrel or ticagrelor a switch to clopidogrel was very common and strongly associated with having a government medication insurance

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Table 1. Studies on $P2Y_{12}$ receptor inhibitor de-escalation

Study (acronym)	Approach	$P2Y_{12}$ receptor inhibitors	No. of patients and study design	Key results	Ref.
TROPICAL-ACS	Effect of PFT-guided de-escalation in PCI-treated patients	Prasugrel Clopidogrel	2,610 ACS patients RCT	Primary endpoint (control vs. PFT-guided de-escalation): Net clinical benefit of CV death, MI, stroke, BARC bleeding ≥2 (9% vs. 7%; HR, 0.81; 95% CI, 0.62–1.06; p=0.0004) Subgroup analysis (escalation vs. de-escalation) - CV death, MI, stroke (3% vs. 3%; p=0.0115) - BARC bleeding events ≥2 (6% vs. 5%; HR, 0.82; 95% CI, 0.59–1.13; p=0.23)	28)29)42)
TOPIC	Effect of unguided de-escalation in PCI-treated patients	Ticagrelor Prasugrel Clopidogrel	646 ACS patients RCT	Primary endpoint: (control vs. unguided de-escalation): CV death, urgent revascularization, stroke, BARC bleeding ≥2 (26.3% vs. 13.7%; HR, 0.48; 95% CI, 0.34–0.68; p<0.01)	27)33)
SCOPE	Investigate the incidence of switching $P2Y_{12}$ blocker and its safety in ACS patients with PCI	Ticagrelor Prasugrel Clopidogrel	1,363 ACS patients Observational study	Primary endpoint: MACE (1.6%) and NACE (5.6%) Switching rate: cath lab (2.3%), discharge (3.3%), follow-up (5.2%) Subgroup analysis (escalation vs. de-escalation) -Patients with escalation: no NACE occurred among patients receiving an escalation (escalation vs. de-escalation: OR, 25.2; 95% CI, 1.4–242.9; p=0.02) -Patients with de-escalation: NACE increased (OR, 5.3; CI, 2.1–18.2; p=0.04)	32)
TRANSLATE ACS	Investigation of post-discharge $P2Y_{12}$ receptor blocker switching	Ticagrelor Prasugrel Clopidogrel	12,365 MI patients Observational study	Primary endpoint: MACE, factors for ADP receptor inhibitor choice Switching rate: overall 7.6% Switch in $P2Y_{12}$ inhibitor groups: ticagrelor (28.3%), prasugrel (15.4%), clopidogrel (3.6%) Main reasons for switching: costs (40.3%), physicians decision (60.7%)	9)30)
PRAGUE-18	Evaluate treatment of ticagrelor versus prasugrel in patients with STEMI undergoing PCI	Prasugrel Ticagrelor	1,230 MI patients RCT	Primary endpoint (prasugrel vs. ticagrelor): CV death, MI, stroke, all-cause mortality, definite stent thrombosis (HR, 1.167; 95% CI, 0.742–1.835; p=0.503), all bleeding (10.9% vs. 11.1%; p=0.999), TIMI major bleeding (6.6% vs. 5.7%, p=0.754) Switching rate: economic (39%), anticoagulation (3.2%), adverse events (4.5%), other 6.8%	10)31)

Studies addressing issues of $P2Y_{12}$ inhibitor switching are described by approach, study design and key results. TROPICAL ACS and TOPIC are randomized controlled trials, whereas SCOPE and TRANSLATE ACS are observational studies on outcomes after switching. PRAGUE-18 was not intended to address $P2Y_{12}$ switching. This post-hoc analysis analyzes DAPT switching one year after randomization.
ACS = acute coronary syndrome; ADP = adenosine diphosphate; BARC = bleeding academic research consortium; CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; NACE = net adverse cerebrovascular events (combination of MACE and bleeding events); NNT = number needed to treat; PCI = percutaneous coronary intervention; PFT = platelet function testing; PRAGUE-18 = Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction; RCT = randomized controlled trial; SCOPE = Switching From Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention; TIMI = thrombolysis in myocardial infarction; TROPICAL-ACS = Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndrome.

and financial hardship of medication costs. Bleeding events and increase in creatinine clearance were also associated factors prior to the switching. By contrast, a higher education was correlated with continuation of $P2Y_{12}$ inhibitors suggesting costs as a main driver of switching. Switching after discharge from prasugrel or ticagrelor to clopidogrel was not associated with a significant increase in thrombotic events and GUSTO moderate/severe bleeding. Comparable results are derived from randomized data of the Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction (PRAGUE-18) trial, which compared ticagrelor versus prasugrel in 1,280 ST-elevation myocardial infarction or high-risk non-ST-elevation myocardial infarction patients. After 12 months no significant differences in the composite endpoint (death, cardiovascular death, myocardial infarction, stent thrombosis, stroke and bleeding) were seen for ticagrelor and prasugrel in the intention to treat analysis (5.7% vs. 6.6%; p=0.50).[31] Approximately half of the patients were switched and de-escalated to clopidogrel at the 12-month follow-up. Interestingly, most of the switches were due to economic reasons and 70% of them occurred early and during the 30-day period after the index event. In the PRAGUE-18 trial, an economically driven de-escalation to clopidogrel was associated with a reduction in thrombotic and bleeding events, whereas a

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non-economically switch was accompanied by a higher ischemic event rate. Overall, patients who de-escalated to clopidogrel due to economic reasons had reduced risk compared with those who continued on ticagrelor or prasugrel. However, it must be emphasized that PRAGUE-18 investigators reported those outcome measures in relation to switch of treatment, while the trial was not specifically designed to address those questions.[10]

Non-randomized registry data from the Switching From Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention (SCOPE) registry in 1,363 patients revealed that ischemic events were substantially increased in patients undergoing a de-escalation approach after PCI for ACS.[32] Such findings should raise a note of caution to an unguided de-escalation approach, although randomized data from a smaller single-center trial is promising. Indeed, the TOPIC trial evaluated the clinical benefit of an unguided DAPT de-escalation by switching from prasugrel or ticagrelor to clopidogrel one month after PCI for ACS (**Figure 3**). This smaller single-center study enrolled 646 patients and the primary end point — a net clinical benefit endpoint consisting of cardiovascular death, urgent revascularization, stroke and bleeding as defined by the Bleeding Academic Research Consortium (BARC) classification — occurred in 13.4% in the switched versus 26.3% in the unswitched group (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.34–0.68; p<0.01). This net benefit favoring DAPT de-escalation was driven by a reduction in overall bleeding events but it must be emphasized that ischemic events like stent thrombosis or myocardial infarctions were not reported in a detailed manner at all. Interestingly, in a platelet function testing (PFT) sub-study of the TOPIC trial (TOPIC-VASP) de-escalated DAPT was superior regardless of initial platelet reactivity, but the benefit was greater in low on-treatment platelet reactivity patients.[33] Considering all the available evidence on an unguided DAPT de-escalation approach it must be emphasized that the data

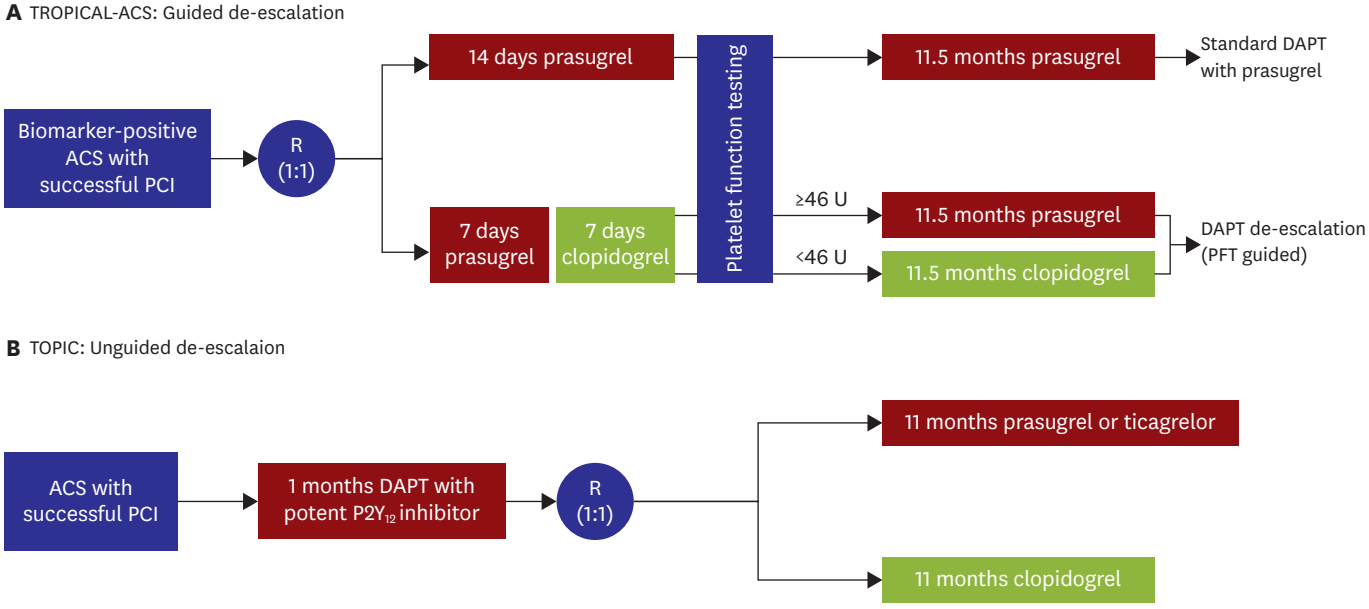

Figure 3. Trials and possible strategies for un-guided and guided DAPT de-escalation. The figure shows studies and strategies on DAPT de-escalation approaches for $P2Y_{12}$ receptor therapy. (A) Guided de-escalation of DAPT investigated in the TROPICAL-ACS trial. Patients were enrolled if they had biomarker-positive acute coronary syndrome with successful PCI and randomly assign to a PFT-based DAPT de-escalation arm or uniform prasugrel treatment. (B) Unguided DAPT de-escalation investigated in the TOPIC trial. Patients with ACS and undergoing coronary intervention, on aspirin and a potent $P2Y_{12}$ blocker were randomly assigned to switch to aspirin and clopidogrel or continuation of their drug regimen with a potent $P2Y_{12}$ inhibitor.
ACS = acute coronary syndrome, DAPT = dual antiplatelet therapy, PFT = platelet function testing; TOPIC = timing of optimal platelet inhibition after acute coronary syndrome; TROPICAL-ACS = Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndrome.

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available is conflicting and that further studies in larger cohorts of patients are urgently needed to lend more support to such an unguided approach of de-escalating DAPT (early or late) in ACS patients after PCI.

GUIDED DAPT DE-ESCALATION

The pro-drug clopidogrel is characterized by a significant response variability and a substantial proportion of patients exhibit a status of high on-treatment platelet reactivity (HPR). This and other circumstances triggered the development of ex-vivo PFT assays.[34-37] Indeed, DAPT de-escalation from a potent $P2Y_{12}$ inhibitor to the less potent clopidogrel should account for the large response variability of the latter[34] and the consequential issue of HPR, which exists in a relevant number of ACS patients.[35][38][39] HPR patients exhibit a higher risk for ischaemic events including myocardial infarction and stent thrombosis.[35][38][39] Hence, PFT could serve to safeguard a DAPT de-escalation by identifying HPR patients on clopidogrel, as those patients may be exposed to a higher risk of thrombotic events due to insufficient $P2Y_{12}$ inhibition and they should therefore continue with potent $P2Y_{12}$ inhibitors. Taking all these relevant aspects into consideration, the objective of the randomized, multi-center investigator-initiated TROPICAL-ACS trial (n=2,610 patients) was to investigate the safety and efficacy of a PFT-guided early de-escalation of antiplatelet treatment compared to standard prasugrel therapy in ACS patients undergoing PCI. The trial met its primary endpoint and demonstrated non-inferiority for a net clinical benefit endpoint in patients scheduled for PFT guided de-escalation vs. conventional prasugrel treatment.[29] Importantly, the rates of ischemic events including CV death, MI or stroke were similar in the guided de-escalation study group vs. control group and a trend towards less bleeding during guided treatment was reported. Therefore, a strategy of guided DAPT de-escalation can be considered in selected ACS patients (NSTEMI and STEMI) as an alternative to 12 months treatment with ticagrelor or prasugrel. It must be acknowledged that such a guided de-escalation strategy results in clopidogrel treatment in most but not in all patients, as some patients would have to be escalated back to prasugrel. The TROPICAL-ACS trial was powered for demonstrating non-inferiority for the primary endpoint (net clinical benefit) and was not powered for ischemic events alone. Thus, large-scale trials would be helpful to corroborate the safety of such a concept with respect to ischemic risk of ACS patients after treatment de-escalation. For the time being and based on the reported results a selective use of a guided DAPT de-escalation strategy seems reasonable and this strategy may be a good alternative for DAPT in selected patients and especially for those who cannot go for 1-year potent platelet inhibition.

Elderly ACS patients have a unique risk profile for both ischemic and bleeding events. The ANTARCTIC trial (Adjust Antiplatelet Therapy in Elderly Patients Stented for an Acute Coronary Syndrome) aimed to assess the safety and efficacy of PFT in 877 ACS patients ≥75 years.[40] The study compared a reduced dose of prasugrel (5 mg/d, as recommended for elderly patients) vs. PFT-guided escalation (10 mg prasugrel) or de-escalation (75 mg clopidogrel) in the intervention arm. Study results were neutral, with similar ischemic and bleeding rates in both groups (28% vs. 28%; HR, 1.003; 95% CI, 0·78–1·29; p=0·98). When interpreting ANTARCTIC results it should be noted that superiority of low-dose prasugrel over standard clopidogrel treatment in terms of clinical outcomes has not been demonstrated, independent of whether or not PFT was included.[41] A subgroup analysis of TROPICAL-ACS also addressed the impact of age on clinical outcomes after guided

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de-escalation. In patients younger than 70 years the incidence of the primary endpoint (cardiovascular death, myocardial infarction, stroke, BARC bleeding) was significantly lower in the guided de-escalation versus the control group (5.9% vs. 8.3%; HR, 0.70; 95% CI, 0.51–0.96; p=0.03; NNT=42) mainly driven by reduced bleeding events. In patients older than 70 years the primary endpoint occurred more frequent but was indistinguishable between both groups (15.5% vs. 13.6%).[42] Thus, the age-dependent results from TROPICAL-ACS confirmed ANTARCTIC study results and a possible benefit of PFT with individualized treatment may be confined to younger patients while effects are neutral in the elderly.

THE EAST-ASIAN PARADOX OF PLATELET INHIBITION

Specific considerations must be reflected for the large population of East Asian patients, who carry a different and very specific risk profile for both ischemic and bleeding complications when compared to the Caucasian population.[43] Related to this, a different and specific genetic profile (higher prevalence for the *CYP2C19*2* and **3* Loss-of-Function [LoF] alleles) is associated with a significantly higher rate of HPR in East Asian patients. Despite this difference and very surprisingly, East Asians do not show an elevated risk for thrombotic complications. In contrast, a significantly lower risk of ischemic events was described leading to a phenomenon further referred to as the 'East Asian paradox.' Thus, based on these specific clinical observations, a right-shifted therapeutic window of on-treatment $P2Y_{12}$-directed platelet reactivity with higher cut-offs for HPR may apply to East Asian patients in contrast to Caucasians and this may have an impact on drugs and drug dosing for those patients. Moreover, with respect to a lower body mass index reduced doses of prasugrel and ticagrelor may be a good choice for East Asian patients specifically.

CONCLUSION AND OUTLOOK

In conclusion and based on the results of the pivotal phase III trials[3,4] a 12 months DAPT that includes prasugrel or ticagrelor for ACS patients after PCI is standard of care in 2018 and beyond.[12-14] However, a DAPT de-escalation must be considered as an attractive alternative treatment concept and may be considered in specific clinical scenarios (bleeding events, high bleeding risk, socio-economic indications) as an alternative to DAPT with potent $P2Y_{12}$ receptor inhibitors (**Figures 1** and **2**). Based upon the current evidence any DAPT de-escalation should be guided and an unguided de-escalation may carry a substantial risk for the patient. Alternative treatment regimens of single antiplatelet therapy after stopping aspirin early after PCI and with continued treatment with a potent $P2Y_{12}$ receptor inhibitor (ticagrelor) are under clinical investigation in the GLOBAL LEADERS (ClinicalTrials.gov, NCT01813435) and TWILIGHT (ClinicalTrials.gov, NCT02270242) trials. Those trials may have the potential to reduce bleeding risk without influencing antithrombotic efficacy. In contrast to a PFT guided adjustment of antiplatelet therapy, the TAILOR PCI (ClinicalTrials.gov, NCT01742117) and POPular Genetics trial (ClinicalTrials.gov, NCT01761786) use a genetic approach of individualized DAPT. As clopidogrel response is dependent on CYP2C19 polymorphisms,[44-47] these trials investigate the usefulness of selective genotyping (CYP2C19) during $P2Y_{12}$ receptor inhibitor treatment. All the published and ongoing trials in concert are important as attempts to move forward and to pave the way for a contemporary concept of a more personalized $P2Y_{12}$ receptor inhibitor therapy that includes both escalation and de-escalation strategies for selected patients.

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