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EDITORIAL COMMENT

Aspirin in Atrial Fibrillation

The Clot Thickens*

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Aspirin is the original "wonder drug," used in various forms for thousands of years for its analgesic, antipyretic, and anti-inflammatory properties (1), and more recently, for its ability to inhibit platelet aggregation, reducing the risk for occlusive vascular events associated with acute coronary syndromes, transient cerebral ischemic attacks and stroke, and peripheral vascular disease (2).

But aspirin is not an anticoagulant; aspirin is ineffective for prevention of thromboembolism related to nonvalvular atrial fibrillation. Multiple randomized clinical trials now provide convincing evidence that oral anticoagulants, such as warfarin or newer non-vitamin K antagonist direct oral anticoagulants (DOACs), are distinctly superior to aspirin in preventing thromboembolic outcomes in those patients who are at moderate to high risk (CHA_2DS_2-VASc scores ≥2) (3–5). Aspirin is associated with a risk of bleeding similar to some of the new DOACs (6,7), but is of little, if any, benefit in the prevention of thromboembolism. Risk without reward is not a good tradeoff.

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Why then are as many as one-half of CHA_2DS_2-VASc ≥2 patients not receiving effective treatment with oral anticoagulants, with many receiving aspirin instead (8–12)? In this issue of the *Journal*, Hsu et al. (13) provide valuable insight. More than one-third of 210,380 patients in the real-world National Cardiovascular Data Registry (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) registry who had CHA_2DS_2-VASc scores ≥2 were treated with aspirin alone, and not with oral anticoagulants as the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) (14), European Society of Cardiology (ESC) (15), and National Institute for Health and Clinical Excellence (NICE) (16) guidelines suggest. Registries, such as the NCDR PINNACLE registry, are important adjuncts to clinical trials in that they tell us what is really going on in the clinical practice, outside the carefully controlled research milieu.

Guidelines, on the basis of sound basic science, randomized controlled trials, clinical registries, meta-analyses, and the experience of experts, are by no means inviolate; clinicians are intended to use guidelines as analytic tools to assist in making rational decisions for each individual patient, weighing many factors, some more tangible than others, including patient choice and compliance. It is nonetheless concerning that the highly motivated, conscientious, and talented cardiologists working in quality-conscious institutions that contribute their data to the NCDR are not prescribing anticoagulation in one-third of their qualifying patients, as defined by our guidelines. This variance from guidelines does not appear to be related to true contraindication to anticoagulation, but may reflect a lack of appreciation that aspirin administration places a patient at significant risk for bleeding, while offering virtually no protection from stroke.

The PINNACLE registry does not detail the bleeding risk in these patients, but it seems unlikely that one-third had objective evidence of an unacceptable increase in the risk of serious bleeding as a contraindication to oral anticoagulation, especially because patients (n = 17,627) deemed by their treating physicians "not able to be prescribed aspirin or oral anticoagulant therapy" were excluded from this analysis. The risk of bleeding associated with anticoagulation is often cited as a contraindication for anticoagulation.

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This risk is real, but may be overestimated or magnified, as physicians prescribing anticoagulation, particularly warfarin, often encounter patients with minor and occasionally serious bleeding, but don't see the strokes that don't occur. Patients understandably wish to avoid bleeding and may discount their chances of suffering a disabling or fatal stroke, choosing less effective or ineffective treatment to prevent thromboembolism, and failing to recognize that aspirin itself may cause bleeding, but no benefit in preventing thromboembolism related to atrial fibrillation.

The presence of comorbid conditions, such as unstable angina, recent myocardial infarction, coronary artery bypass grafting, or peripheral arterial disease, which might have warranted treatment with antiplatelet agents such as aspirin, was greater in the PINNACLE group treated with aspirin alone than in those receiving anticoagulation. But neither aspirin alone nor dual antiplatelet therapy without anticoagulants are effective in preventing thromboembolism related to nonvalvular atrial fibrillation (17). Anticoagulants, not antiplatelet agents alone, are indicated to prevent thromboembolism related to atrial fibrillation in patients with unstable atherosclerotic syndromes, even if antiplatelet agents are also needed to prevent platelet-initiated thrombosis related to arterial disease, acknowledging that the risk of bleeding is increased when anticoagulants and antithrombotic agents are administered together (18,19). Even when an antiplatelet agent needs to be added to an anticoagulant regimen, clopidogrel is often a better choice than aspirin alone (16). Many patients in the PINNACLE registry treated with aspirin alone appear not to have had comorbid conditions warranting treatment with aspirin, and many others who may have had an initial indication for antiplatelet therapy may have entered a stable phase of their atherosclerotic disease, for which aspirin has no proven benefit (17).

The PINNACLE data reported here were collected before newer, non-vitamin K antagonist anticoagulants, which do not require monitoring of the international normalized ratio and are associated with fewer serious bleeding complications than warfarin, were in widespread use. Indeed, some newer DOACs may have an even lower risk of bleeding than aspirin (7). There is little rationale for prescribing aspirin, rather than either warfarin or DOACs, to prevent thromboembolism related to atrial fibrillation, even if bleeding is a concern. The ACC/AHA/HRS 2014 Guidelines (14) give tepid support to the use of aspirin in patients with low risk (CHA_2DS_2-VASc $\leq$1) of thromboembolism—"aspirin may be considered[…] equivalent to no treatment[…]based on diverging expert opinion." However, the ESC (15) and NICE (16) guidelines are unequivocal: aspirin is not recommended to prevent thromboembolism in atrial fibrillation in any circumstance.

What other reasons might explain avoidance of antithrombotic agents in these patients if bleeding risk or an independent indication for antiplatelet agents is not a compelling argument? Cognitive dissonance (think of death-defying helmetless motorcycle riders and perpetually optimistic slot machine players) and unconscious bias (20) may play a role in justifying continuation of old habits, denying new evidence that requires uncomfortable and inconvenient change. Patient choice and the "art of medicine" may be cited to rationalize illogical decisions that conflict with scientific evidence. The process of anticoagulation is not a particularly attractive proposition, entailing compliance with a long-term regimen that many patients and their physicians find burdensome, with inevitable nuisance, expense, annoying minor side effects, and infrequent, but devastating, complications, such as intracerebral hemorrhage, and with only an abstract future benefit for perhaps 4 or 5 of 100 patients who would suffer a stroke if they did not receive anticoagulation.

Atrial fibrillation is a chronic disease requiring long-term treatment. On the basis of our frequent contact with other patients with chronic diseases, such as hypertension, obesity, hyperlipidemia, diabetes, atherosclerosis, and heart failure, we are frustrated by high rates of noncompliance, especially with anticoagulant regimens. Patients and their physicians are bombarded with conflicting and potentially confusing billion-dollar advertising campaigns, sponsored by pharmaceutical companies promoting DOACs and attorneys hoping to obtain monetary compensation for patients who have suffered complications from anticoagulation. We may be tempted to avoid controversy and assume that the benefit of general preventive measures, such as diet and exercise, statins, antihypertensive agents, and yes, aspirin, is enough to reduce stroke risk in patients with atrial fibrillation. We could be experiencing "guideline fatigue" and cognitive dissonance, seeking justification for lower-grade therapy, despite new and definitive evidence that anticoagulation, not aspirin, is the treatment of choice to prevent strokes related to atrial fibrillation.

Hsu et al. (13) and the participants in the NCDR PINNACLE registry are to be congratulated for providing provocative introspection of our practice habits. Physicians and their patients should not sidestep the real risks of thromboembolism due to atrial fibrillation and the benefits of real anticoagulation,

relying instead on aspirin, which has bleeding risk, but little, if any, therapeutic benefit. "Take 2 aspirin and call me in the morning" is not appropriate treatment for a patient with atrial fibrillation at risk for thromboembolism. The clot only thickens.

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