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Ineligibility for Anticoagulation in Patients with Atrial Fibrillation

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ABSTRACT

Although anticoagulation therapy markedly reduces the risk of stroke in patients with atrial fibrillation, up to 50% of these patients are deemed ineligible for anticoagulation. In this manuscript we provide a framework to assess the net clinical benefit of anticoagulation in patients with atrial fibrillation with an increased risk of bleeding. We also review recent data related to the novel oral anticoagulants targeting thrombin or factor Xa, and discuss how the introduction of these agents raises the distinction between eligibility for vitamin K antagonist therapy specifically, and eligibility for anticoagulation in general.
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KEYWORDS: Anticoagulation; Atrial fibrillation; Bleeding; Eligibility; Stroke

The clinical significance of atrial fibrillation derives largely from its association with cardioembolic stroke, which is often fatal or neurologically devastating. In a meta-analysis of 29 trials that enrolled over 28,000 patients with atrial fibrillation, dose-adjusted warfarin led to a 64% reduction in the risk of stroke compared with patients receiving either no treatment or placebo.[1] More recently, novel oral anticoagulants have been developed, including the direct thrombin inhibitor dabigatran, and inhibitors of activated factor X, including rivaroxaban, apixaban, and edoxaban.[2-5] These agents have been evaluated as alternatives to the vitamin K antagonist (VKA) warfarin and appear at least comparably effective, yet have several advantages including relatively few drug and food interactions, and stable pharmacodynamic and pharmacokinetic properties that avoid the need for frequent laboratory monitoring of coagulation intensity (**Table 1**).

For anticoagulation therapy to be of benefit, the decrease in stroke risk must outweigh the risk of serious bleeding. Although anticoagulation therapy uniformly reduces the risk of stroke across all patients with atrial fibrillation, the benefit of anticoagulation is proportional to the absolute risk of stroke. Practice guidelines in the US[6] recommend the use of the $CHADS_2$ score (assigning points for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or transient ischemic attack [2 points]) for assessment of stroke risk (**Table 2**).[6-11] In contrast, European guidelines[10] recommend use of the CHA_2DS_2-VASc score (assigning points for Congestive heart failure, Hypertension, Age ≥ 75 years [2 points], Diabetes mellitus, prior Stroke or transient ischemic attack [2 points] – Vascular disease, age 65-74 years, female sex), a revised and probably superior form of the $CHADS_2$ schema that incorporates additional stroke risk factors that were previously underappreciated, such as age of 65-74 years, presence of atherosclerotic vascular disease, and female sex (**Table 2**). Based on validation studies, the main advantages of CHA_2DS_2-VASc over $CHADS_2$ include its ability to identify patients who, despite having a $CHADS_2$ score of zero, are at increased risk of stroke and may benefit from anticoagulation, and its ability to identify patients who are truly at low risk of stroke (eg, CHA_2DS_2-VASc = 0) and who are unlikely to benefit from antithrombotic therapy.[7]

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Current guidelines recommend oral anticoagulation for patients with $CHADS_2$ or CHA_2DS_2-VASc scores of 2 or greater (risk of stroke of about 3%-4% per year or greater); and either antiplatelet or anticoagulation therapy for patients with $CHADS_2$ or CHA_2DS_2-VASc scores of 1 (risk of stroke 1%-2% per year),[6,10,11] although recent guidelines favor anticoagulation in these patients.[11] Patients with CHA_2DS_2-VASc scores of zero are at very low risk of stroke (0.0%-0.78% per year) and may be managed without any form of antithrombotic therapy (**Table 2**).[6,10,11]

Several independent bleeding risk factors have been identified and incorporated into clinical scores, such as HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly),[12] $HEMORR_2HAGES$ (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age [>75 years], Reduced platelet count or function, Rebleeding risk [2 points], uncontrolled Hypertension, Anemia, Genetic factor, Excessive fall risk, and Stroke),[13] or the ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) bleeding risk index[14] (**Tables 3**, **4**).[15] European guidelines recommend calculating a HAS-BLED score to estimate a patient's risk of major hemorrhage. However, there are several important limitations with these scales: they are derived from datasets of patients initially deemed eligible for anticoagulation and may therefore not accurately reflect the patient populations clinicians encounter in practice. Also, these scores have not been extensively validated, and their ability to predict major bleeding appears to be modest, with C statistics ranging from 0.61 to 0.66 in validation studies.[16] Lastly, these scales include many of the risk factors associated with an increased risk of major stroke (eg, older age, prior stroke, or hypertension), and are therefore not useful in informing about net benefit of anticoagulation. Overall, bleeding risk scores should be used in patients at intermediate risk of stroke (eg, $CHADS_2 = 1$) in whom deferral of anticoagulation may be reasonable. An elevated bleeding score, however, should not be the basis for withholding anticoagulation in patients at high risk of stroke.

Table 1 Comparison of Features of New Oral Anticoagulants with Those of Vitamin K Antagonists

Feature	Vitamin K Antagonists	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes[a]	No

[a]Vitamin K and fresh frozen plasma (FFP) reverse the anticoagulant effect of vitamin K antagonists. However, the effect of FFP is transient, and restoring hemostasis with vitamin K administration usually takes several days.

CLINICAL SIGNIFICANCE

- Patients with atrial fibrillation at high risk of stroke are often felt to be ineligible for anticoagulation based on psychosocial factors or increased bleeding risk.
- To deem a patient with atrial fibrillation ineligible for anticoagulation, the risk of serious bleeding during anticoagulation must exceed the benefit of stroke prevention.
- The new oral anticoagulants represent an attractive alternative in at least some patients previously deemed ineligible for anticoagulation with vitamin K antagonists.

NET BENEFIT OF ANTICOAGULATION

To deem a patient with atrial fibrillation ineligible for anticoagulation, the risk of serious bleeding during anticoagulation must exceed the benefit of stroke prevention. Because strokes associated with atrial fibrillation are particularly devastating, the types of hemorrhagic events that would negate the benefits of anticoagulation in atrial fibrillation should be as clinically overwhelming as cardioembolic stroke. Clearly, the most worrisome hemorrhagic complication in patients receiving anticoagulation therapy is fatal or permanently disabling bleeding, as is typical of intracranial hemorrhage.

Singer et al[17] analyzed a cohort of over 13,500 "real world" patients with atrial fibrillation—yielding 66,000 patient-years of follow-up—to assess the incidence of ischemic stroke, systemic embolism, and intracranial hemorrhage among patients receiving VKAs versus no anticoagulation. The investigators estimated a net clinical benefit of VKAs, preventing more strokes than causing intracranial hemorrhage. VKAs decreased the annual rate of ischemic stroke or systemic embolism from 2.1% to 1.3%. The cost was an increase in intracranial hemorrhage, from 0.3% per year in patients not receiving VKAs to 0.6% per year in patients receiving VKAs. Treatment with VKAs prevented 0.80 adverse events per 100 patients per year, with even greater net benefit in higher-risk patients, such as those 85 years or older or with $CHADS_2$ scores of 4 to 6.

More recently, Friberg et al evaluated the net benefit of VKAs in over 170,000 Swedish patients with atrial fibrillation at various risks of stroke and bleeding based on the HAS-BLED score.[18] Net benefit was estimated as the rate of stroke prevented by VKAs minus the rate of intracranial hemorrhage attributable to anticoagulation. A weighting factor of 1.5 was used to adjust for the greater severity of intracranial hemorrhage. Similar to the study by Singer