JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 16, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.06.042

EDITORIAL COMMENT

Percutaneous Coronary Interventions in Patients Requiring Long-Term Oral Anticoagulation

Is the Drug-Coated Stent a Potential Game Changer?*

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In the current era, percutaneous coronary intervention (PCI) stenting is increasingly being performed in patients with comorbid conditions, resulting in both ischemic and bleeding post-procedural risks. In particular, more than 5% of patients undergoing PCI carry a concomitant clinical indication, such as atrial fibrillation (AF) or mechanical cardiac valves, requiring long-term oral anticoagulation (OAC) (1). Given that major bleeding is a powerful predictor of morbidity and mortality after PCI, the optimal management of this subset of patients remains highly challenging (2). In such conditions, choosing the appropriate type of stent during PCI and the optimal post-procedural antithrombotic strategy largely depends on the individual balance between relative risk of thrombotic events and the probability of major bleeding complications. The latest clinical practice guidelines currently favor a period of triple therapy (TT) combining dual antiplatelet therapy (DAPT) and an anticoagulant agent among PCI patients on OAC for AF indication (3). Although physicians commonly follow this recommendation, compelling evidence from large-scale registries suggests that both early and delayed bleeding risks are significantly increased with TT exposure (4). In this context, there is a strong rationale to develop strategies to shorten TT duration to avoid bleeding events. This "as short as possible triple therapy" concept implies that the choice of implanted device during PCI also merits particular attention.

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In this issue of *JACC: Cardiovascular Interventions*, Carrié et al. (5) report the results of a pre-specified analysis of the LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent) trial involving the subset of patients scheduled to remain on OAC after PCI. Briefly, the LEADERS FREE trial originally randomized in a double-blind fashion 2,466 patients with high bleeding risk scheduled for PCI to received either a novel polymer-free drug-coated stent (DCS) (n = 1,239) or a bare-metal stent (BMS) with a similar platform (n = 1,227) (6). Both groups were treated with short-term DAPT for 1 month. At 390 days, this study showed the superiority of the DCS for the primary safety endpoint (a composite of cardiac death, myocardial infarction, or stent thrombosis) and the primary efficacy endpoint (clinically driven target lesion revascularization). The 2-year results confirmed superiority of the investigational device for both the primary safety and the primary efficacy endpoints (7). In the LEADERS FREE OAC substudy, DCS was compared with BMS in patients requiring long-term OAC (n = 879; 35.6% of the whole population) after

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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1- and 2-year clinical follow-up (5). The type and duration of antithrombotic therapy combinations were at the discretion of the physician. The main findings of this subanalysis are the following: 1) for the primary efficacy endpoint, the between-groups difference was statistically significant at 1 year (hazard ratio: 0.57; 95% confidence interval: 0.33 to 0.99; $p = 0.0425$) in favor of the DCS, with a trend toward greater efficacy at 2 years (hazard ratio: 0.63; 95% confidence interval: 0.40 to 1.01; $p = 0.0514$); 2) for the primary safety endpoint, the cumulative incidence of cardiac death, myocardial infarction, and definite or probable stent thrombosis did not significantly differ between groups after both 1- and 2-year follow-up; and 3) major bleedings (BARC [Bleeding Academic Research Consortium] 3 to 5 events) occurred with a 2-year incidence of 10.7% and 12.9%, respectively, for the DCS and BMS groups with no significant differences between them.

This LEADERS FREE OAC substudy (5) represents to date the first randomized trial testing the efficacy/safety profile of an active stent (biolimus A9) in a large sample of patients on long-term OAC initially treated with a 1-month duration of DAPT. As emphasized by the authors, although the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) and RESET (Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stent Implantation) randomized trials documented the safety of 3 months of DAPT with the same first-generation rapid-elution drug-eluting stent, both studies selected patients at low risk of bleeding and without OAC indication (8,9). By contrast, some limitations to this subanalysis have to be considered. Although every patient entered into the analysis was treated with a pre-specified 1-month DAPT, the duration and type of OAC on discharge were not randomized, resulting in a wide variability of antithrombotic combinations and TT durations. Given that long-term exposure to TT has been linked to higher bleeding risk compared with less intensive regimens (4), this limit probably merits particular attention regarding interpretation of the results. Furthermore, as underlined by the authors, non-vitamin K antagonist (VKA) oral anticoagulants were used in <9% of the study population, and an alternative antithrombotic regimen using clopidogrel alone + VKA after PCI ("WOEST regimen") was administrated in only 6.6% of patients, suggesting that these DCS results cannot be extrapolated to variations of antithrombotic strategies.

Beyond the device perspective, many efforts have been recently undertaken to randomly investigate the effectiveness and safety of alternative antithrombotic strategies. In this setting, results of the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial (clopidogrel alone + VKA vs. TT) and the ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients with Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) study (6 weeks vs. 6 months of TT) support the benefit of shorter TT duration (10,11). More recently, the PIONEER AF trial (A Study Exploring Two Strategies of Rivaroxaban [JNJ39039039; BAY-59-7939] and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) disclosed encouraging results in favor of the use of rivaroxaban compared with standard VKA therapy (12). Ongoing randomized trials testing together other combinations with dabigatran (NCT02164864), apixaban (UMIN000015923), or endoxaban (NCT02866175) will also provide us new critical answers to optimize management of these patients (3,13,14).

In the management of PCI patients requiring long-term OAC, DCS technology could be an important step forward. However, as suggested by the still-high rates of bleedings observed in the LEADERS FREE OAC cohort, strategies combining both pharmacological and device approaches are required. As a future perspective, results of ongoing pharmacological trials and development of new coronary stents with safer platforms shortening the duration of DAPT will undoubtedly help us to define the optimal cocktail of pharmacology and device approaches to improve the care of this subset of patients.

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KEY WORDS bleeding risk, drug-coated stent(s), oral anticoagulation, PCI