Prevention of Bleeding in Patients With Atrial Fibrillation Undergoing PCI (PIONEER): Three May End Up Being a Crowd

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The PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with AF who Undergo Percutaneous Coronary Intervention) is an ambitious, open-label comparison of 3 regimens, almost exclusively in Caucasians, all of whom had coexisting atrial fibrillation and atherosclerotic coronary artery disease requiring stenting (PCI-S).¹ These 2 conditions when they coexist pose a clinical challenge, necessitating concurrent usage of dual antiplatelet and anticoagulation therapy, a cocktail which presents major bleeding risks. Because anticoagulation therapy is suboptimal in preventing stent thrombosis and dual antiplatelet therapy is inadequate in averting embolic stroke in atrial fibrillation, neither treatment is sufficient and they must be combined.

The study has a unique design and consists of 2 treatment arms and a control (see Figure 1 for trial design), each with about 700 patients and a 20% dropout rate in groups 1 and 2 but a statistically greater rate of 29% in group 3. Both treatment arms are modeled upon previous studies, which involved patients with the need for both antiplatelet therapy and anticoagulation (see Figure 2 for derivation of trial from WOEST and ATLAS-TIMI 51).

The control arm, designated group 3 in the trial, consists of the US standard of practice regimen, in this situation, called “triple therapy,” consisting of aspirin 100 mg/d, clopidogrel 75 mg/d, and warfarin maintaining the INR between 2 and 3. About 7% of patients in groups 1 and 2 received a different P2Y₁₂ inhibitor, either prasugrel or ticagrelor, and about 4% in group 3. Prominent among the numerous exclusions were patients with a previous stroke and a creatinine clearance of under 30 mL/min. In arm 1, patients with a creatinine clearance between 30 and 60 mL/min received a lower dose of 10 mg of rivaroxaban.

The first treatment arm, called arm 1, is a reprisal of the treatment arm of the Belgian 2013 WOEST trial which showed that clopidogrel 75 mg and warfarin, maintaining an INR of 2 to 3, were associated with less combined TIMI major and minor bleeding as well as no increase in cardiac or neurological

thrombotic complications when compared to the same control arm as is in this study.² Despite having studied only 573 patients for just a year, WOEST was influential in generating the recommendation (level B) from the European Society of Cardiology to use this regimen in some people at high risk for bleeding with stents who also require anticoagulation.³

Furthermore in PIONEER, arm 1, rivaroxaban 15 mg has been substituted for warfarin; otherwise, the other trial drugs are identical to those in WOEST. A compelling question posed by this arm of the study, although not the primary end point of the study, is whether equivalent stent patency or prevention of atherosclerotic or thromboembolic complications can be achieved with only a single antiplatelet drug throughout the entire 12 months of treatment, including the vital first month poststent. Also addressed is whether the WOEST results can be replicated substituting rivaroxaban, a drug that offers several advantages over warfarin. In treatment group 1, one would intuitively expect confirmation of the bleeding advantage observed in WOEST, since it contains 2 drugs versus the 3 in the control group, and therefore would be expected to be associated with less bleeding in group 1 versus group 3.

The second treatment group is based on the 2012 ATLAS ACS 2-TIMI 51 trial and consists of very-low-dose rivaroxaban 2.5 mg twice a day along with clopidogrel 75 mg/d and aspirin 100 mg/d.⁴ An interesting point of arm 2 versus 3, although again not the primary end point, is if a dosage of rivaroxaban, which is only 25% of the FDA-approved dose of that needed to treat atrial fibrillation, would be adequate in preventing embolic strokes. One would anticipate in group 2 that the dual antiplatelet therapy would be equally effective in preventing stent occlusion and recurrent coronary events as the control

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Figure 1. Adapted by Sara R Vazquez, PharmD from Pioneer trial.

Figure 2. Derivation of Pioneer trial.

arm since the two arms are identical in this regard. With respect to the primary end point, one would again expect substantially less bleeding in treatment arm 2 versus the control group, given that one is comparing 25% rivaroxaban dose versus full-dose warfarin.

No surprise, the results do indeed confirm less bleeding in the 2 treatment groups (1 and 2) versus control (3). There was 16.8% in group 1, 18% in group 2, and 26.7% in group 3. This designated end point of the trial was labeled clinically significant bleeding, a combination of TIMI major and minor bleeding plus bleeding requiring medical attention. These findings were supported by the observations of a lower incidence in

groups 1 and 2 than in group 3 of major bleeding according to ISTH criteria and severe bleeding according to the GUSTO bleeding scale.

Interestingly, the reduced bleeding in the treatment groups was entirely driven by “bleeding requiring medical attention” and did not reach statistical significance for TIMI major or minor bleeding or a combination as it did in WOEST. “Bleeding requiring medical attention” entails bleeding that doesn’t qualify as major or minor. Consequently, it does not measure blood loss, only whether a procedure needs to be performed or whether anticoagulation needs to be discontinued.

Few thrombotic events were noted in the efficacy measurements in all 3 arms. Rates of death from cardiovascular causes, myocardial infarction, or stroke were 6.5% in group 1, 5.65% in group 2, and 6.0% in group 3. Stent thrombosis was 0.8%, 0.9%, and 0.7%, respectively. However, these findings are only partially reassuring. In group 2, it is encouraging that despite the very low dosage of rivaroxaban, there were few cerebral emboli. However, these data carry with it a wide confidence interval (CI), 0.68 to 15.78, which calls the precision of these results into question. Also of concern is the 6-month data showing 6 ischemic strokes in group 2 versus none in group 3. However, the good news is that in group 1, despite the use of a single antiplatelet agent, including the critical first month postprocedure, there were few coronary complications (Hazard Ratio [HR] of group 1 vs group 3 was 1.21) with a respectable CI (0.76-1.92).

So what does this study show? It achieved superiority in the designated end point of decreased bleeding in the 2 rivaroxaban groups versus the control, but this was predictable based on the composition of these 3 groups. There were fewer dropouts in the rivaroxaban-treated patients, probably reflecting this bleeding advantage. Very important is that the reduction in bleeding spared patients and families costly and stressful hospitalizations, emergency department visits, and expensive interventions on the basis of reduction of bleeding requiring medical attention.

With respect to efficacy, although underpowered for ischemic events, it appears that group 1 approached replicating the persuasive WOEST trial against the same control group with a respectable confidence interval. However, in group 2, concerns about the use of 25% of the FDA-approved dosage of rivaroxaban are reinforced by finding a wide confidence interval as well as the 6 ischemic strokes observed at 6 months versus none in the control group. However, when it came to

hospitalizations, there was a significant decrease in hospitalizations due to ischemic events⁵ in the 2 rivaroxaban groups.

Whether or not it is due to the emergence of superior stents at this time, it appears that in patients with concomitant atrial fibrillation and PCI, aspirin may be on the way out.

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