Underuse of Oral Anticoagulants for Nonvalvular Atrial Fibrillation:

Past, Present, and Future

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Nonvalvular atrial fibrillation (AF) is the most widespread cardiac arrhythmia of clinical significance worldwide, and its prevalence is increasing.^{1,2} Atrial fibrillation is a substantial health problem because it significantly increases the risk of thromboembolic events, particularly that of stroke.³ Moreover, strokes associated with AF are more severe, involve larger vascular territories, and cause more morbidity and death than do strokes from other causes.⁴

Oral anticoagulant (OAC) therapy can substantially reduce the risk of stroke from AF.⁵ However, this therapy also carries risk, particularly of bleeding events: intracranial hemorrhage is chief among these. Accordingly, much effort has been devoted to identifying the subset of patients with AF for whom the benefit of stroke prevention outweighs the risk of major bleeding.⁶⁻⁹ This has led to the development of the CHADS₂ and CHA₂DS₂-VASc scores, which have been robustly validated as tools to stratify patients on the basis of their thromboembolic risk.^{8,10-15} Guidelines from cardiovascular societies endorse the clinical use of these risk scores to help select those patients who might benefit from anticoagulant therapy. These guidelines include strong recommendations for OAC use in patients whose CHA₂DS₂-VASc score is 2 or higher, and weaker recommendations when that score is 1.¹⁶⁻¹⁹ Despite this, there is evidence that a substantial number of patients for whom OAC therapy is indicated do not receive appropriate treatment. In a systematic review of numerous cohort studies of individuals who had AF and a prior history of stroke (one of the highest-risk groups for recurrent thromboembolism), OAC usage rates were less than 60% in most of the populations studied.²⁰ Usage rates among patients who had high CHA₂DS₂-VASc scores were similarly poor. Although shared decision-making, patients' preferences, and noncompliance with medical regimens are certainly factors in OAC underuse, clinicians' judgment appears to play the chief role.²¹⁻²⁴ The reasons typically cited for not prescribing OACs are bleeding risk, older age, the risk of falls, and patient noncompliance.²³⁻²⁵ In fact, two of the strongest risk factors for stroke in AF—prior stroke and increasing age—are actually indicators of withholding appropriate anticoagulant therapy.²⁶

Bleeding risk is probably grossly overestimated by clinicians. Several scores have been developed to help estimate the risk of bleeding events in OAC use, analogous to the CHA₂DS₂-VASc score for stroke. However, all of these risk scores have performed relatively poorly in subsequent cohorts, and none is better than physician estimation alone.^{27,28} Nonetheless, there is concern that clinicians are using these scores inappropriately, in an attempt to determine a net clinical benefit of OAC therapy in individual circumstances. The bleeding-risk scores have not been validated for this use; rather, they are designed to aid the clinician in identifying potentially modifiable risk factors such as high blood pressure, abnormal renal or liver function, potential medication interactions, and alcohol use. Hypertension, increasing age, and prior stroke—3 of the risk factors included in the most popular risk score, HAS-BLED²⁹—are also risk factors for thromboembolism in AF. Indeed, stroke risk and the consequent clinical benefit of anticoagulation increase along with higher HAS-BLED scores within a given CHA₂DS₂-VASc risk category.⁶

Similarly, the contribution of fall risk to bleeding events (while patients are taking OACs) is most likely overestimated. Clinicians might fear increased possibilities of traumatic intracranial hemorrhage and therefore hesitate to prescribe OACs to patients who are perceived to be at high risk of falling; however, the risk of major bleeding events is not significantly higher in this population.³⁰ In fact, it is estimated that a patient would need to fall approximately 300 times in one year for the risk of increased intracranial hemorrhage to outweigh the benefits of anticoagulation in thromboembolic prevention.³¹ In addition, older patients are often thought to be too frail or too high-risk to tolerate anticoagulants, yet again there is strong evidence that patients ≥ 75 years of age particularly can benefit from OAC therapy.³²

Previously, vitamin K antagonists such as warfarin were the only OACs approved for chronic stroke prevention in patients who had AF. Clinicians' overestimation of bleeding risk—as well as their concerns about regimen noncompliance, variable pharmacokinetic profiles, and the need for serial monitoring—lessened the appeal of warfarin as a therapeutic option. This has resulted in undertreatment or in the inappropriate substitution of other antithrombotic agents, such as aspirin. Contrary to popular opinion, aspirin has not significantly lowered the risk of stroke from AF in any single randomized trial^{5,33} and is especially inferior to OAC therapy in the elderly population, where aspirin is often used.^{32,34} However, since approximately 2010, several novel OACs (NOACs) have become available, including the direct thrombin inhibitor dabigatran³⁵ and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.^{36–38} In randomized clinical trials involving patients who had nonvalvular AF, all the NOACs were not inferior to warfarin in stroke prevention, and most showed a signal for superiority.³⁹ In addition, NOAC use was associated with a significantly lower rate of intracranial hemorrhage than was warfarin.

The NOACs are promising therapeutic alternatives to warfarin for the prevention of thromboembolism in AF; however, they present new challenges and considerations. One perceived major advantage of the NOACs is their more predictable pharmacokinetic profile and therefore obviation of the need for serial therapeutic-drug monitoring. This benefit would make NOAC therapy more convenient for patients but might hinder evaluation of patient compliance. The lower rate of intracranial hemorrhage in NOAC use might appeal to clinicians who have concerns about bleeding or fall risk; however, the current lack of reversal agents for most NOACs might mitigate that potential advantage. The higher cost of these novel agents and their various dosing schedules also might influence therapeutic decisions. Finally, research continues into whether NOACs are effective for specific indications in AF, such as short-term anticoagulation around the time of cardioversion.^{40,41}

The NOACs expand the therapeutic arsenal for thromboembolic prophylaxis in AF. However, many data currently available about the rates of OAC use in real-world AF cohorts come from the pre-NOAC years. Little is known about how the introduction of NOACs has changed the prescribing patterns of OACs for AF.⁴² A recent analysis of visit-level data from a nationally representative outpatient survey suggested that trends toward increased adoption of NOACs are associated with an overall increase in rates of OAC use⁴³; however, no contemporary patient-level data include all the currently available NOACs. Moreover, after the U.S. Food and Drug Administration's recent approval of idarucizumab—the first reversal agent for dabigatran⁴⁴—it remains to be seen how OAC prescription patterns might further evolve. Future investigators should continue to evaluate patterns of OAC prescription and use for AF, identifying areas of noncompliance with well-established, guideline-directed management recommendations as targets for improvement in patient safety and quality of care.

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