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EDITORIAL COMMENT

Is it Time to Abandon Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Atrial Fibrillation on Anticoagulation?*

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In the early days of coronary stenting, the relative efficacy of antiplatelet versus anticoagulant therapy for stent thrombosis prevention was unclear. Mechanistic research revealed that an elevated surface level of inducible fibrinogen receptors on platelets strongly predicted thrombosis in a stented vessel, whereas hemostatic variables did not (1). Subsequent randomized controlled trials investigating the use of aspirin, ticlopidine, or warfarin after percutaneous coronary intervention (PCI) with Palmaz-Schatz coronary stents demonstrated that antiplatelet medications were the agents of choice to prevent stent thrombosis, with increased efficacy of dual antiplatelet therapy (DAPT) (2). Two decades of observational and randomized controlled trial data cemented the utility of DAPT for the prevention of stent thrombosis (3).

Parallel studies in patients with atrial fibrillation (AF) demonstrated superiority of anticoagulants over antiplatelet agents for stroke prevention (4,5). Thus, given concerns for the simultaneous risks of stent thrombosis and stroke in patients with AF undergoing PCI, the basis for "triple therapy" (the use of therapeutic anticoagulation in addition to DAPT) was born. Ameliorating these fears came at the cost of clinically significant bleeding rates of over 15% per year with "triple therapy" (6).

Fortunately, over this period, novel polymers and antiproliferative drugs used for drug eluting stents were developed, stent cell shapes were optimized, stent struts thinned to reduce the risk of stent thrombosis, and intravascular imaging techniques were developed to optimize stent expansion and apposition (7,8). These advancements allowed investigators to challenge the necessity of extended DAPT after PCI (9,10) and, by extension, the need for triple therapy after PCI in patients with AF.

Recently, the PIONEER AF-PCI study (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) investigated varying strategies of antiplatelet and anticoagulant therapies, comparing therapeutically dosed rivaroxaban (we will consider the 15-mg daily dose used in the trial a therapeutic dose for the purposes of this discussion) with an isolated $P2Y_{12}$ inhibitor ($P2Y_{12}$i), very-low-dose rivaroxaban (2.5 mg twice daily) with DAPT for 1, 6, or 12 months, and dose-adjusted warfarin with DAPT for 1, 6, or 12 months. Therapies including rivaroxaban were associated with a lower risk of bleeding with no apparent differences in major adverse cardiovascular events (a composite of stroke, myocardial infarction, and cardiovascular death), though the latter endpoint came accompanied by wide confidence intervals (11).

Despite the clear reduction in the risk of bleeding, with possible equipoise regarding ischemic events with rivaroxaban and $P2Y_{12}$i monotherapy, there remained significant concern in using $P2Y_{12}$i monotherapy in those patients with the highest risk of stent thrombosis. These risk factors include patient characteristics such as an acute coronary syndrome presentation, renal insufficiency, and heart failure with reduced ejection fraction, as well as procedural characteristics such as multivessel PCI, multiple

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lesions within a vessel, long lesion length, bifurcation lesions, in-stent restenosis, vein graft interventions, left main lesions, thrombus-containing lesions, and prior brachytherapy (3).

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In this issue of *JACC: Cardiovascular Interventions*, Kerneis et al. (12) have performed an important analysis of treatment-level heterogeneity within the PIONEER AF-PCI trial to understand patient and procedural effects on ischemic and bleeding outcomes. Both treatment strategies using rivaroxaban were associated with reduced bleeding events, independent of access site. There was also no interaction between the use of a vascular closure device and the effect of rivaroxaban, and there was no other effect modification by procedural or lesion characteristics on the safety endpoint. These results are consistent with the overall trial findings, demonstrating reduced risks of bleeding with strategies that avoided classical "triple therapy." However, it is unsurprising that lesion and procedural characteristics do not influence the long-term risk of bleeding, because it has been previously demonstrated that patient-level factors such as older age, smoking, diabetes, congestive heart failure, and chronic kidney disease drive this risk (13). The study also underscores the potential bleeding advantages seen in prior studies of a strategy using a single, therapeutically dosed anticoagulant with single antiplatelet therapy (14,15).

Although this analysis also demonstrated a similar rate of ischemic events with 15 mg of rivaroxaban and $P2Y_{12}$i compared with warfarin and dual antiplatelet therapy (5.7% vs. 5.7%; $p = 0.92$), this finding must be viewed with caution. The main study and subgroup analyses are underpowered to detect any differences in ischemic endpoints. It should be noted that the point estimates for some procedural characteristics known to be associated with a higher risk of stent thrombosis suggest the possibility of increased risk ischemic events when a strategy of rivaroxaban with $P2Y_{12}$ monotherapy is used. Specifically, the upper end of the 95% confidence interval hazard ratios for ischemic events in patients with multivessel disease, bifurcation lesions, and long stent length are 5.69, 11.48, and 6.41, respectively. These may be the patients that benefit most from DAPT, and these differences were not as consistent and pronounced when comparing the 2 arms of the trial that used DAPT.

Notably, it is this specific group of patients in whom the use of rivaroxaban 2.5 mg twice daily and DAPT is most attractive. After all, in addition to equivalence with regard to ischemic endpoints, this strategy continued to provide bleeding benefits when compared with traditional triple therapy in these patients. The unresolved question remains the efficacy of stroke prevention in the absence of a therapeutically dosed anticoagulant, a question that the PIONEER AF-PCI trial was underpowered to address.

The authors should be congratulated for performing a rigorous subanalysis of the PIONEER AF-PCI trial in an attempt to make the data even more relevant to the care of the individual patient. Though the reduced bleeding risks of rivaroxaban-based treatment strategies appear consistent despite access and procedural characteristics, the equivalence of ischemic endpoints is less clear. More evidence is needed before recommending utilization of therapeutic anticoagulation and single antiplatelet therapy in anatomically complex circumstances, and further details on long-term stroke prevention are needed regarding the regimen of rivaroxaban 2.5 mg twice daily and DAPT, a potentially ideal solution for this group.

Thus, in patients with anatomically simple disease without high-risk features for stent thrombosis, a strategy of 15-mg rivaroxaban and $P2Y_{12}$i monotherapy is an excellent option. However, for those AF patients with anatomic complexity, we have still not fully adjudicated the complicated balance between long-term bleeding, ischemic endpoints, and stroke prevention. To answer this question with more certainty, future pooled analyses of randomized trials and nuanced observational analyses of large registries are eagerly anticipated.

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