How Will New Bioresorbable Polymer Drug-Eluting Stents Impact DAPT Duration?

Current bioresorbable polymer, everolimus-eluting stent technology appears well suited for abbreviated-duration dual-antiplatelet therapy.

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The evolution of percutaneous coronary intervention (PCI) from plain old balloon angioplasty in 1977, to bare-metal stents (BMS) in 1986, through the revolutionary introduction of drug-eluting stents (DES) in 2003 (which successfully treated the Achilles heel of BMS [neointimal proliferation and restenosis]) has provided significant iterative improvement in platform design and performance. Adverse clinical events out to 1 year after stent deployment have been progressively reduced.[1,2] Nevertheless, beyond the first year after PCI, even the best currently available permanent polymer DES have been associated with a 2% to 4% per year incidence of target lesion failure events (TLF; composite of cardiac death, target vessel myocardial infarction [MI], and ischemia-driven target lesion revascularization),[3,4] possibly related to incomplete vascular healing, polymer hypersensitivity/inflammation, and/or stent fracture.[5] Going forward, future efforts in DES development should be focused on optimizing vessel healing and, hopefully, reducing the persistent hazard of very late events. Whether these iterations will reduce the need for prolonged dual-antiplatelet therapy (DAPT) has been the subject of debate.

Stents that deliver antiproliferative drugs from a durable polymer have reduced both clinical and angiographic restenosis compared with BMS without increasing adverse events, including death or MI.[1,2] However, permanent polymers may be associated with hypersensitivity reactions, as well as delayed and/or incomplete vascular healing that may contribute to an increased risk of both late (30 days to 1 year) and very late (beyond 1 year) stent thrombosis, which was particularly evident after first-generation DES.[5,6] Even newer durable polymers with enhanced biocompatibility and improved clinical outcomes have still been incriminated in chronic inflammation, thrombosis, and neoatherosclerosis (which occurs earlier and with increased prevalence after implantation of both first- and second-generation DES).[7-9]

BACKGROUND

To reduce the risk of stent thrombosis and MI, the 2016 American College of Cardiology/American Heart Association Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease provides guidance regarding the duration of DAPT after DES deployment for both stable coronary artery disease as well as acute coronary syndromes.[10] Patients should receive clopidogrel (or an alternative P2Y12 inhibitor) in addition to aspirin for a minimum of 6 months (stable coronary artery disease) or 12 months (acute coronary syndromes), unless there is high bleeding risk.[10] Longer-duration treatment may be prescribed on an individualized basis for patients with higher ischemic risk but lower bleeding risk using a novel clinical risk predictive tool (DAPT score [see subsequent paragraph]).[11] Shorter-duration treatment may be reasonable for patients with higher bleeding risk (eg, age ≥ 75 years, previous major bleeding or stroke, chronic kidney disease, and those taking oral anticoagulants). Aspirin (81 mg daily) should usually be continued indefinitely in patients with coronary artery disease.

The recent DAPT study suggested that even longer-duration therapy (≥ 30 months) provided additional isch-

emic event reduction when compared with 12 months of treatment.[12] However, the DAPT study included only durable polymer DES or BMS, and patients with high bleeding risk were excluded by protocol. The major findings of the DAPT study included relative reductions in stent thrombosis (71%), MI (53%), and major adverse cardiac and cerebrovascular events (MACCE; composite of cardiac death, MI, and stroke; 29%), and a higher risk of GUSTO moderate/severe bleeding (61%) with 30 months (vs 12 months) of DAPT.[12] In a subanalysis, Yeh et al used multivariable models to predict the composite of MI or stent thrombosis (ischemia model) or GUSTO moderate/severe bleeding (bleeding model) among 11,648 patients who were free of MACCE and major bleeding, as well as compliant with dual therapy at 1 year and who were randomized to either continued dual therapy or placebo (plus aspirin) for an additional 18 months.[11] Data from these models were then combined into a positive or negative integer, called the DAPT score.

TABLE 1. DAPT SCORE POINTS

Variable	Points	Variable	Points
Age		MI at presentation	1
≥ 75 years	−2	Previous PCI or previous MI	1
65 to < 75 years	−1	Stent diameter < 3 mm	1
< 65 years	0	CHF or LVEF < 30%	2
Current cigarette smoker	1	Vein graft PCI	2
Diabetes mellitus	1	Paclitaxel-eluting stent	1

Abbreviations: CHF, congestive heart failure; DAPT, dual-antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

This study elegantly demonstrates the power of standard clinical variables to personalized medicine. Moreover, it offers a simple solution to a daily clinical problem encountered by practicing cardiologists and physicians. Although the ischemia and bleeding models moderately predicted MI or stent thrombosis and bleeding events after 12 months, they were weakly correlated between 12 and 30 months. Older age exclusively predicted increased bleeding risk, whereas history of PCI or MI, stent diameter < 3 mm, chronic heart failure or left ventricular ejection fraction < 30%, and MI at presentation were exclusive predictors of ischemic events. Characteristics that predicted both bleeding and combined ischemic events had a minimal impact on net treatment effect and were left out of the final DAPT score assessment. The DAPT score ranges from -2 to 10 (median, 2) and comprises nine readily available clinical variables (Table 1). A clear gradient effect was observed, with a DAPT score ≥ 2 predicting an ischemic benefit without excess bleeding risk and a score < 2 predicting bleeding risk without ischemic benefit for prolonged DAPT (beyond 12 months). Patients with scores < 2 had a higher incidence of bleeding ($P < .001$), whereas those with scores of ≥ 2 had a lower incidence of death, MI, or stent thrombosis ($P < .001$).

Despite limitations (need for replication in other data sets, modest discrimination within the ischemic and bleeding models, and restricted ability to identify rare or unmeasured predictors of events), this score appears to more accurately predict benefit versus risk of therapy for an individual patient and allows risk reclassification for an important minority of patients after PCI. In fact, an additional DAPT study subgroup analysis by MI status (history of previous MI or index hospitalization MI vs no MI history) demonstrated that MI was a risk predictor for subsequent ischemic events both during the 12 months after enrollment (despite DAPT) and after randomization.[13] Extended (beyond 1 year) DAPT reduced ischemic events (MI, stent thrombosis) regardless of MI status but increased bleeding events as well. Stratification by DAPT score showed approximately 33% of patients with a history of MI had a low DAPT score, and approximately 33% of patients with no history of MI had a high DAPT score. These patients derived bleeding risk without ischemic benefit (low score) despite a history of MI, or ischemic benefit without bleeding risk (high score) despite no history of MI, respectively. Thus, the DAPT score provides a more accurate benefit-versus-risk assessment upon which individualized prolonged thienopyridine therapy may be more appropriately prescribed.[13] Importantly, any predictive score must be used in combination with good clinical judgment to facilitate personalized care.

In addition, multiple meta-analyses have examined the impact of prolonged DAPT after DES implantation on clinical outcomes (pooling data from 10 trials with > 30,000 participants).[14-16] These meta-analyses have concluded that prolonged therapy was associated with a lower risk of definite/probable stent thrombosis and MI compared with shorter-duration DAPT, although this benefit was attenuated after second-generation DES use (compared with first-generation use).[14] Ischemic event benefit was offset by a higher risk of bleeding and all-cause mortality when compared with shorter-duration therapy.[14-16] Prolonged DAPT after MI reduced major adverse cardiovascular events and cardiovascular mortality but was associated with a higher risk of nonfatal major bleeding, especially after treatment with the newer, more potent P2Y12 antagonists. Accordingly, the optimal duration of DAPT in patients at high risk of bleeding remains unknown.

DEVICE OVERVIEW

The Synergy stent (Boston Scientific Corporation) incorporates multiple design features specifically aimed toward enhanced stent healing with the potential to reduce risk of late/very late stent thrombosis and the need for prolonged DAPT. First, the platinum chromium metal alloy platform has thin struts (74–81 µm) and an offset peak-to-peak design with two connectors between rings throughout the body of the stent that enhances device flexibility/conformity and thus, improves deliverability and reduces geometric distortion, which may limit the propensity for stent fracture.[17] When compared with polyvinylidene fluoride copolymer in cell assay, bare platinum chromium accelerated both the time course and extent, as well as the function and maturity of endothelial cell coverage, and was associated with less platelet adhesion. Second, the bioresorbable polymer coating is 4-µm thin and is applied to the abluminal stent surface only. Abluminal polymer distribution (vs conformal) enhances endothelial cell coverage and healing.[18,19] Third, the polylactic-co-glycolic acid polymer elutes everolimus with a dose density of 100 µg/cm^2 and has a synchronous resorption-drug elution profile with complete resorption occurring within 4 months, leaving behind an endoluminal mural depot of everolimus.[20] Optical coherence tomography at 3 months after deployment of the Synergy stent suggests rapid stent healing with well over 90% stent coverage.[21] Finally, the safety and effectiveness of the Synergy stent has been demonstrated in the EVOLVE and EVOLVE II trials. The Synergy stent was demonstrated to be noninferior to the Promus Element stent (Boston Scientific Corporation) for the primary angiographic endpoint of late lumen loss at 6 months by quantitative coronary angiography in the EVOLVE trial.[22] EVOLVE was not powered to evaluate clinical outcomes.

DATA REVIEW

In the pivotal EVOLVE II randomized controlled trial for US Food and Drug Administration regulatory approval, the Synergy stent was compared to the durable polymer Promus Element Plus everolimus-eluting stent with a noninferiority design for the primary clinical endpoint of TLF (composite occurrence of cardiac death, MI related to the target vessel, and ischemia-driven target lesion revascularization) at 1 year.[17] By intention-to-treat analysis, TLF was observed in 6.7% of patients treated with Synergy and 6.5% of patients treated with Promus Element Plus (P = .0005 for noninferiority). Per-protocol analysis demonstrated 1-year TLF to be 6.4% in both groups (P = .0003 for noninferiority). Neither TLF nor TLF component outcomes were different between the stent types at either 1- or 2-year follow-up. Importantly, stent thrombosis through 2-year follow-up (Academic Research Consortium [ARC] definite/probable definition) was observed in only six patients treated with Promus Element Plus and three patients treated with Synergy (0.8% vs 0.4%, respectively; hazard ratio, 0.5; 95% confidence interval, 0.12–1.95; P = .31).[23] Remarkably, no definite stent thrombosis occurred in a patient treated with Synergy beyond the first 24 hours after PCI, and one of the two patients with definite stent thrombosis observed during the first 24 hours did not receive aspirin before the PCI. Landmark analysis performed at 24 hours (through 2 years) demonstrated stent thrombosis in 0.8% of the Promus Element Plus treated patients versus 0.1% in the Synergy treated patients (hazard ratio, 0.16; 95% confidence interval, 0.02–1.37; P = .056), with only a single probable stent thrombosis observed in the Synergy group at day 6. Thus, definite stent thrombosis was not observed after 24 hours, and no stent thrombosis was observed beyond 6 days in 846 patients treated with the Synergy stent followed through 2 years. Of note, EVOLVE II enrolled the most complex clinical and angiographic cohort of patients ever included in a regulatory trial for new stent approval in the United States.

Finally, the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) provides real-world clinical experience with Synergy in an all-comers population.[24] Among 83,334 patients treated with DES from 2007 to 2015 (7,880 with Synergy), Synergy had the lowest rate of definite stent thrombosis at 1-year follow-up (0.25%) compared with all other DES. It would appear that the Synergy stent design, which is focused on early and complete vascular healing, is supported by optical coherence tomography observations, as well as large-scale clinical trials (EVOLVE II) and registries.

Based on these studies, the Synergy stent is being evaluated in the EVOLVE Short DAPT study, which will enroll approximately 2,000 Synergy-treated patients who are at perceived high risk for bleeding (based on age ≥ 75 years, history of major bleed or stroke, chronic renal insufficiency, or chronic oral anticoagulation) and who will receive 3 months of DAPT after PCI. The coprimary endpoints of (1) death or MI, and (2) ARC definite/probable stent thrombosis will be analyzed between 3 and 15 months after the index PCI procedure, and outcomes will be compared with historic controls.

Evolution in coronary stent technology has allowed for the development of both nonpolymeric drug-coated stents and drug-eluting bioresorbable scaffolds in an effort to optimize vascular healing and improve late/very late clinical events compared with currently available devices. The pivotal ABSORB III trial enrolled patients with noncomplex obstructive coronary artery disease who were randomly assigned to treatment with either the everolimus-eluting

bioresorbable vascular scaffold (Absorb, Abbott Vascular) or the everolimus-eluting cobalt-chromium stent (Xience, Abbott Vascular).[25] This trial proved the noninferiority of Absorb (vs Xience) for the primary clinical endpoint of TLF at 1 year, and no differences in TLF components were observed between the devices. However, the point estimates for both device thrombosis (ARC definite/probable) and target vessel MI were numerically higher at 1 year for Absorb. A first-in-man trial of the novel BioFreedom drug-coated stent (Biosensors Europe SA), which incorporates a thin-strut, stainless steel platform with surface modification to allow adhesion and release of Biolimus A9, demonstrated noninferiority for TLF at 1 year compared with the first-generation paclitaxel-eluting stent, with no stent thrombosis observed to 5 years after implantation following the BioFreedom drug-coated stent.[26] Clear limitations of this trial are its small sample size and comparison to a first-generation DES.

SUMMARY

Presently, the demonstrated safety and efficacy of the Synergy bioresorbable polymer, everolimus-eluting coronary stent appears well suited for evaluation in trials of abbreviated duration DAPT. It should also be appreciated that at times, it is suboptimal stent deployment that results in thrombogenicity and not the stent itself.[27] Important aspects of stent deployment include procedural optimization of minimum lumen diameter and maximum stent area through adequate vessel preparation which includes pre- and postdilatation and adjunctive intravascular imaging, as well as patient education about the need for DAPT and the potentially catastrophic consequences of early cessation. These additional factors are controllable and, when coupled with the dynamic iterations in stent design noted previously, bode well for the future. As noted in a recent editorial by Dr. Antonio Colombo, "Looking forward, there is no darkness or uncertainty in the tunnel of stent thrombosis. We are in control, and we can shed the light!"[28] ■

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