Individualized approaches to thromboprophylaxis in atrial fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia worldwide. The prevalence of AF in persons older than 55 years is at least 33.5 million globally and is predicted to more than double in the next half-century. Anticoagulation, heart rate control, and heart rhythm control comprise the 3 main treatment strategies in AF.

Anticoagulation is aimed at preventing debilitating stroke, systemic embolism, and associated mortality. Historically, anticoagulation in AF was achieved with a vitamin K antagonist such as warfarin, which is supported by evidence demonstrating reduced incident stroke and all-cause mortality. However, warfarin has unpredictable pharmacokinetics with many drug-drug interactions that require regular monitoring to ensure patients remain in the therapeutic anticoagulant range. Non–vitamin K antagonist oral anticoagulants including dabigatran, rivaroxaban, apixaban, and edoxaban provide a possible solution to these issues with their more predictable pharmacokinetics, rapid onset of action, and greater specificity. Results from large randomized, controlled trials indicate that these agents are at least noninferior to warfarin in prevention of stroke. These trials also demonstrate a consistently lower incidence of intracranial hemorrhage, almost always all life-threatening bleeds, and many forms of major bleeds with the possible exception of gastrointestinal and some other forms of mucosal bleeding, compared with warfarin.

Patients with AF are a heterogeneous population with diverse risk of stroke and bleeding, and different subgroups respond differently to anticoagulation. Important clinical questions have arisen regarding optimal anticoagulation drug selection in distinct populations such as those with renal impairment, older age, coronary artery disease, and heart failure as well as those at particularly high risk for bleeding or thromboembolism. In this review, treatment strategies in AF management are discussed in the context of different individual subgroups of patients. (Am Heart J 2016;173:143-58.)

Atrial fibrillation (AF) is the most common arrhythmia, affecting 1% to 2% of the population in North America and Europe.[1] Atrial stasis, endothelial dysfunction, and increased coagulability lead to thrombus formation resulting in a 4- to 5-fold increased risk of ischemic stroke relative to the nonaffected population.[2] Atrial fibrillation is responsible for at least 15% of all strokes, rising to 25% in the elderly (≥70 years).[3,4] Strokes resulting from AF are more severe than those of other etiology, with a higher mortality and greater functional deficit.[5]

The last few years has seen a dramatic increase in the options available for AF thromboprophylaxis. Aspirin, once widely used, is inferior to warfarin and is not significantly better than placebo in stroke prevention.[6–8] The National Institute for Health and Care Excellence (NICE) along with the European Society of Cardiology (ESC) guidelines no longer recommend antiplatelet therapy unless a patient refuses anticoagulation[9,10] (Table I). Well-controlled warfarin therapy is extremely effective in reducing the risk of ischemic stroke (relative risk [RR] reduction of 64%).[11] Achieving good control requires careful monitoring, with regular dose adjustments to remain within a target international normalized ratio (INR) range. This is complicated by genetic variation involved in warfarin metabolism, slow onset of action, and complex pharmacology with many drug-drug and dietary interactions.

Unlike warfarin, the non–vitamin K antagonist oral anticoagulants (NOACs) have more predictable pharmacokinetic profiles, wide therapeutic windows, and minimal drug-drug interactions and do not require regular therapeutic monitoring. NOACs are at least equal in efficacy to warfarin for stroke prevention in AF; however, each agent exhibits a unique set of clinical properties that may favor their use in particular individuals.[12–16]

Realizing the full potential of recent advances in AF management options will require individualized treatment strategies, incorporating individual patients' views and preferences. In this review, we consider the evidence relating to oral anticoagulation in patients at thromboembolic risk, specifically focusing on distinct subgroups of the AF population.

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Table I. Anticoagulation guidelines in AF

Guideline	CHA_2DS_2-VASc = 0	CHA_2DS_2-VASc = 1	CHA_2DS_2-VASc ≥ 2
AHA/ACC/HRS 2014[17]	Reasonable to omit antithrombotic therapy	Consider aspirin or no antithrombotic therapy	Recommend: dabigatran, rivaroxaban, apixaban, warfarin. In CKD moderate-severe, consider reduced dose dabigatran, rivaroxaban, or apixaban. If CrCl <15 mL/min, prescribe warfarin
ESC 2012[23]	Recommend no antithrombotic therapy	Best option: dabigatran, rivaroxaban, apixaban. Alternative option: adjusted dose VKA (INR 2-3) Female patients <65 y and lone AF: no antithrombotic therapy	Best option: dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban Alternative option: adjusted dose VKA (INR 2-3) If CrCl <30 mL/min, avoid NOACs
NICE 2014[9]	Do not offer stroke prevention therapy	Men with CHA_2DS_2-VASc = 1: consider anticoagulation including rivaroxaban, dabigatran, apixaban, and VKA; take bleeding risk into account. Female CHA_2DS_2-VASc = 1: do not offer stroke prevention therapy	Offer anticoagulation, including rivaroxaban, dabigatran, apixaban, and VKA. Take bleeding risk into account
CCS 2014[147]	No additional risk factors: no antithrombotic	≥65 y: OAC Prior stroke or TIA; or hypertension; or HF; or diabetes: OAC CAD or vascular disease: ASA NOAC should be used in preference to warfarin in nonvalvular AF	Offer OAC. NOAC should be used in preference to warfarin in nonvalvular AF

Abbreviations: AHA, American Heart Association; ACC, American College of Cardiology; ASA, acetylsalicyclic acid; CCS, Canadian Cardiovascular Society; HRS, Heart Rhythm Society; OAC, oral anticoagulant.

Classification of AF

Atrial fibrillation is not a homogenous arrhythmia and has been classified by presentation and duration of the arrhythmia. The ESC has adopted the following 5 types[10]:

1. First diagnosed with AF
2. Paroxysmal AF
3. Persistent AF
4. Long-standing persistent AF
5. Permanent AF

The American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 guidelines do not recognize first-diagnosed AF as a distinct entity but instead include an additional group named "nonvalvular AF," in whom there is absence of rheumatic mitral stenosis, prosthetic mechanical heart valve, or mitral valve repair.[17] This was supported by the finding that AF increases stroke risk 4- to 5-fold, whereas mitral stenosis or prosthetic heart valve–related AF confers a 20-fold increase in risk compared with patients in sinus rhythm.[2,18] Paroxysmal AF appears to be associated with less thromboembolic events than persistent or permanent AF,[14,16] but regardless, all categories of nonvalvular AF should be managed with the same thromboprophylactic approach based on risk factors and patient preferences irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.[19]

Although helpful to guide prescribing, these categories fail to adequately classify all patients with AF. Remote continuous cardiac monitoring by virtue of cardiac implantable electronic devices has revealed cases of subclinical AF, associated with increased risk of embolic events.[20] A further subgroup of unclassified patients are those with a "pre-AF" status. This population, with a high burden of vascular risk factors, is at significant risk for developing AF. It is unknown whether protection with anticoagulation for near-inevitable atrial tachyarrhythmia provides benefit, but some pilot studies are underway including REVEAL AF[21] and ASSERT-II.[22]

The current AF classification schemes are restricted by simplicity. Many risk factors predict the onset of AF, and a more comprehensive classification system is required that incorporates AF duration and symptoms combined with a risk score for AF onset, persistence, progression, and complications along with markers of atrial remodeling, This model would improve the clinicians' ability to risk stratify their patients and hence guide personalized treatment.[23] This individualized management approach to AF would also benefit from integrating the pathophysiologic type of AF addressing atrial morphology, genetic predisposition, and markers of inflammation and cardiac strain.[24]

Anticoagulation therapies—a multitude of choice

Warfarin is an excellent anticoagulant in AF that reduces stroke by 64% and all-cause mortality by 26%,[8,25] but despite this, physicians underuse it, particularly in elderly patients.[26] This may be partly explained