Despite the overwhelming success of percutaneous cardiac interventions, the interventional practitioner is commonly faced with a number of very simple questions, the answers of which should be obvious but in truth are completely unknown. Perhaps the most common such question concerns the appropriate duration of dual antiplatelet therapy (the combination of aspirin and an inhibitor of platelet P2Y$_{12}$) in patients who have received intracardiac stents. Most interventional cardiologists receive several such calls per week from patients and professional colleagues and often have to spend a considerable amount of time negotiating antithrombotic drug treatment strategies in patients who need to undergo noncardiac surgical procedures.

The truth is that as we enter the third decade of stent use, we know much less about the need for antithrombotic therapy after stent implantation than we (and our patients) would like. Much of our current knowledge is derived from early studies in patients receiving bare metal stents. When stents were first implanted, the recommended antithrombotic therapy included a variety of marginally effective antiplatelet therapies and toxic doses of warfarin and heparin. In 1995, Colombo et al observed that optimization of stent deployment with ultrasound followed by treatment with aspirin and ticlopidine was associated with lower rates of stent thrombosis, less bleeding, and shorter hospital stays than historical reports. We probably never would have entered the modern stent era without these important observations, which were rapidly confirmed by a series of randomized trials. However, the appropriate duration of thienopyridine therapy after stenting was unknown. Whereas 1 report indicated that a 2-week course might be sufficient, the randomized Clopidogrel for the Reduction of Events During Observation (CREDO) trial showed that a year of dual antiplatelet therapy reduced the rate of a combined end point of death, myocardial infarction, or stroke by 27% compared with 30 days of therapy. In fact, this trial, performed >10 years ago, was the only trial until 2010 that tested the required duration of thienopyridine therapy after stenting.

Drug-eluting stents (DES) have been in widespread use for more than a decade and are used in the majority of patients receiving intracoronary stents. In the initial trials, dual antiplatelet therapy was recommended for 3 months after sirolimus-eluting stents and for 6 months after paclitaxel-eluting stents were implanted, although many patients in these trials received the drugs for longer periods. The importance of continuing thienopyridine therapy during these periods was strongly reinforced by the observation that premature discontinuation (<3 months for sirolimus-eluting stents and <6 months for paclitaxel-eluting stents) was an extremely powerful risk factor for stent thrombosis. An early report indicated that neointimal coverage of stent struts was nearly complete within 30 days after implantation in experimental animals. However, clinical experience rapidly showed that endothelialization of a first-generation DES is incomplete in humans with atherosclerosis, leaving stent struts exposed to the arterial lumen months to years after stent implantation, and that thrombi formed at the exposed sites. Such early reports were followed by reports of a continuous hazard of stent thrombosis as high as 0.5%/y for $\geq$5 years after DES placement. Coupled with observations of unexpected stent thrombosis after clopidogrel was stopped in the Basel Stent Cost-Effectiveness Trial–Late Thrombotic Events (BASKET LATE), in the Duke data bank, and in the Kaiser Permanente database, as well as suggestions of a “rebound” phenomenon in patients whose clopidogrel was terminated after an acute coronary syndrome, such observations led to recommendations for prolonged courses of therapy with clopidogrel after DES placement. An American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American College of Surgeons/American Dental Association science advisory recommends treatment with aspirin and a thienopyridine (presumably extensible to all P2Y$_{12}$ antagonists) for a minimum of 1 year after DES implantation, and such recommendations have found their way into various guidelines in the United States and Europe. Some observers have recommended an “indefinite” duration of therapy in patients at low risk for bleeding. However, in many other observations, the duration of therapy with thienopyridines beyond either 6 or 12 months had little bearing on the likelihood of late stent thrombosis.

Thus, the dilemma faced by clinicians is clear. There is ample evidence that patients who have received DES face a prolonged period during which they are at risk of stent
thrombosis and its clinical sequelae. On one hand, the mechanistic explanations would seem to favor continued vulnerability to platelet-mediated thrombosis. However, clinical data concerning the need for prolonged dual antiplatelet therapy are at best equivocal. Of course, answering this question would require a randomized trial to overcome the complex confounding that is inevitable in registry and data bank studies. The Clopidogrel Use and Long-Term Safety After Drug-Eluting Stents Implantation (ZEST-LATE) trial and the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated With Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE) trial randomized patients who had been event free after 12 to 18 months of dual antiplatelet therapy following stent implantation to continue aspirin and clopidogrel or aspirin alone. Follow-up lasted 19 months. Most patients received sirolimus-eluting stents, with about one fourth receiving paclitaxel-eluting stents and about 20% receiving zotarolimus-eluting stents. The trials were designed with an expected event of 5% at 2 years, but observed rates were <2% with a trend favoring the shorter duration of therapy. Valgimigli and the PRODIGY investigators have provided a major next step to answering this issue by extending the population to include more current-generation stents and by shortening the duration of 1 arm to 6 months of dual antiplatelet therapy. They performed a factorial randomization of >2000 patients to receive a thin-strut bare metal stent, a paclitaxel-eluting stent, a zotarolimus-eluting stent, or an everolimus-eluting stent and to receive either 6 or 24 months of dual antiplatelet therapy. All patients received aspirin. Patients receiving bare metal stents who were randomized to 6 months of therapy could have stopped the therapy at 30 days. Randomization to an antiplatelet strategy was performed 30 days after implantation; the study was designed with 80% power to detect a 40% reduction in a primary end point of all-cause mortality, myocardial infarction, or stroke. At 2 years, event rates were considerably higher (10%) than in the LATE trials; no difference was observed in the primary end point, any of its components, or the risk of definite stent thrombosis. There was, however, an excess of bleeding in patients assigned to 24 months of thienopyridine therapy.

Thus, 2 trials comprising nearly 5000 patients indicate that courses of clopidogrel exceeding 12 months do not contribute favorably to patient outcomes and may in fact be detrimental. Both trials included the majority of patients screened and had relatively high proportions of patients with multivessel disease, complex lesions, and long stents. Is it now time to recommend that thienopyridine therapy be terminated after 6 or 12 months of therapy after DES implantation? The answer is probably not, for several reasons. First, and most obvious, a much larger trial, the Dual Antiplatelet Therapy Study (DAPT), is in the process of enrolling >23 000 patients with DES and approximately 3 000 patients with bare metal stents to either 12 or 30 months of dual antiplatelet therapy, with patients identified at the time of stent implantation and stratified according to clinical and angiographic “complexity.” Results are scheduled to be available in 2014. Unlike the 2 preceding trials, therapy will be blinded and allocation will be masked. Thus, it would make little sense to establish a firm policy while this large and methodologically rigorous trial is underway.

A number of other issues should cause the PRODIGY and LATE trials to be regarded as preliminary. Neither trial thus far has been designed to distinguish outcomes between patients with features that suggest high risk (acute coronary syndrome, long stents, bifurcation stents, kidney disease, diabetes mellitus) and those whose baseline risk is low. It is entirely conceivable that there will be heterogeneity between such groups. Another important issue to consider is that an increasing number of patients receive treatment with the third-generation P2Y12 antagonists prasugrel and ticagrelor. These drugs have greater activity against platelet aggregation than does clopidogrel; the balance between bleeding risk and ischemic event prevention may differ between short- and long-term therapy when these drugs are used. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial, a 15-month course of prasugrel proved superior to treatment with clopidogrel in patients who underwent coronary interventions for acute coronary syndromes; landmark analysis confirmed that the event curves remained divergent for the full 15-month period. Additionally, an unanticipated mortality benefit was observed in the Comparison of AZD6140 and Clopidogrel in Patients With Acute Coronary Syndrome (PLATO) trial of ticagrelor compared with clopidogrel. If verified in subsequent trials, these findings may provide rationale for continuing long-term P2Y12 antagonism with newer drugs after the implantation of stents in patients with acute coronary syndromes.

Several other questions also require answers. A curious and often underappreciated feature of the BASKET LATE trial was that although stent thromboses appeared to cluster after clopidogrel was stopped, they did not occur only during the 7- to 10-day period when one would have expected the platelet pool to be renewed and circulating platelets to be fully susceptible to activation. Rather, the median time to stent thrombosis was ~90 days. This finding is quite concerning and supports the need for prolonged follow-up to allow the accurate assessment of the risk (or benefit) of stopping P2Y12 antagonists after stent implantation. The thrombotic system consists of a complex series of prothrombotic and antithrombotic systems that are perpetually in flux but are usually well balanced. Temporal fluctuations in platelet reactivity and in thrombin generation have been documented repeatedly over the last several decades. It may well be that a rare but temporary imbalance between these 2 systems favoring thrombosis may be all that is required to cause an incompletely endothelialized stent to develop in situ thrombosis after having been stable for a considerable period of time. When one considers that ~5% of patients undergo major noncardiac surgery within the first year after stent placement and the risk of myocardial infarction is considerably increased in this setting, the case for even longer periods of follow-up can be made strongly.
A final issue concerns heterogeneity among stent types. There is histopathological evidence that endothelial coverage of stent struts may be greater with current designs compared with early-generation DES, and reported rates of stent thrombosis appear to be lower. The LATE trials included patients with predominantly first-generation sirolimus-eluting stents. In PRODIGY, only one fourth of patients received a paclitaxel-eluting stent; twice as many received everolimus- or zotarolimus-eluting stents. Thus, the power to discern a difference between short- and long-term dual antiplatelet therapy for paclitaxel-eluting stents is limited; for a large number of patients who have previously undergone implantation of a first-generation DES, the requisite duration of antiplatelet therapy is still unknown and may well be different from that for patients with current-generation stents.

How does the overall picture look? There does not seem to be much current evidence favoring indefinite dual antiplatelet therapy. However, the view is clouded by the high degree of heterogeneity among patient characteristics, among stent designs, and possibly among drug treatments. The conservative (and default) view ought to be that the 12-month duration of therapy was established by the CREDO trial and that the findings of TRITON-TIMI 38 favor extended therapy in high-risk patients. These findings notwithstanding, the logical approach remains continuing dual antiplatelet therapy for a minimum of 12 months in patients who have received DES, with longer durations currently reserved for patients who have had complex presentations or difficult stent procedures and earlier termination reserved for patients with poor drug tolerance, all the while awaiting the results of the more definitive DAPT study.

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References


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