Antithrombotic Therapy for Patients With Atrial Fibrillation and Atherothrombotic Vascular Disease
Striking the Right Balance Between Efficacy and Safety

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Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, is estimated to affect 1.5% to 2.0% of the general population, that is, at least 100 million people worldwide. Left untreated, patients with nonvalvular AF (NVAF) are exposed to an annual risk of thromboembolic stroke of ≈5%, resulting in 5 million AF-related strokes each year. Properly dosed anticoagulation (eg, warfarin adjusted to an international normalized ratio of 2.0–3.0) is extremely effective in preventing AF-related strokes, reducing risk by two thirds compared with no therapy and by one-half compared with aspirin. In contrast, aspirin alone achieves a 21% relative reduction in risk of nonfatal stroke compared with no treatment, and aspirin plus clopidogrel yields an additional 11% reduction compared with aspirin alone. Thus, anticoagulation is the unchallenged current treatment of choice for patients with NVAF at moderate to high risk of thromboembolic complications.

Whether patients with NVAF for whom oral anticoagulation (OAC) is indicated who have stable atherothrombotic vascular disease should also use low-dose aspirin to prevent major coronary events is still debated because the efficacy and safety of combining antiplatelet and anticoagulant agents have not been adequately tested in this clinical setting. A systematic review and meta-analysis of 10 randomized, controlled trials comparing combined aspirin-OAC therapy with OAC alone in 4180 patients, in whom OAC was administered to achieve the same target international normalized ratio or was given at the same fixed dose in both treatment arms, found that combined aspirin-OAC therapy was associated with one-third lower risk of vascular events compared with OAC therapy alone. However, these benefits were limited to patients with a mechanical heart valve. There was no significant difference in the risk for arterial thromboembolism with these treatments in patients with AF or coronary artery disease, but estimates of treatment effects were statistically uncertain because of the small sample size of the trials. The risk for major bleeding was higher in patients receiving aspirin-OAC therapy compared with OAC alone (odds ratio, 1.43; 95% confidence interval, 1.00–2.02).

The average patient in recent AF trials and registries was ≥70 years of age, was mostly hypertensive (4 of 5), and frequently had diabetes mellitus (1 of 3) or prior myocardial infarction (1 of 6), a clinical profile for which aspirin would be commonly prescribed. In fact, in recent trials, baseline aspirin intake was reported in one third of NVAF patients. Moreover, 30% to 40% of patients with AF have concomitant atherothrombotic vascular disease, and 10% of patients with an acute coronary syndrome or undergoing coronary stenting have concomitant AF. For the latter patients, US guidelines recommend warfarin plus clopidogrel, whereas European guidelines suggest a triple combination of warfarin, aspirin, and clopidogrel for periods of up to 12 months. The discrepancy between European and US guidelines is more apparent than real: Both recommend combining a vitamin K antagonist with 1 or 2 antiplatelet agents for up to 12 months, depending on type of stent, and both acknowledge a Level of Evidence C (ie, expert opinion in the absence of randomized evidence). The only difference is that the authors of the US guidelines state that “the most important agent for the maintenance of coronary and stent patency is the thienopyridine derivative clopidogrel and that the addition of aspirin to the chronic anticoagulant regimen contributes more risk than benefit.”

The evidence underlying this statement is unclear in the absence of a randomized head-to-head comparison of clopidogrel and aspirin in this setting. The recently published American College of Chest Physicians guidelines suggest a graded approach for the first 12 months after intracoronary stent placement based on stroke risk (CHADS₂ score) and type of stent, ranging from dual antiplatelet therapy for AF patients at low to intermediate risk of stroke to vitamin K antagonist plus dual (first 1–6 months) or single (either clopidogrel or aspirin for up to 12 months) antiplatelet therapy for AF patients at high risk of stroke. All 3 guidelines give a consistently weak recommendation (2C or IIbC, indicating uncertain benefit/risk ratio with limited evidence) in favor of adjusted-dose vitamin K antagonist therapy alone (international normalized ratio, 2.0–3.0) rather than the combination of vitamin K antagonist therapy and aspirin for patients with AF and stable coronary disease, as well as for AF patients 12 months after undergoing elective stenting.

In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), Steinberg et al report the prevalence and predictors of aspirin use and the associated outcomes at the 6-month follow-up among 7347 US outpatients with AF on OAC. The median patient age was 75 years; 85% had hypertension; 30% had diabetes mellitus;
and 34% had heart failure. Aspirin plus OAC was prescribed in 35%, a rate very similar to that of recent AF trials.1 The daily aspirin dose was 81 mg in 89% and 325 mg in 11%, reflecting awareness of enhanced bleeding risk with increasing aspirin dose.5 Somewhat surprisingly, atherothrombotic vascular disease was absent in 39% of patients on OAC plus aspirin compared with 63% of those on OAC alone, whereas the risk of bleeding assessed by the ATRIA score (anemia, severe nephropathy, age ≥75 years, prior bleed, hypertension) was similar in the 2 groups.4 The adjusted hazard ratio for major bleeding associated with OAC plus aspirin compared with OAC alone was 1.53 (95% confidence interval, 1.2–1.96; P=0.0006), with patients >70 years of age showing the greatest absolute increase. Crude rates of ischemic events (myocardial infarction, revascularization, stroke, transient ischemic attack) were low in both groups. In an adjusted regression model (to minimize confounding associated with propensity to receive OAC plus aspirin), the strongest predictors of aspirin intake were coronary artery disease, prior surgical AF intervention, history of drug-eluting stenting, and prior stroke but also, to a lesser extent, prior valve replacement/repair, hypertension, dyslipidemia, diabetes mellitus, and smoking.4

Clinical registries, unlike randomized trials, are limited by known and unknown confounders such as the factors that influence physicians’ choice of one treatment over another. Registries are therefore less than ideal for drawing firm conclusions on treatment effects. In ORBIT-AF,4 for instance, the patients receiving additional antiplatelet therapy had higher baseline ischemic risk compared with those on OAC alone; thus, little can be inferred from the event rates registered at follow-up in the 2 groups other than the expected higher bleeding rates with dual compared with single antithrombotic treatment.5,6 In addition, information on patients with valvular AF is lacking. Despite these limitations, Steinberg et al6 provide important data on the contemporary management of AF in the United States and identify potential determinants leading to combined antithrombotic therapy.

The current US practice of using OAC plus low-dose aspirin in AF patients with stable atherothrombotic vascular disease, largely prescribed by cardiologists and electrophysiologists rather than by primary care providers,4 may not be unreasonable given the lack of randomized trials in this specific clinical setting and despite the weak recommendations from both US4 and European guidelines that discourage such practice because antiplatelet therapy with low-dose aspirin is effective and without major safety concerns in the secondary prevention of atherothrombosis.5 Moreover, before stopping aspirin because of a new diagnosis of AF and initiation of OAC or at 12 months after an acute coronary syndrome or coronary stenting, physicians should carefully consider the potential consequences of unopposed thromboxane-dependent platelet activation after aspirin withdrawal.9,10 Thus, in patients prescribed low-dose aspirin for the secondary prevention of cerebrovascular or cardiovascular events, discontinuation of antiplatelet therapy was associated with a 40% increase in the risk of ischemic stroke9 or myocardial infarction,10 respectively, compared with continuation of therapy in UK primary care observational studies.

However, the practice of using OAC plus low-dose aspirin in AF patients without symptomatic vascular disease4 is probably questionable because of the uncertain balance of cardiovascular benefits and bleeding risks associated with aspirin use in primary prevention, particularly in the elderly.11

An indirect benefit of the ORBIT-AF registry4 is to highlight the need for an adequately sized randomized trial comparing OAC alone against OAC and low-dose aspirin in patients with atherothrombotic vascular disease and NVA1 moderate to high thromboembolic risk to settle the debate on whether aspirin should be added to OAC in such patients. To date, this question has not been answered, not by the recent What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial12 comparing ciloprodregrel alone with ciloprodregrel and aspirin in patients requiring OAC and undergoing percutaneous coronary intervention because the trial was underpowered for efficacy (573 patients followed up for 1 year) and almost half of the patients did not have AF,12 nor by the Warfarin, Aspirin, Reinfarction Study (WARIS II) of 3630 patients <75 years of age with acute myocardial infarction randomized to aspirin plus warfarin at an international normalized ratio of 2.0 to 2.5, warfarin alone at an international normalized ratio of 2.8 to 4.2, or aspirin alone because none of these patients had concomitant AF.13 The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS; http://clinicaltrials.gov/show/NCT01776424) trial is currently testing the efficacy and safety of anticoagulation alone with rivaroxaban against aspirin monotherapy or the combination of aspirin and low-dose anticoagulation in ≈20000 patients with coronary or peripheral artery disease followed up for >5 years, reflecting the continued interest and need for very large trials in the area of combined antiplatelet and anticoagulant therapy.

Several new elements should be considered in this evolving scenario: (1) the recent marketing of 3 new OACs, dabigatran, apixaban, and rivaroxaban, with an improved benefit/risk profile compared with warfarin1; (2) the availability of 2 additional P2Y12 blockers, prasugrel and ticagrelor, with an improved benefit/risk profile compared with ciloprodregrel14; (3) the introduction of drug-eluting coronary artery stents with a reduced propensity for thrombosis and the prospect of fully bioresorbable drug-eluting vascular scaffolds;15 and (4) increasing awareness of potential nonvascular health benefits (eg, prevention of colorectal cancer) of long-term aspirin therapy.16 It is hoped that these novel therapeutic options and areas of knowledge will be integrated with more widespread assessment of the individual AF patient’s ischemic and bleeding risks, as well as of his or her values and preferences, to inform personalized antithrombotic therapy in this setting.

Disclosures

During the last 2 years, Dr Patrono has received consulting and speaker fees from AstraZeneca, Bayer AG, Eli Lilly, and Merck. Dr Andreotti has received consulting and speaker fees from Bayer AG, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, and Eli Lilly.

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