The introduction of drug-eluting stents (DES) was heralded by euphoria when early reports suggested near zero percent restenosis. However, pre-clinical DES studies had suggested less-complete vessel healing, and the initial recommendation was to increase the use of dual antiplatelet therapy to 3 to 6 months. This initial excitement was significantly tempered by the realization of late (>1 year) stent thrombosis and potentially of death and myocardial infarction (MI). This was documented by a variety of sources, including the Food and Drug Administration (FDA); case reports (1); and clinical studies and registries such as BASKET-LATE (Basel Stent Cost-Effectiveness Trial—Late Thrombotic Events) (2), SCAAR (Swedish Coronary Angiography and Angioplasty Registry) (3), and the Denmark registries (4). Subgroup analyses demonstrated that stent thrombosis was more prevalent in several clinical (diabetes, older age, renal failure) and angiographic subsets (ostial, bifurcation, overlapping stents, prior brachytherapy) and was particularly potentiated by clopidogrel withdrawal (5). For example, Airoldi et al. (6) showed that stent thrombosis occurred on average after 13 days if clopidogrel was discontinued within the first 6 months of stent placement. However, if clopidogrel was discontinued after 6 months of stent placement, stent thrombosis occurred on average 90 days later, suggesting different pathophysiological mechanisms of subacute and late stent thrombosis.

The rapid penetration of DES use (near 90%) resulted in significant application in “off-label” indications, which are associated with increased adverse events for both DES and BMS (7). Interestingly, long-term follow-up of patients in randomized trials has not shown an increased cumulative risk of death/MI, but some landmark analyses censoring events before 6 months have shown an additional 0.1% to 0.5% risk of DES thrombosis starting at 6 months after stent deployment (8,9). These findings led to major debate regarding the clinical usefulness of DES in scientific circles, regulatory agencies, and the public, leading to a reassessment of the appropriate indications for DES, which hitherto had only shown a decrease in target vessel revascularization (TVR) but not death and MI (10). In a case of the perfect storm, concurrent publication of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial intensified the debate of the role of percutaneous coronary intervention (PCI) in stable angina, leading to a downward re-equilibration of DES use (11).

Compared with BMS, DES resulted in markedly reduced neointima formation but also in delayed endothelialization, more inflammation, hypersensitivity, thrombus formation, and outward remodeling, which might prolong the window of vulnerability to stent thrombosis (12). With increasing concern about late stent thrombosis, the FDA along with the American Heart Association/American College of Cardiology (AHA/ACC) and recently updated PCI guidelines (13) have empirically suggested at least 1 year of clopidogrel in patients not at high risk for bleeding, making this a Class I, Level of Evidence: B indication. Clopidogrel use beyond 1 year was designated a Class IIb, Level of Evidence: C indication.

In this issue of the Journal, Brar et al. (14) provide valuable information regarding the duration of clopidogrel therapy after DES. They evaluated a consecutive series of 749 diabetic patients for 18 months who underwent first-time PCI with either DES or BMS at a pre-paid system with near complete access to the number of clopidogrel prescriptions filled, dose, and number of pills dispensed. Increased duration of clopidogrel use was associated with a significantly lower incidence of death and MI (3.2%, 9.4%, and 16.5% for clopidogrel duration >9 months, 6 to 9 months, and <6 months, respectively) in both the DES and BMS groups. Furthermore, this finding persisted even when data in the first 6 months were censored, consistent with a durable effect. In a secondary analysis, the incidence of death and MI did not differ by stent type, but this analysis is likely underpowered. This study also lacks data on nondiabetic patients, and this system of health care delivery is...
not representative of that for most patients who are receiving DES in the U.S. Nonetheless, it provides important data in a patient subgroup that is at highest risk of stent thrombosis, restenosis, progression of atherosclerosis, and new thrombotic events (15).

These data are consistent with and extend the findings of Eisenstein et al. (16), who also showed that extended clopidogrel use was associated with lower adjusted rates of death and MI. In that study, adjudication of clopidogrel use was less reliable, because it was based on patient self-report and the incidence and outcomes in diabetic patients was not reported. These 2 studies in composite provide reassuring data that extended clopidogrel use is associated with improved outcomes and substantiate the AHA/ACC recommendation for 1 year of clopidogrel in patients receiving DES. Both of these studies are limited by the observational nature, the presence of several important baseline differences in groups, lack of reporting on rates of major bleeding, and undeniable physician selection bias in choosing the duration of clopidogrel. Therefore, these findings need to be validated in randomized clinical trials.

The initial reports of increased death and MI in DES registries have recently been counterbalanced by several new analyses (Ontario, Massachusetts, and New York registries) showing at least similar if not better overall clinical outcomes of DES versus BMS with continued reduction in TVR (17). Furthermore, the initial worse outcomes in patients receiving DES in the SCAAR registry have not been confirmed in longer-term follow-up. Finally, data from a Medicare database of over 75,000 patients suggest a mortality benefit of DES compared with BMS (18). The reasons for these disparate results are not yet clear but might reflect better patient selection, increased use of BMS in patients who cannot sustain prolonged clopidogrel treatment, and increasing duration of clopidogrel therapy. However, it is evident that significant improvements must be made in reducing restenosis in a safer manner and in a manner that does not hold patients and physicians captive to long-term thienopyridine use. These include newer generation of stents with low risk of thrombogenesis, novel pharmacologic therapies, and identification of factors mediating platelet resistance, particularly in diabetic patients (19). The continued evolution of thienopyridine therapy for stent thrombosis has reached a crescendo of “treat as long as the patient can tolerate it,” and it will likely change again as new data are published, particularly with evolving data on the risk of bleeding with long-term thienopyridine use. In the meantime, in patients who have already received DES and who are not at high risk of bleeding, it seems prudent to continue dual antiplatelet therapy indefinitely until new data emerge demonstrating otherwise.

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