Dual Antiplatelet Therapy De-escalation Strategies

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Dual antiplatelet therapy (DAPT), the combination of aspirin (ASA), and a $P2Y_{12}$ inhibitor, protects against stent thrombosis and new atherothrombotic events after a stent implantation or an acute coronary syndrome, but exposes patients to an increased risk of bleeding. In most current practices, the $P2Y_{12}$ inhibitor is stopped at 6 to 12 months and ASA is continued indefinitely. The advent of safer stents, with less risk of stent thrombosis, has challenged this standard of care, however. A number of alternative strategies involving earlier de-escalation of the antiplatelet therapy have therefore been proposed. In these approaches, standard DAPT is switched to a less potent antithrombotic combination at an earlier time-point than recommended by guidelines. Three different de-escalation variations have been tested to date. The first one maintains DAPT but switches from the potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel to either a lower dose or to clopidogrel, while maintaining ASA. The 2 other approaches involve changing DAPT to a single antiplatelet at some earlier time-point after the percutaneous coronary intervention procedure, by stopping either the $P2Y_{12}$ inhibitor or ASA. These strategies have all demonstrated some benefit in clinical trials so far, but especially the contribution of ASA in secondary prevention is clearly evolving as its role in increasing bleeding complications while not providing increased ischemic benefit is becoming more and more clear. In contemporary practice, the type and duration of DAPT should now be based on an individualized decision, and the de-escalation strategies, if used wisely, can be added to the existing options. **(Am J Cardiol 2021;144:S23−S31)**

After percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS), patients require dual antiplatelet therapy (DAPT) to minimize the risk of new atherothrombotic events. DAPT usually consists of low-dose aspirin (ASA) with either clopidogrel in stable coronary artery disease (CAD) or the more potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor after ACS. The default guideline-recommended length of DAPT after PCI for stable CAD is 6 months, and is at least 12 months after ACS, although longer DAPT durations should be considered in patients with high ischemic risk and shorter in those with high bleeding risk.[1,2] At these time-points, the P2Y12 inhibitor is in most current practice usually discontinued, and low-dose ASA is continued indefinitely. The rationale behind stopping the $P2Y_{12}$ inhibitor and continuing only ASA is that the risk of thrombotic events is especially high in the first months after the intervention, but decreases afterwards.

The downside of DAPT, however, is that it exposes patients to an increased risk of bleeding. With the advent of safer stents and implanting techniques, the focus has shifted to the prevention of bleeding complications while keeping ischemic risk low, rather than vice versa.

Stents now have biocompatible (or no) polymers, safer antiproliferative drugs and thinner struts. With contemporary stents, the process of re-endothelialization is largely completed within a few months, protecting the stented segment against stent thrombosis thereafter. In addition, the stent platforms have improved, making drug-eluting stents (DES) much safer to deliver. Implanting techniques with the help of intracoronary imaging modalities have also been optimized, with the intent to minimize the risk of stent thrombosis. Even so, with contemporary DES, DAPT remains necessary for most PCI patients without an indication for oral anticoagulation.

Although it is clear that periprocedural DAPT is absolutely essential,[3] the evolving interventional and antithrombotic therapies have thus made it less straightforward to decide what the subsequent default DAPT strategy should be, and for how long it should be maintained. As it has become clear over the years that not only serious but also minor bleeding complications contribute to new ischemic events, a number of alternative strategies involving de-escalating the antiplatelet therapy have been proposed. What these approaches all have in common is that standard DAPT is switched or "de-escalated" to a less potent antithrombotic combination at an earlier time-point than recommended by guidelines. Three different variations to antiplatelet de-escalation have been tested to date, and will form the focus of this review (Figure 1). The first one maintains DAPT but switches from the potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel to either a lower dose or to clopidogrel, while maintaining ASA. The 2 other strategies involve changing DAPT to a single antiplatelet at some earlier time-point after the PCI procedure, by stopping either the $P2Y_{12}$ inhibitor or ASA.

De-escalation of the $P2Y_{12}$ Inhibitor

The landmark subanalyses from Platelet inhibition and patient Outcomes (PLATO) and Trial to Assess Improvement

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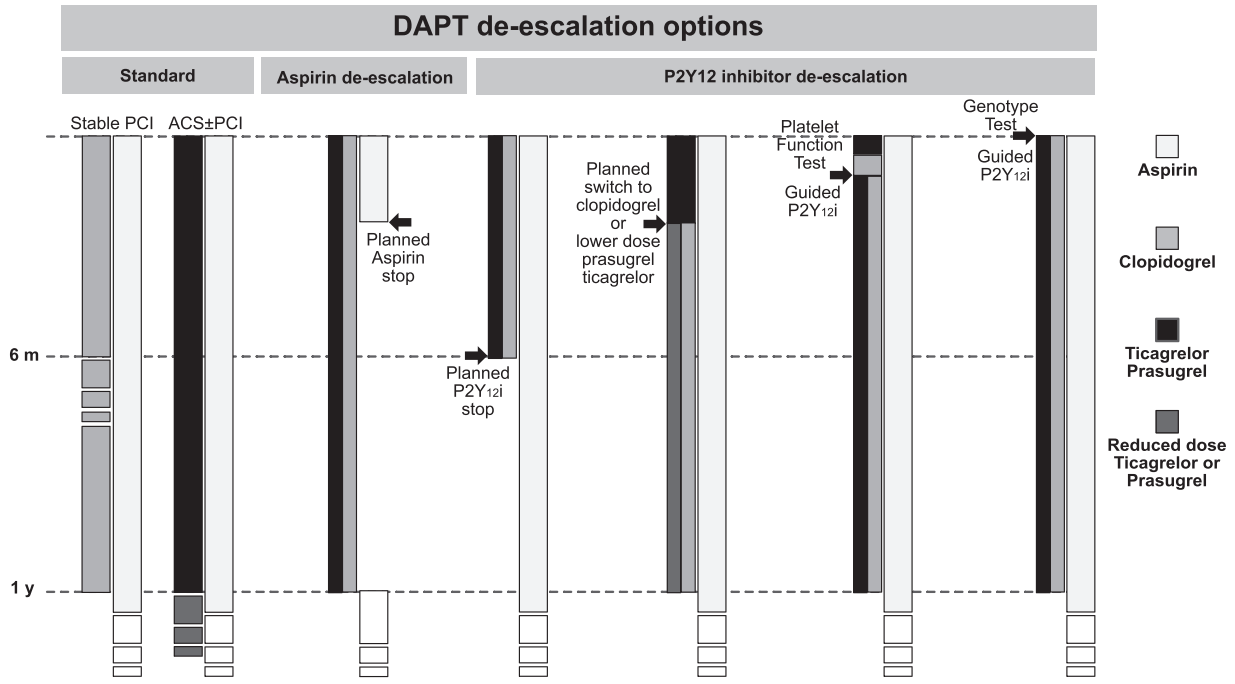

Figure 1. Dual antiplatelet (DAPT) de-escalation options. $P2Y_{12}i$ = P2Y12 inhibitor; ACS = Acute Coronary Syndrome; PCI = percutaneous coronary intervention.

in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction suggest that most of the benefit in reducing ischemic complications with a more potent $P2Y_{12}$ inhibitor occurs early after an ACS.[4,5] Consequently, as a strategy to lower bleeding risk, it makes sense to downgrade to a less potent antiplatelet combination after the early phase. De-escalation while maintaining DAPT can be done by switching ticagrelor or prasugrel from their normal dose to a lower, less potent dose, or to the less potent $P2Y_{12}$ inhibitor clopidogrel while continuing ASA, or by selecting the $P2Y_{12}$ based on platelet function or genetic testing.

The first de-escalation study was the open label single-center timing of platelet inhibition after acute coronary syndrome (TOPIC) study, which examined the impact of a planned default, unguided de-escalation at 1 month

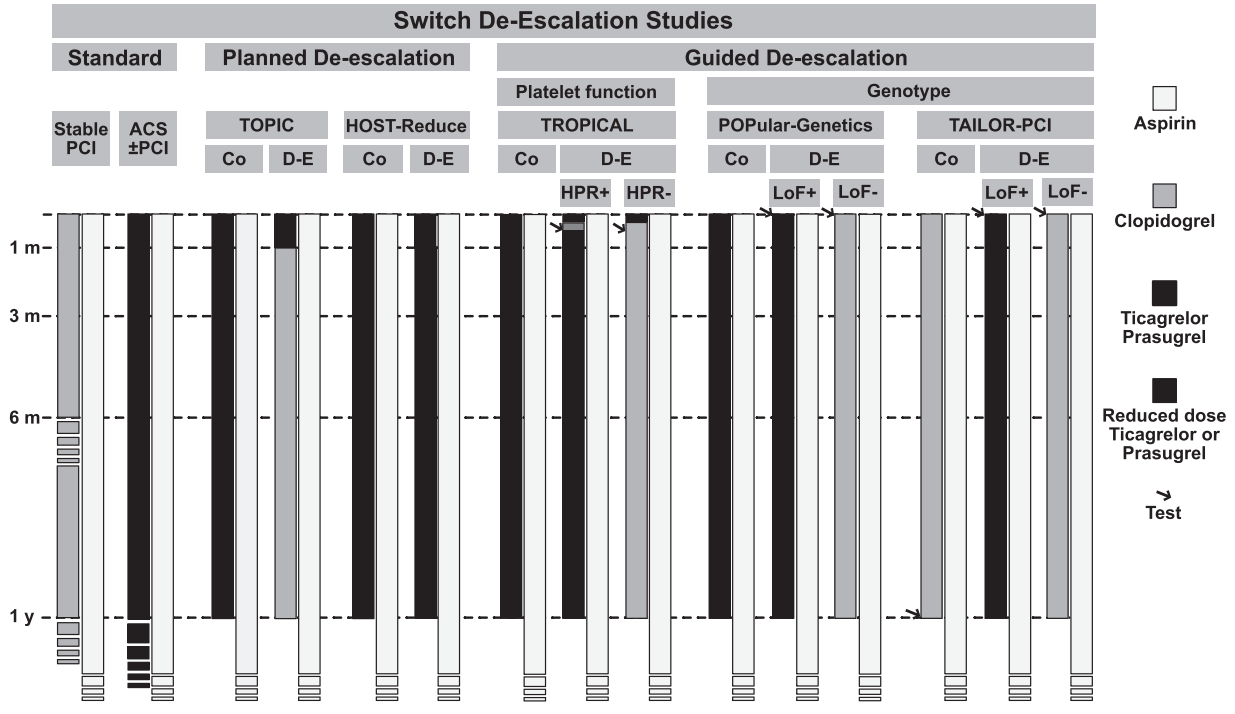

Figure 2. De-escalation studies in which either the $P2Y_{12}$ inhibitor or aspirin was discontinued. ACS = Acute Coronary Syndrome; PCI = percutaneous coronary intervention; Co = Control arm; D-E = de-escalation arm; LoF= loss-of-function allele on genotyping; HPR = high platelet reactivity.

(Figure 2).[6] TOPIC randomized 646 ACS patients on ticagrelor or prasugrel who underwent a PCI and remained without adverse events at 1 month after the procedure to either continuing the same $P2Y_{12}$ inhibitor or to a switch to the less potent clopidogrel. ASA dosing was not changed. The primary end point, a net composite of cardiovascular death (CVD), urgent revascularization, stroke and BARC classification ≥2 bleeding 1 year after the ACS, was significantly lower in the switched arm (13.4%) than in the continuation arm (26.3%, hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.34 to 0.68). This difference seemed to have been mainly driven by a lower risk of minor bleeding complications with clopidogrel. Although the number of ischemic events in this single-center study was too small to draw general conclusions, no difference in ischemic complications was observed.

Another approach to limiting bleeding risk is to guide the choice between a potent $P2Y_{12}$ inhibitor versus clopidogrel by the patient's antiplatelet response to clopidogrel. Indeed, patients with sufficient platelet inhibition under clopidogrel might not require the extra protection against new ischemic events provided by a more potent $P2Y_{12}$ inhibitor. Such a strategy was tested with the guidance of platelet function testing in the Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) study, and with genotype-guided platelet function prediction in POPular-Genetics and Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI).

The open-label TROPICAL-ACS study randomized 2,610 ACS patients who underwent a PCI to standard prasugrel for one year versus a platelet-function guided strategy.[7] All patients received 1 week of prasugrel (10 or 5 mg) followed by 1 week of clopidogrel and then underwent a platelet function test; patients with sufficient platelet inhibition were then kept on clopidogrel, whereas the other patients (39%) were switched back to prasugrel. The primary end point, a net clinical benefit combination of CVD, myocardial infarction (MI), stroke, or BARC classification ≥2 bleeding, was not different between the 2 treatment strategies (noninferiority p = 0.004). The rates of individual ischemic and bleeding end points were low and also not different between the 2 arms. Given the absence of a reduction in both minor and major bleeding after de-escalating to clopidogrel, it remains unclear what the benefit of such a strategy involving multiple drugs and an early revisit for platelet function testing could be, apart from cost. In addition, with such an approach all patients are in fact de-escalated to clopidogrel 1 week after their acute event, and this practice might not be sufficiently safe in patients with a very high ischemic risk.

The choice between clopidogrel and a more potent $P2Y_{12}$ inhibitor can also be guided by genotyping for the presence of gene variants that contribute to poor antiplatelet response to clopidogrel. Such an approach was tested in the open-label POPular-Genetics study, in which 2,488 primary PCI patients were randomized to standard ticagrelor, or a *CYP2C19*-genotype-guided approach.[8] In the genotype-guided arm, patients were tested for the presence of the *2 and *3 loss-of function alleles of this gene; noncarriers received clopidogrel (61%), while carriers were treated with ticagrelor or prasugrel (39%). The co-primary end points at 1 year were a net benefit composite of all-cause death, MI, stent thrombosis, stroke, or major bleeding, and PLATO-defined major or minor bleeding. The primary combined end point was similar with both treatment strategies: 5.1% in the genotype-guided arm versus 5.9% in the standard arm (noninferiority p <0.001). Major and minor bleeding, however, were significantly lower in the de-escalation arm (9.8%) than in the standard arm (12.5%, HR 0.78, 95% CI 0.61 to 0.98). This benefit was entirely driven by fewer minor bleeding complications in the guided arm.

A genotype-guided strategy was also tested in the TAILOR-PCI study.[9] Here, the aim was to test such a strategy among all loss-of-function allele carriers. Post-PCI patients (n = 5,302, 82% with an ACS) were randomized to a genotype-guided *escalation* strategy in which loss-of-function allele carriers received ticagrelor and noncarriers clopidogrel, versus a conventional 12-month clopidogrel-based DAPT strategy with genotyping at 12 months. The rates of the primary end point, CVD, MI, stroke, stent thrombosis and severe recurrent ischemia at 12 months, were numerically lower in the genotype-guided group although not statistically different between the 2 strategies. Among all loss-of-function allele carriers, the rate was 4.0% in the genotype-guided group and 5.9% in the conventional group (HR 0.66, 95% CI 0.43 to 1.02). Thrombolysis in myocardial infarction (TIMI) major or minor bleeding occurred infrequently and to a similar extent in both groups. Based on the results of these 2 studies, a genotype-guided strategy hence seems to avoid minor bleeding when de-escalating from ticagrelor-based DAPT, or to reduce ischemic risk when escalating from clopidogrel-based DAPT. An easy point-of-care CYP2C19 test is available and provides a result within 1 hour, although the costs for test kits and acquisition of the analysis equipment might be prohibitive for healthcare systems in less affluent regions and in any event would contribute to overall cost of such strategy.

A final and practical option is to decrease the dose of the potent $P2Y_{12}$ inhibitor rather than switching to clopidogrel, at an early time-point after the PCI. This approach was tested in the recent open-label HOST-REDUCE trial. In this trial, 2,338 ACS patients treated with PCI were randomized to conventional DAPT with 10 mg prasugrel or a de-escalation strategy with switching the prasugrel dose to 5 mg at 1 month. Most patients in HOST-REDUCE were eligible for the standard 10 mg dose of prasugrel. The primary end point was a net clinical composite of all-cause death, MI, stent thrombosis, repeat revascularization, stroke, and BARC class 2−5 bleeding. At 1 year, the primary end point occurred less frequently in the de-escalation group (7.2%) than in the conventional group (10.1%, HR 0.70, 95% CI 0.52 to 0.92). Bleeding complications were halved with the lower prasugrel dose (HR 0.48, 95% CI 0.32 to 0.73), although this benefit was completely driven by a reduction in minor (BARC 2) bleedings. Ischemic adverse events were low and similar with both strategies. As HOST-REDUCE was performed in an East Asian PCI population, it remains unclear whether these results also

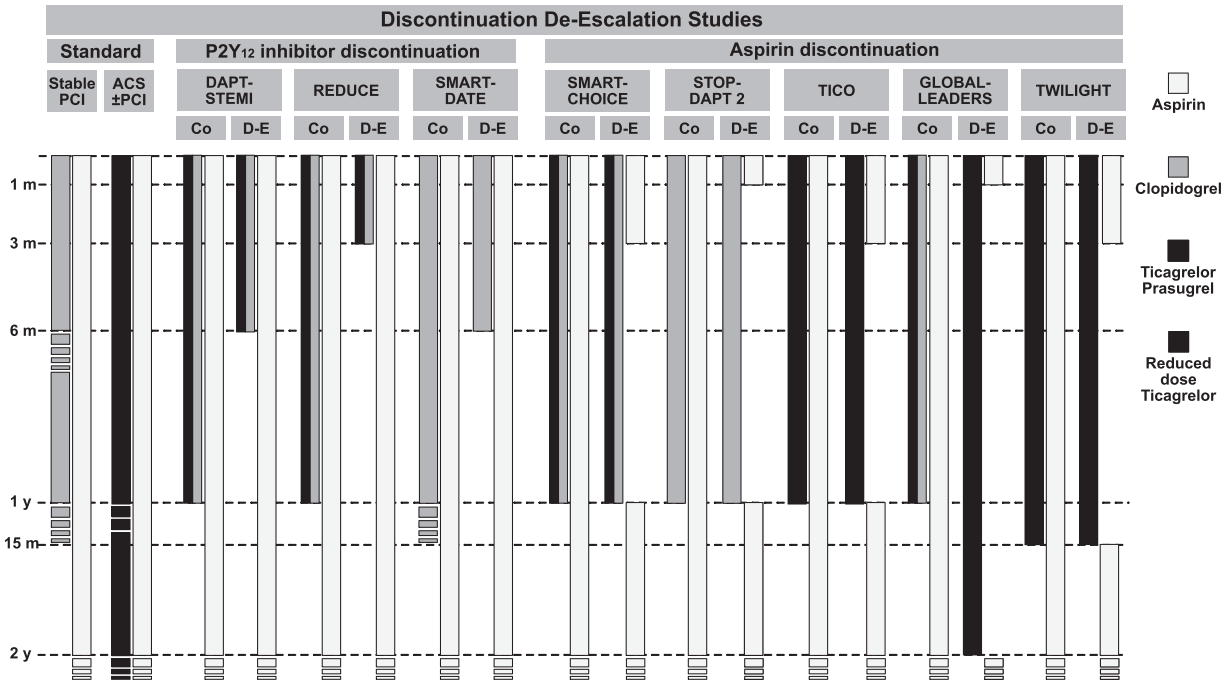

Figure 3. De-escalation studies in which either the $P2Y_{12}$ inhibitor or aspirin was discontinued. ACS = Acute Coronary Syndrome; PCI = percutaneous coronary intervention; Co = Control arm; D-E = de-escalation arm.

pertain to a western population that is usually less prone to bleeding but more prone to ischemic events.[10] Still, decreasing the dose of prasugrel or ticagrelor beyond the acute phase may be a promising de-escalation strategy in need of further study.

Early P2Y12 Discontinuation

An alternative for guided de-escalation or planned switching to clopidogrel is to de-escalate to ASA monotherapy at an earlier time-point after an ACS or PCI. This relatively straightforward strategy was tested in 3 studies of ACS patients treated with a contemporary DES (Figure 3). In the first trial, DAPT-STEMI, primary PCI patients who were event-free at 6 months (n = 870) were then randomized to ASA only versus DAPT continuation for an additional 6-month period.[11] At 2 years after the primary PCI, the primary net end point of death, MI, any revascularization, stroke or TIMI major bleeding was similar in both groups: 4.8% with ASA monotherapy after 6 months versus 6.6% with DAPT up to 1 year (HR 0.73, 95% CI 0.41 to 1.27, noninferiority p = 0.004). More than half of these events, however, were revascularization procedures, precluding any conclusion from this open-label study in relatively low-risk patients.

In the second study, REDUCE, 1,496 ACS patients were randomized to a 3-month versus 12-month DAPT regimen after successful DES placement.[12] Only 60% of the patients were discharged on prasugrel or ticagrelor. The primary net end point of death, MI, stent thrombosis, stroke, target vessel revascularization, and bleeding (BARC 2, 3, and 5) occurred to the same extent in both treatment arms at 12 months (8.2% vs 8.4% for 3 m vs 12 m, noninferiority p <0.001) and at 24 months (11.6% vs 12.1%, noninferiority p <0.001). Major bleeding was not different, whereas all-cause mortality was numerically higher with ASA monotherapy from 3 months onward (3.1% vs 2.2% with DAPT, p = 0.27). There were also twice as many patients with stent thrombosis that occurred with ASA alone (12 vs 6).

Finally, in the SMART-DATE study, a 6-month DAPT duration followed by ASA monotherapy was compared with 12-month or longer DAPT treatment in 2,712 ACS patients mainly on clopidogrel after DES implantation.[13] The primary end point was the composite of all-cause death, MI or stroke at 18 months, and occurred at a similar rate in both groups (4.7% with 6-m DAPT vs 4.2% with ≥12-m, noninferiority p = 0.03). MI, however, was significantly more frequent with the shorter DAPT regimen: 1.8% versus 0.8% with ≥12-m DAPT (HR 2.41, 95% CI 1.15 to 5.05). Stent thrombosis rates were low, but numerically higher with the shorter DAPT regimen as well (15 vs 10). Bleeding complications (BARC 2-5) were not significantly different between the 2 strategies (2.7% with 6-m DAPT vs 3.9% with ≥12-m DAPT, p = 0.09). Taken together, the results from these trials do not really support a systematic, planned early de-escalation to ASA monotherapy in ACS patients treated with a DES. Still, such a strategy might still be warranted in patients with a high bleeding risk, and is to some extent supported by results from trials comparing BMS versus DES in such populations.[14,15] Registries suggest that such an approach occurs frequently in daily practice.[16,17]

Aspirin Discontinuation

The most recently studied early de-escalation alternative consists of stopping ASA while maintaining the $P2Y_{12}$ inhibitor. There are several good arguments to opt for such

a strategy. $P2Y_{12}$ inhibition in monotherapy appears to inhibit platelets in vivo to approximately the same extent as with DAPT.[18] Indeed, because $P2Y_{12}$ receptor activation is a critical step in thromboxane A2-mediated platelet aggregation in vitro, ASA does not seem to further block platelet aggregation when added to a $P2Y_{12}$ inhibitor.[19,20] Moreover, it has even been hypothesized that ASA in the presence of strong $P2Y_{12}$ inhibition could actually even increase ischemic risk due to off-target cyclo-oxygenase inhibition.[21] As a consequence, ASA discontinuation, at least at some timepoint beyond the acute phase, might be safer for PCI patients without compromising the protection against ischemic events. Five studies so far have tested this strategy, 3 moderate-sized studies from Asia (Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES (SMART-CHOICE), Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 trial (STOPDAPT-2) and Ticagrelor With or Without Aspirin in Acute Coronary Syndrome After PCI (TICO)) and 2 large international studies (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation (GLOBAL-LEADERS) and Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT)) (Figure 3).

STOPDAPT-2 (n = 3,045) and SMART-CHOICE (n = 2,993) both randomized patients after a DES to standard DAPT for 1 year versus 1 or 3 months of DAPT, respectively, followed by $P2Y_{12}$ inhibitor monotherapy (clopidogrel only in STOPDAPT-2 and clopidogrel, prasugrel or ticagrelor (non-randomized) in SMART-CHOICE).[22,23] In both studies, ischemic events were very low and not different between the 2 strategies, while bleeding risk was significantly lower in the de-escalation arm. The recent TICO trial randomized 3,056 ACS patients who underwent a PCI with a DES to either ticagrelor and ASA for 3 months followed by ticagrelor monotherapy up to 1 year versus standard ASA plus ticagrelor for 1 year.[24] In TICO, the investigators chose a net adverse clinical benefit endpoint combining bleeding and ischemic risk at 1 year, which included TIMI major bleeding, death, MI, stent thrombosis, stroke, and target-vessel revascularization. The incidence of the primary end point was significantly lower in the monotherapy arm than in the DAPT arm (3.9% vs 5.9%, HR 0.66, 95% CI 0.34 to 0.91). This benefit was largely driven by a 1.3% absolute reduction in the risk of major bleeding (HR 0.56, 95% CI 0.34 to 0.91). There appeared to be no excess of ischemic complications in the monotherapy arm; stent thrombosis occurred only in 6 patients in the monotherapy versus 4 in the DAPT arm (p = 0.53). In an unpublished prespecified subanalysis in only primary PCI patients in TICO, ticagrelor monotherapy was associated with a lower risk of major bleeding (0.9% vs 2.9% with DAPT, HR 0.32, 95% CI 0.12 to 0.87), while adverse ischemic events remained similar between the 2 strategies (*TICO-STEMI, presented on Oct 14 2020 at TCT*). As in SMART-CHOICE and STOP-DAPT, the event rate in TICO was low, perhaps in part reflecting the relatively lower risk usually observed in Asian PCI patients.[10]

GLOBAL-LEADERS was the first large-scale international trial (n = 15,968) comparing $P2Y_{12}$ monotherapy versus DAPT after PCI with a DES.[25] The design was somewhat complex: PCI patients were randomized to open-label DAPT with ticagrelor plus ASA for 1 month followed by ticagrelor monotherapy up to 2 years versus standard DAPT (with either ticagrelor or clopidogrel) for 1 year followed by an additional year with only ASA. The primary end point at 2 years was a composite of all-cause death and adjudicated Q-wave MI, the latter being a rather strict criterion by which to define MI, excluding smaller (non-Q-wave) infarctions. The trial failed to meet its primary objective: at 2 years, ticagrelor monotherapy (3.8%) was not superior to conventional DAPT (4.4%, RR 0.87%, 95% CI 0.75 to 1.01, p = 0.073). There was also no difference in the rates of stent thrombosis or major bleeding complications. Before the GLOBAL-LEADERS study was finished, the investigators introduced a noninferiority substudy termed The GLOBAL LEADERS Adjudication Sub-StudY (GLASSY).[26] GLASSY differed from the main trial by assessing both noninferiority and superiority of an expanded primary combined end point now including death and centrally adjudicated MI, stroke, or urgent target revascularization. It showed that ticagrelor monotherapy was noninferior (but not superior) to a traditional DAPT regimen in preventing ischemic events. There was no reduction in major bleeding complications, however. Landmark analyses on the other hand did show that the rates of myocardial infarction and stent thrombosis were lower with ticagrelor monotherapy *after* but not *before* day 365, the timepoint at which the $P2Y_{12}$ inhibitor was stopped in the comparator arm.

TWILIGHT, the second large trial studying ticagrelor monotherapy had a more straightforward design and was set up as a double-blind study.[27] TWILIGHT randomized 7,119 patients at 3 uneventful months on ticagrelor DAPT after PCI to either ticagrelor monotherapy or to continued ticagrelor DAPT. The primary end point was BARC type 2, 3, or 5 bleeding up to 1 year after randomization. The risk of bleeding was significantly lower in patients on ticagrelor monotherapy (4%) than in those on DAPT (7.1%, HR 0.56, 95% CI 0.45 to 0.68). The rate of all-cause death, MI, or stroke was identical in both groups (3.9%, p <0.001 for noninferiority). In addition, the rates of individual ischemic end points including MI and stent thrombosis were low and similar with both strategies. Thus, in PCI patients who have been uneventful on ASA plus ticagrelor for 3 months, discontinuing ASA significantly reduces the risk of bleeding but does not appear to expose them to a higher risk of ischemic events up to 15 months after the procedure.

A recent network meta-analysis combining these 5 trials on (early) ASA discontinuation and including over 32,000 patients set out to overcome the issue of the low rates of adverse cardiac events in each individual trial.[28] Major bleeding complications defined as BARC 3 or 5 bleeding at 12 to 15 months after PCI were found to be 40% lower on $P2Y_{12}$ monotherapy versus DAPT after PCI (HR 0.60, 95% CI 0.42 to 0.86). No excesses in adverse cardiovascular events (HR 0.88 95% CI 0.77 to 1.02), death (HR 0.85, 95% CI 0.70 to 1.03) or MI (HR 0.85, 95% CI 0.69 to 1.06) were observed. Stent thrombosis rates were very low: 0.50% in patients on $P2Y_{12}$ inhibitor monotherapy versus 0.42% with DAPT (HR 1.17, 95% CI 0.84 to 1.63).

Numerically, there was an excess of 13 stent thrombosis cases with monotherapy (n = 80) compared with DAPT (n = 67) but this appeared to be offset by fewer deaths (n = 200 vs 236) or MI (n = 173 vs 203) with monotherapy. Importantly, the results remained consistent when restricting the analyses to patients who only had a PCI for an ACS: among these patients, study-defined bleeding risk was halved with $P2Y_{12}$ monotherapy (HR 0.50, 95% CI 0.41 to 0.61), without a price to pay in terms of adverse cardiovascular events (HR 0.85, 95% CI 0.70 to 1.03). Taken together, $P2Y_{12}$ monotherapy de-escalation appears to be an attractive and safe post-PCI DAPT strategy.

Default De-escalation in High-Risk Patients?

After decades of DAPT trials, it is now clear that a uniform DAPT strategy for all PCI or ACS patients is no longer tenable. In fact, guidelines already endorse an individualized approach to DAPT, with a shorter DAPT duration for patients with a high risk of bleeding complications, and a longer one for those with a high ischemic risk.[1,2] With the net clinical benefit demonstrated in recent de-escalation trials, there are now even more options. For the physician, however, this means that it has become even more difficult to choose one of the many variations on the DAPT theme for the individual patient with a distinct ischemic/bleeding risk profile. While the evidence in general indicates that de-escalation reduces bleeding risk, the question remains whether such a strategy is a safe option for patients with a high atherothrombotic risk.

Patients who recently had a PCI for an ACS or who had a complex PCI procedure are considered to be at particularly high risk for new thrombotic events. ACS patients have a higher thrombotic state whereas patients who underwent a complex PCI often have more extensive CAD, more stents implanted, and, often, overlapping stents. Hence, one might question the appropriateness of early DAPT de-escalation in such patients, and many physicians might still prefer to keep them on DAPT for a (much) longer period. However, the same patients often have comorbidities predisposing them not only to a higher risk of ischemic events, but to bleeding complications as well. Indeed, guideline-defined high-risk features for stent-related ischemic events equally predict the risk of bleeding complications after PCI.[29] The PRECISE-DAPT investigators also elegantly showed that complex PCI patients only seem to benefit from longer-term DAPT when they also have a low risk of bleeding.[30] In other words, in patients with both ischemic and bleeding risk, bleeding risk itself and not ischemic risk should inform the DAPT strategy.[30]

Did high-ischemic risk patients in the de-escalation studies also benefit from an earlier ASA discontinuation? Additional insights come from a GLOBAL-LEADERS subanalysis in the 4,570 patients who underwent an intervention for complex disease PCI.[31] The investigators labeled an intervention as "complex" when it was a multivessel PCI or involved 3 or more stents, 3 or more lesions, a bifurcation procedure with at least 2 stents, or when the total stent length exceeded 60 mm. During the 2 years of follow-up, patients who underwent a complex PCI were more likely to experience an MI or a revascularization procedure than patients who had undergone a simple PCI. They also had a higher risk of bleeding complications. At 2 years after a complex PCI, monotherapy ticagrelor led to a lower incidence of the primary end point of death or Q-wave infarction (HR 0.64, 95% CI 0.45 to 0.85) than therapy with conventional DAPT for 1 year followed by ASA monotherapy. This benefit was driven by a significantly lower risk of both all-cause mortality (HR 0.67, 95%CI 0.48 to 0.93) and new Q-wave infarction (HR 0.53, 95% CI 0.31 to 0.91), and was in essence not observed in patient undergoing a "simple" PCI procedure (interaction p = 0.015). Interestingly, the benefit of ticagrelor monotherapy appeared to become larger as the number of high-risk features of complexity increased. In a landmark analysis, the benefit also seemed to have been confined to the first year after the intervention. During the second year, when the complex PCI patients were either taking ticagrelor or ASA, there were no differences in ischemic or bleeding rates. Bleeding risk, in contrast, was not different between the 2 treatment strategies, regardless of the number of complex features. When stratifying for type of presentation at baseline, the benefit of early ASA discontinuation was mainly observed among ACS patients. The same issue was analyzed from a slightly different perspective in 3 related reports, 2 in patients undergoing a PCI for multivessel PCI or those undergoing a bifurcation procedure, and a third one in ACS patients only.[32-34] The results of these analyses led to relatively similar conclusions and implications. These secondary analyses suggest that early ASA discontinuation could benefit high ischemic-risk patients, but also that potent platelet inhibition might not be necessary beyond the first year after PCI, regardless of the complexity of the procedure or the type of presentation at time of the intervention.

As in GLOBAL-LEADERS, the TWILIGHT investigators examined the effect of early ASA discontinuation on outcomes according to the complexity of the PCI procedure.[35] Here, the definition of a complex procedure was somewhat broader, and included a 3 vessels PCI, or having 3 lesions or more stented, a total stent length of more than 60 mm, a bifurcation with 2 stents implanted, atherectomy device use, left main PCI, bypass graft PCI or a chronic occlusion procedure. One year after randomization, ASA discontinuation resulted in fewer bleeding complications (BARC 2,3, & 5): 4.2% compared with 7.7% with DAPT (HR 0.54%, 95% CI 0.38 to 0.76). This was not associated with a higher risk of ischemic events, including definite or probable stent thrombosis (n = 5 (0.4%) vs n = 9 (0.8%) with DAPT, p = 0.54). Similar observations were made in diabetic patients, who often have more diffuse and complex CAD.[36]

Thus, judging from the available evidence so far, patients can benefit from an ASA-free de-escalation strategy, regardless of their ischemic risk. If available, platelet function or genotyping tests are also valid options to guide an individualized DAPT strategy, although the evidence for this approach is less convincing. Alternatively, de-escalation to a lower dose of prasugrel may also be an attractive strategy but requires confirmation in a broader population. Although the evidence for an early planned "downgrade" to clopidogrel after an ACS is weak, the lower cost with such a simple

approach will undoubtedly remain popular with many physicians throughout the world. In fact, the recent 2020 ESC NSTE-ACS guidelines now explicitly discuss these various forms of DAPT de-escalation as potential alternatives to standard 12-month DAPT with a potent $P2Y_{12}$ inhibitor.[37] The practical implementation of such an approach will still require careful and individualized judgment of the patient's risk, however, not only at the time of discharge but during the subsequent weeks or months as well. Hence, while in daily practice a decision to de-escalate may be discussed at the time of discharge, a careful re-evaluation at the time of the planned de-escalation will be advisable.

Next Steps

Although the evidence in favor of a default DAPT de-escalation strategy after a PCI and/or ACS is growing, several questions remain. First, when is the optimal timing for discontinuing ASA: at 1 month as in GLOBAL-LEADERS or at 3 months as in TWILIGHT? It might well be that discontinuing ASA at an even earlier stage, for example, at discharge, might be as safe and as efficient as a later transition to $P2Y_{12}$ monotherapy. Evidence from the dual versus triple therapy trials in atrial fibrillation patients undergoing PCI, however, suggest that this might expose some high-risk patients to an increased risk of adverse ischemic events.[38] A default immediate $P2Y_{12}$ monotherapy after an ACS is currently being studied in the Percutaneous Coronary Intervention followed by Monotherapy Instead of Dual Antiplatelet Therapy in the Setting of Acute Coronary Syndromes: The NEO-MINDSET Trial (NCT04360720). Additional insights will also come from other ongoing studies, including Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen (NCT03023020), A-CLOSE (NCT03947229) and Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis- Extended Antiplatelet Monotherapy (NCT2044250). Second, ASA might not necessarily need to be discontinued entirely in patients on a potent $P2Y_{12}$ inhibitor; perhaps a lower but twice a day ASA dosing scheme can maintain the antithrombotic benefit of ASA while lowering bleeding risk. Indeed, in the WilL Lower Dose Aspirin be More Effective Following ACS? pilot study, a 20 mg ASA bid dose provided adequate thromboxane-related platelet inhibition in ACS patients on ticagrelor, but with a reduced bleeding time.[39]

Third, the optimal timing to switch from a potent $P2Y_{12}$ inhibitor to low-dose ASA maintenance therapy after an ACS remains unclear. So far, the evidence still favors a transition at 1 year or later. Fourth, larger studies addressing the safety of switching prasugrel to a lower dose are needed. In addition, the risk/benefit of the 60 mg BID dose of ticagrelor in de-escalation strategies during the first year after an ACS requires further study. In the 52-patient ELECTRA pilot study, lowering the maintenance dose of ticagrelor from 90 mg bid to 60 mg bid at day 30 after a primary PCI yielded a similar level of platelet inhibition. A low dose ticagrelor de-escalation strategy is hence being compared with standard DAPT with clopidogrel after a complex PCI in the TAILORED trial (NCT03465644). Finally, more solid evidence on the safety of an early de-escalation strategy in high-risk STEMI or primary PCI patients is necessary. The TALOS (NCT 02018055) and ULTIMATE DAPT (NCT03971500) trials are currently studying standard DAPT versus ticagrelor monotherapy after 1 month in ACS patients, while a TWILIGHT-STEMI trial is in its design phase.

In conclusion, the different early DAPT de-escalation strategies have demonstrated some benefit so far, and although more solid support from large studies will be required before one or several of these options should overtake standard DAPT, the role of ASA in secondary prevention is clearly evolving as its role in increasing bleeding complications while not providing increased ischemic benefit is demonstrated. In any case, the type and duration of DAPT has more and more become an individualized decision, and the de-escalation strategies, if used wisely, should now be added to the existing options.

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