A tailplate therapy with aspirin is a cornerstone of secondary prevention in coronary artery disease (CAD), mainly to prevent recurrent ischemic events. Specifically, it is recommended to use aspirin indefinitely in all revascularized patients. This “secondary preventive effect” of antiplatelet therapy is even more important in patients at high risk, such as those with acute coronary syndromes. In these patients, dual antiplatelet therapy (DAPT) with clopidogrel in addition to aspirin should be given for 9–12 months, as evidenced by the Percutaneous Coronary Intervention subgroups of the Clopidogrel in Unstable angina to prevent Recurrent Events trial (PCI-CURE). However, in the large Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, DAPT was not superior to aspirin monotherapy. Thus, there is no firm trial evidence for a possible longer-term benefit of DAPT in CAD in high-risk patients with or without revascularization.

More recently, DAPT has been used successfully to prevent stent thrombosis (ST) after coronary stent implantation. According to the AHA/ACC guidelines for coronary intervention, DAPT is recommended for 1 month in patients with bare-metal stents without acute coronary syndromes and for 12 months in patients with bare-metal stents with acute coronary syndromes and for all patients with drug-eluting stents (DES). However, the 2010 European guidelines on myocardial revascularization state that convincing evidence for the duration of DAPT after DES implantation exists only up to 6 months, keeping in mind that the 12-month time period was suggested primarily for safety reasons. Main concerns against a DAPT duration ≥6 months after DES are the following: increased bleeding rates and costs; occurrence of ST irrespective of DAPT beyond 6 months; “premature” interruption of DAPT in case of unplanned surgery; and decreased ST rates beyond 6 months because of improved implantation techniques and newer generations of DES.

In view of the inconsistent and individually variable therapeutic effects of clopidogrel, two newer and more potent P2Y12 receptor inhibitors, prasugrel and ticagrelor, have been tested against clopidogrel. Both compounds showed superior outcomes, reducing ST-related clinical events up to 12 to 15 months. However, bleeding rates not related to coronary artery bypass surgery were increased with both drugs. This led to restrictions for the use of both drugs: prasugrel is contraindicated in patients with a history of a recent cerebrovascular event, whereas for patients weighing <60 kg and those >75 years of age, a reduced dose of the drug was suggested. For ticagrelor, a high rate of dyspnea and bradycardia was observed, concomitant doses of aspirin >100 mg seemed to mitigate the benefit, and renal insufficiency was a relevant contraindication. Importantly, the benefit of prasugrel was seen within the first days to months, and the Kaplan-Meier event curves continued to separate after 6 months. In contrast, the benefit of ticagrelor only appeared after 1 month, and the event curves stayed fairly parallel after 6 months. The lack of an early benefit of ticagrelor was puzzling, leading to the question of whether this would also be true in very high-risk patients.

In the current issue of Circulation, there are two studies that should shed more light on DAPT. Whereas Gwon et al addressed the ideal duration of clopidogrel in the Efficacy of Xience/Promus versus Cypher to Reduce Late Loss after stENTing (EXCELLENT) trial, Armstrong et al investigated a subgroup of the PLATelet inhibition and patient Outcomes (PLATO) trial with ST-elevation myocardial infarction in order to assess whether the effect of ticagrelor versus clopidogrel could be attributed to an early benefit of the drug in such high risk patients or rather to a later prevention of recurrent events only.

In EXCELLENT, 1443 patients receiving DES for stable CAD or acute coronary syndromes were randomized to 6 versus 12 months of clopidogrel in addition to continued aspirin treatment. Target vessel failure (ie, a composite of cardiac death, myocardial infarction, or ischemia-driven target-vessel revascularization up to 12 months) occurred at similar rates (4.8% and 4.3% for 6 versus 12 months DAPT, respectively). Thus, 6-month DAPT was not inferior to 12-month DAPT (P=0.001 for noninferiority with a margin of 4.0%). Bleeding rates were low and not significantly different between the two groups, although it was numerically at least twice as frequent in the 12- versus the 6-month treatment group. Patients with diabetes mellitus, a prespecified subgroup, benefited by fewer target vessel failures with 12-month compared with 6-month DAPT. These findings are in agreement with several observational reports concluding that DAPT may not be necessary beyond the initial 6 months, at least in low-risk patients. Recently, the results of the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY) were
presented.14 PRODIGY randomized 1970 patients 30 days after stenting to 6 versus 24 months of clopidogrel-based DAPT and thus excluded early procedure-related ST events. After 2 years, there was no benefit of prolonged DAPT in reducing ST or related events, but there was a significantly increased bleeding rate. In view of the low event and bleeding rates in both trials, these findings are not definitive, and larger randomized comparisons are needed. In fact, four other ongoing trials will compare 12-month clopidogrel with a shorter duration, Safety and Efficacy of Six Months Dual Antiplatelet Therapy after Drug-Eluting Stenting (ISARSAFE) trial (NCT00661206), Second-Generation Drug-Eluting Stent Implantation followed by Six versus Twelve Month Dual Antiplatelet Therapy (SECURITY) trial (NCT00944333), Is There A Life for Drug-Eluting Stents after Discontinuation of Clopidogrel (ITALIC) trial (NCT00780156), and Effect of Image Optimization with Contrast on the Diagnostic Accuracy of Dobutamine Echoangiography in Coronary Artery Disease (OPTIMIZE) trial (NCT01113372). Overall, in almost 20 000 patients a 3- to 6-month regimen will be compared with 12-month clopidogrel-based DAPT. Other ongoing trials will address whether even longer-term DAPT may reduce late recurrent event rates, the large Dual Antiplatelet Therapy (DAPT) trial (NCT00977938),15 Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents (DES-LATE) trial (NCT01186146), Double Randomization of a Monitoring Adjusted Antiplatelet Treatment versus a Common Antiplatelet Treatment for DES Implantation, and an Interruption versus Continuation of Double Antiplatelet Therapy one Year after Stenting (ARCTIC) trial (NCT00827411), and Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation (OPTIDUAL) trial (NCT00822536) (all at www.clinicaltrials.com). Overall, some 30 000 randomized patients will help to decide whether clopidogrel-based DAPT prolonged >1 year may provide any clinical benefit and, if so, in which patients and at what bleeding risk.

The hypothesis that a P2Y12 inhibitor more potent than clopidogrel could provide an even greater benefit in DAPT was positively answered in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI 38)9 and in PLATO.10 In this issue of Circulation, Armstrong and colleagues report on a subgroup of 3211 ticagrelor-treated patients and 3084 clopidogrel-treated patients at highest risk; that is, those with ST-elevation myocardial infarction and at least 1 mm ST-elevation in 2 leads of their qualifying electrocardiograms.12 They observed that patients with greater ST-segment shift had higher rates of 1-year vascular death/myocardial infarction, and patients with incomplete resolution of their ST-segment shift (defined as <50% resolution of the sum of ST-deviation) had a worse outcome than those with more complete ST-resolution. Of note, a tendency to provide a greater benefit in patients with greater ST-segment resolution was noted for ticagrelor, but none of these relations were significantly affected by treatment assignment. The authors conclude that even in these high-risk patients, the main benefit of ticagrelor observed in the PLATO trial does not seem to be attributable to enhanced early reperfusion but rather attributable to the prevention of late recurrent vascular events. Thus, ticagrelor seems to have its greatest benefit not in the primary/early prevention of ST, but rather in the later phase in which prevention of recurrent ischemic events is key. This would parallel observations from the TRITON-TIMI 38 trial, in which a late benefit of prasugrel was also documented.10 Unfortunately, both trials were terminated after 12 and 15 months, respectively; thus, it remains unknown whether their “secondary preventive” effect would continue if the drug would have been given for a longer time. However, in view of the increased rate of nonbypass surgery-related bleedings with both drugs, the risk-benefit balance must be questioned. Obviously there is no sharp cut-off time between the occurrence of ST and that of recurrent ischemic events; however, the rate of ST markedly decreases after 6 months, whereas the rate of events related to CAD progression increases with similar rates of target-vessel versus remote vessel origin after 3 years.16

What do these two studies in the current issue of Circulation teach the cardiologist treating individual patients? First, DAPT with clopidogrel and aspirin given for 6 months to prevent ST during this most “vulnerable” healing phase after stent implantation seems to be sufficient in most patients. Second, there is increasing doubt that the benefit of reducing late ST events outweighs the risk of bleeding events with longer-term DAPT for this indication (ie, prevention of ST) in the majority of DES patients. Third, although prevention of ST and late recurrent ischemic events is improved with DAPT using more potent antiplatelet drugs than clopidogrel within the initial 6–12 months, it is still unknown whether DAPT given beyond 1 year will also achieve this goal. Finally, only higher-risk patients (ie, those with unstable disease presentation and extensive/complex CAD) may qualify for prolonged DAPT, and factors such as type of stent used, result of the procedure, bleeding risk, and patient compliance have to be considered. Last but not least, another still unanswered question is the role of aspirin in a prolonged antiplatelet treatment regimen. Does aspirin add to the benefit of more potent P2Y12 inhibitors at all, or does it only increase the unwanted bleeding risk? Recent analyses suggest that higher aspirin doses may just do the latter, such that doses >100 mg/d should be avoided in DAPT. Trials in this field are warranted to tailor future DAPT “sizes” to individual patients.

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References


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Matthias Pfisterer, Christoph Kaiser and Raban Jeger

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