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EDITORIAL COMMENT

Practice Variation in Patients Eligible for Triple Therapy

Designing Systems to Assess Risk and Tailor Treatment*

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For at least the last half-century, providers have been challenged with providing the optimal oral outpatient antithrombotic strategy that reduces global ischemic risk while minimizing the likelihood of significant bleeding complications. Although therapeutic options had been previously limited, the last decade has brought about more potent and targeted therapies directed toward inhibiting the $P2Y_{12}$ receptor (prasugrel, clopidogrel) and the coagulation cascade (dabigatran, rivaroxaban, apixaban, edoxaban). After including warfarin and variable doses in aspirin therapy, there are up to 72 possible combinations of aspirin, $P2Y_{12}$ inhibition, and anticoagulant therapies in patients meeting indications for dual antiplatelet therapy on a background of oral anticoagulation, not even accounting for variable treatment duration. Given this multitude of therapeutic options, it is unfortunate that there are very limited randomized data regarding the optimal treatment strategy in these patients. Hence, in the absence of clear guidelines and limited data, the environment is ripe for significant practice variation.

In this issue of *JACC: Clinical Electrophysiology*, Wasfy et al. (1) seek to quantify the degree of practice-level variation among patients meeting indication for dual antiplatelet therapy on background oral anticoagulation. Using the National Cardiovascular Data Registry's outpatient PINNACLE Registry, they identified 79,875 patients with atrial fibrillation/flutter and either acute myocardial infarction or percutaneous coronary intervention (PCI) in the previous 12 months. Within this population, 3,568 (4.5%) patients were on triple therapy at the most recent eligible visit; on multivariable analysis these patients were more likely to have a prior embolic event (including stroke/transient ischemic attack), diabetes, heart failure, and dyslipidemia. After accounting for patient factors, the investigators find significant practice-level variation, demonstrating almost 3-fold difference in the likelihood that similar patients would receive triple therapy based on provider.

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There are several possible explanations for this degree of practice-level variation. First, the evidence base for managing patients needing dual antiplatelet therapy on background oral anticoagulation remains sparse and ill-defined, and the observed safety signals are especially concerning, with prior large observational studies demonstrating an association between triple therapy and increased bleeding risk (2,3). A recent analysis using the National Cardiovascular Data Registry's ACTION Registry – Get With the Guidelines demonstrated an association between discharge on triple therapy and major bleeding without apparent effect in mortality or ischemic endpoints (4). Additionally, the traditional triple therapy treatment paradigm was challenged by the WOEST (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) trial, which randomized 573 patients with atrial fibrillation undergoing PCI to dual or triple therapy and demonstrated significantly lower bleeding and

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comparable efficacy among dual therapy patients (5). Importantly, this small trial was not powered to detect differences in the rate of stent thrombosis, the feared complication of withholding dual antiplatelet therapy in patients with drug-eluting stent (DES).

Second, optimal antithrombotic strategy selection depends heavily on objective assessment of thrombotic risk (which includes stent thrombosis, stroke/systemic embolism, and secondary myocardial infarction prevention) and bleeding risk. Although tools, such as the CHA_2DS_2-VASC and HAS-BLED risk scores, among others, are helpful in global risk assessment, in clinical practice there may be significant overlap in individual risk predictors, highlighting the challenge in disentangling ischemic and bleeding risk. Unfortunately, the authors were unable to fully characterize bleeding risk using this dataset, but it is likely that many patients at high thrombosis risk were also at increased bleeding risk.

Third, the time period for this study, 2008 to 2013, was underscored by significant improvements in DES technology. The use of newer-generation DES, coupled with more refined deployment techniques, has significantly lowered the risk of stent thrombosis compared with first-generation DES and bare metal stents (6,7). Thus, it is possible that providers may have felt more comfortable withholding long-term triple therapy in contemporary patients receiving these stents.

The study investigators note that only 4.5% of patients in their study population were treated with triple therapy at the most recent eligible visit. However, it is unclear whether some patients actually should be on triple therapy for *any* considerable period of time. In the wake of WOEST, coupled with lower observed rates of stent thrombosis with newer-generation DES, there is considerable interest in pursuing a dual therapy strategy of oral anticoagulation and a single antiplatelet agent. For patients presenting with NSTE-ACS undergoing PCI, the most recent European Society of Cardiology guidance recommends risk stratification by HAS-BLED score (8). For patients at high risk for bleeding (HAS-BLED $\geq$3) undergoing PCI, triple therapy is recommended only for 4 weeks; for medically managed patients, dual therapy with oral anticoagulation and either aspirin or clopidogrel is recommended from the outset. The most recent North American expert consensus statement from 2011 suggests risk stratification based on bleeding and stent thrombosis risk, with variable-duration triple therapy directed by stent selection (9). Additionally, North American guidance seems to be directed more toward stent selection (favoring bare metal stenting in patients at high bleeding risk) than shorter courses of antiplatelet therapy (10,11).

So what are providers to do when they encounter patients with atrial fibrillation and an indication for dual antiplatelet therapy? At least for now, the best answer may be to enroll them in a randomized trial. Given the considerable clinical interest in answering this question, there are three ongoing trials evaluating the optimal antithrombotic strategy for these types of patients. The REDUAL-PCI (NCT02164864) trial is evaluating two doses of dabigatran (150 mg or 110 mg) plus a single antiplatelet agent versus traditional therapy with warfarin and two antiplatelet agents. The PIONEER-AF PCI (NCT01830543) trial is studying a WOEST-like dual pathway strategy (rivaroxaban 15 mg + clopidogrel 75 mg daily) versus an ATLAS-like strategy (low-dose rivaroxaban, clopidogrel, and aspirin) versus traditional therapy with vitamin K antagonist, clopidogrel, and aspirin (12). The AUGUSTUS (NCT02415400) trial, using a 2 $\times$ 2 factorial design, randomizes patients with either PCI or medically managed acute myocardial infarction to open-label vitamin K antagonist versus apixaban and blinded aspirin versus placebo, with $P2Y_{12}$ inhibitor choice at the discretion of the investigator. Together, these trials should provide additional guidance, especially with respect to the novel factor-specific agents, on the optimal strategy for this high-risk population.

In the absence of clear, randomized data, observational platforms, such as the PINNACLE Registry, provide unique opportunities to identify contemporary treatment patterns and may provide a roadmap to offer dynamic risk assessment in specific patient populations (13). Although PINNACLE offers only outpatient-level data, the ultimate goal for the learning healthcare system may be to integrate detailed clinical data captured by registries or electronic health records across the inpatient and outpatient settings and use advances in modern informatics and machine learning to perform detailed, outcomes-based clinical risk assessment. However, to achieve these goals, the clinical community needs to embrace standardized data elements in the electronic health record with ubiquitous and compatible connections to national registries and data warehouses. Indeed, it may soon seem antiquated to use only 7 static characteristics to assess stroke or bleeding risk. Currently, significant practice-level variation exists as a result of incomplete risk assessment and minimal randomized data. The aspirational goal, therefore, may be to promote the current care, noted for significant variation, in the context of a learning health system to promote more complete risk assessment and tailored treatment

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regimens optimizing the balance between reducing ischemic outcomes while minimizing bleeding risk. It is only with such a system in place that the clinically meaningful questions can be answered rapidly as they arise.

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