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, i.e., at least 100 million people worldwide. Left untreated, patients with nonvalvular AF (NVAF) are exposed to an annual risk of thromboembolic stroke of approximately 5%, resulting in 5 million AF-related strokes each year. Properly dosed anticoagulation (e.g., warfarin adjusted to an international normalized ratio [INR] of 2.0 to 3.0) is extremely effective in preventing AF-related strokes, reducing risk by two-thirds compared with no therapy, and by one-half compared to 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 to 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 and 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 INR 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 (OR, 1.43; 95% CI, 1.00-2.02).²

The average patient in recent NVAF trials³ and registries⁴ was aged ≥ 70 years, mostly hypertensive (four out of five), and frequently with diabetes mellitus (one out of three) or prior myocardial infarction (MI) (one out of six), a clinical profile for which aspirin would be commonly prescribed.⁵ In fact, in recent trials, baseline aspirin intake was reported in one-third of NVAF patients.³ Moreover, 30% to 40% of patients with AF have concomitant atherothrombotic vascular disease, and approximately 10% of patients with an acute coronary syndrome (ACS) and/or undergoing coronary stenting have concomitant AF.¹²,⁴ For the latter patients, US guidelines recommend warfarin plus clopidogrel,⁵ while European guidelines⁷ 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 (VKA) with one or two antiplatelet agents for up to 12 months depending on type of stent, and both acknowledge a C level of evidence (i.e., 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”.⁶ The evidence underlying this statement is unclear, in the absence of a randomized head-to-head comparison of clopidogrel versus aspirin in this setting. The recently published American College of Chest Physicians (ACCP) guidelines¹ 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 VKA 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 three guidelines give a consistently weak recommendation (2C or IIbC, indicating uncertain benefit/risk with limited evidence) in favor of adjusted-dose VKA therapy alone (INR 2.0 to 3.0) rather than the combination of VKA therapy and aspirin for patients with AF and stable coronary disease, as well as for AF patients 12 months after undergoing elective stenting.\textsuperscript{1,6,7}

In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), Steinberg et al.\textsuperscript{4} report the prevalence and predictors of aspirin use, and the associated outcomes at 6 month follow-up, among 7,347 US outpatients with AF on OAC. The median patients' age was 75 years, 85% had hypertension, 30% diabetes and 34% heart failure. Aspirin plus OAC was prescribed in 35%, a rate very similar to that of recent AF trials.\textsuperscript{3} The daily aspirin dose was 81 mg in 89% and 325 mg in 11%, reflecting awareness of enhanced bleeding risk with increasing aspirin dose.\textsuperscript{5} Somewhat surprisingly, atherothrombotic vascular disease was absent in 39% of patients on OAC plus aspirin compared to 63% of those on OAC alone, while the risk of bleeding assessed by the ATRIA score (anemia, severe nephropathy, age $\geq$75 yrs, prior bleed, hypertension) was similar in the two groups.\textsuperscript{4} The adjusted hazard ratio for major bleeding associated with OAC plus aspirin compared to OAC alone was 1.53 (95% CI 1.2-1.96; p=0.0006), with patients $>$70 years showing the greatest absolute increase. Crude rates of ischemic events (MI, revascularization, stroke, transient ischemic attack) were low in both groups. In an adjusted regression model (to minimize confounding associated with propensity to get OAC plus aspirin), the strongest predictors of aspirin intake were coronary artery disease, prior surgical AF intervention, history of drug eluting stenting, prior stroke, but also - to a lesser extent – prior valve replacement/repair, hypertension, dyslipidemia, diabetes and smoking.\textsuperscript{4}
Clinical registries, unlike randomized trials, are limited by known and unknown confounders, such as the factors that influence physicians’ choice of one versus another treatment. Registries are therefore less than ideal for drawing firm conclusions on treatment effects. In ORBIT-AF, for instance, the patients receiving additional antiplatelet therapy had higher baseline ischemic risk compared to those on OAC alone; thus, little can be inferred from the event rates registered at follow-up in the two groups, other than the expected higher bleeding rates with dual compared with single antithrombotic treatment. Also, information on patients with valvular AF is lacking. Despite these limitations, Steinberg et al. provide important data on the contemporary management of AF in the US 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, may not be unreasonable given the lack of randomized trials in this specific clinical setting and despite the weak recommendations from both US 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. Moreover, before stopping aspirin because of a new diagnosis of AF and initiation of OAC, or 12 months after an ACS and/or coronary stenting, physicians should carefully consider the potential consequences of unopposed thromboxane-dependent platelet activation following aspirin withdrawal. 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 stroke or myocardial infarction, 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 disease\(^4\) 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 registry\(^4\) 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 NVAF at moderate-to-high thromboembolic risk, in order to settle the debate on whether or not aspirin should be added to OAC in such patients. To date this question has not been answered, neither by the recent What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial\(^12\) comparing clopidogrel alone to clopidogrel and aspirin in patients requiring OAC and undergoing percutaneous coronary intervention, as the trial was underpowered for efficacy (573 patients followed 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 younger than 75 years with acute myocardial infarction randomized to aspirin plus warfarin at INR 2.0-2.5, warfarin alone at INR 2.8-4.2 or aspirin alone, as none of these patients had concomitant AF.\(^13\) The Cardiovascular OutcoMes for People using Anticoagulation StrategieS trial (COMPASS, http://clinicaltrials.gov/show/NCT0177642426) 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 about 20,000 patients with coronary or peripheral artery disease followed for approximately five 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: i) the recent marketing of three new OAC, i.e., dabigatran, apixaban and rivaroxaban, with an improved benefit/risk profile as compared with warfarin; ii) the availability of two additional P2Y\textsubscript{12} blockers, i.e., prasugrel and ticagrelor, with an improved benefit/risk profile as compared with clopidogrel; iii) the introduction of drug-eluting coronary artery stents with a reduced propensity towards thrombosis and the prospect of fully bioresorbable drug-eluting vascular scaffolds; iv) increasing awareness of potential non-vascular health benefits (e.g., prevention of colorectal cancer) of long-term aspirin therapy. 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 of his/her values and preferences to inform personalized antithrombotic therapy in this setting.

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