# Combined Antiplatelet and Anticoagulant Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: Navigating Between Scylla and Charybdis

In *The Odyssey*, Ulysses navigates between 2 hazards, a rock shoal commandeered by a 6-headed monster (Scylla) and a whirlpool known for gobbling up ships and claiming their crews (Charybdis). The more he tries to avoid one hazard, the more vulnerable he becomes to the other. We face an analogous situation when caring for patients with atrial fibrillation (AF) after coronary stent placement who require anticoagulation to mitigate stroke risk and antiplatelet therapy to promote stent patency. We want to avoid bleeding events—which are increased with combination therapy—while also avoiding ischemic events, such as stent thrombosis, myocardial infarction, and ischemic stroke.

Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, are alternatives to vitamin K antagonists (VKAs) for stroke prevention in patients with AF. Clinical trials demonstrate equivalence or superiority of these agents over warfarin in reducing risk for ischemic stroke and bleeding, including intracranial hemorrhage (1). Trials also show that the addition of antiplatelet therapy, including low-dose aspirin, increases bleeding risk with both warfarin and DOACs (1). Antiplatelet therapy, usually dual antiplatelet therapy, is indicated after stenting to avoid stent thrombosis and other major adverse cardiovascular events. Prior experience suggests high bleeding risk when using warfarin-based triple therapy (TAT; dual antiplatelet therapy plus warfarin) and high thrombotic risk when withholding warfarin to mitigate bleeding risk.

The first indication that an alternative to TAT may exist was the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) (1), which looked at the use of warfarin with either dual antiplatelet therapy or a single antiplatelet agent, clopidogrel (dual or double antithrombotic therapy [DAT]). Bleeding events were reduced in the DAT group, with no increase in ischemic events. In an effort to devise combination regimens that reduce bleeding risk, 4 clinical trials compared standard TAT with DOAC-based regimens, mostly with a single antiplatelet agent (2–5). All were powered to detect differences in the safety end point of bleeding but not in avoidance of thrombotic events.

The RE-DUAL PCI trial (Randomized Evaluation of DAT With Dabigatran vs. TAT With Warfarin in Patients With Nonvalvular AF Undergoing Percutaneous Coronary Intervention [PCI]) (2) studied 2 dosing regimens, one of which (dabigatran, 110 mg twice daily) is not available in the United States. The dosages of rivaroxaban in PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral VKA Treatment Strategy in Subjects With AF Who Undergo PCI) (3), 15 mg daily and 2.5 mg twice daily, are not approved for stroke prevention in the United States in patients with AF and preserved renal function. AUGUSTUS (Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. VKA and Aspirin vs. Aspirin Placebo in Patients With AF and Acute Coronary Syndrome or PCI) (4) compared apixaban versus warfarin with a backdrop of P2Y12 inhibitor therapy with or without low-dose aspirin in a 2 × 2 factorial design. Bleeding risk was reduced with apixaban versus warfarin and with no aspirin versus aspirin. The apixaban group had fewer deaths and hospitalizations, with no significant difference in ischemic events. ENTRUST-AF PCI (Edoxaban Treatment vs. VKA in Patients With AF Undergoing PCI) (5) showed that edoxaban-based DAT, compared with warfarin-based TAT, was associated with a reduction in major and clinically relevant nonmajor bleeding, without a significant increase in a combined end point for thrombotic events. Most patients in these trials received clopidogrel as the antiplatelet agent.

Because none of these studies were powered to detect an increase in thrombotic events with DAT compared with TAT, Khan and colleagues' meta-analysis (6) is important. Using robust methods, the authors searched the literature and identified the 4 aforementioned studies as meeting their eligibility criteria. Excluding patients who received the unavailable 110-mg dose of dabigatran, their meta-analysis included 7953 patients. The authors found high-certainty evidence that use of DAT compared with TAT was associated with a reduction in major bleeding events. They found low-certainty evidence of inconclusive effects of DAT compared with TAT on all-cause mortality, cardiovascular mortality, myocardial infarction, stent thrombosis, and stroke at the "upper bounds . . . compatible with a possible increased risk" (6). How does this signal of excess net risk with TAT compare with findings of other meta-analyses?

In a meta-analysis that included the same 4 trials but evaluated both dabigatran DAT regimens, 110 mg and 150 mg, Gargiulo and colleagues (7) concluded that a DOAC-based DAT regimen was associated with reductions in major and clinically relevant nonmajor bleeding and intracranial hemorrhage compared with warfarin-based TAT (7). All-cause mortality, cardiovascular death, stroke, and major adverse cardiovascular events did not differ. However, there was a significant difference in stent thrombosis (relative risk, 1.59) and a

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trend toward more myocardial infarctions in the DAT regimens.

Are these separate meta-analyses compatible, and did Khan and colleagues get it right? I believe that the answer to both questions is yes. Because bleeding events are much more frequent than thrombotic events, even after pooling data from 4 trials, it is difficult to know definitively whether and to what extent thrombotic events are increased with DAT. This is not meant to minimize the importance of bleeding events. In addition to the immediate consequences of such an event, patients who do not resume anticoagulation afterward may have an increase in thrombotic events and death compared with those who resume anticoagulation (8).

What do available guidelines suggest we do when faced with this conundrum? European guidelines (9) released before the availability of the 4 trials advocate combined therapy with a DOAC in lieu of warfarin for both elective PCI and PCI after acute coronary syndrome. They suggest shorter-duration combination therapy in the setting of high bleeding risk or low atherothrombotic risk, and they often recommend a DOAC alone in the chronic phase. A guideline from the American College of Cardiology and American Heart Association (10), which predates the results of AUGUSTUS and ENTRUST-AF PCI, emphasizes the importance of examining thrombotic risk and recommends anticoagulation when the $CHA_2DS_2$-VASc score is 2 in men and 3 in women. This guideline also favors clopidogrel over prasugrel to mitigate bleeding risk in patients with AF. It gives a class IIa recommendation to lower-dose rivaroxaban (15 mg) with clopidogrel, as well as to dabigatran (150 mg) with clopidogrel.

Where does this leave us today as we face the hazard of bleeding on one side and thrombosis on the other? Lesion complexity, patient-specific bleeding risk, and whether stenting is elective or emergent are factors to weigh in determining the duration and intensity of combined anticoagulant and antiplatelet therapy. Navigating the competing risks remains a challenge. Stent technology is maturing, and which P2Y12 inhibitor to prescribe remains a question, especially when treatment with clopidogrel is unsuccessful. Stay tuned, because practice will surely continue to evolve.

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