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Care of Patients with Dysrhythmias

Use of novel oral anticoagulants for patients with atrial fibrillation: Systematic review and clinical implications

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ABSTRACT

Atrial fibrillation (AF), a common arrhythmia, increases the risk of ischemic stroke. Stroke and bleeding scores for patients with AF can help to stratify risk and determine the need for antithrombotic therapy, for which warfarin has been the gold standard. Although highly effective, warfarin has several limitations that can lead to its underuse. Data from randomized, Phase III clinical trials of the novel oral anticoagulants, dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, both factor Xa inhibitors, indicate these drugs are at least noninferior to warfarin for the prevention of stroke and systemic embolism. They are easier to administer, and have an equivalent or lower risk of bleeding versus warfarin. A better understanding of the risks and benefits of the novel oral anticoagulants, and their use in clinical practice, will prepare clinicians to anticipate and address educational and clinical needs of AF patients and their families, and promote evidence-based prescription of appropriate and safe anticoagulation therapy.

Introduction

Atrial fibrillation (AF), the most common arrhythmia encountered in clinical practice, is characterized by uncoordinated activation of the atria.[1–3] AF causes deterioration in cardiac function and is associated with increased morbidity, mortality, and costs, particularly due to ischemic stroke.[1,4] After accounting for standard stroke risk factors (e.g., age, hypertension, and heart failure), AF was associated with a 4- to 5-fold increased risk of ischemic stroke[5]; however, stroke in AF can be reduced by over 60% with antithrombotic therapy.[1,6] Until recently, the primary treatment for thromboembolism prevention was limited to anticoagulation with warfarin. However, several novel oral anticoagulants have been approved by the US Food and Drug Administration for the prevention of stroke or systemic embolism in patients with AF as well as for the treatment and/or prevention of venous thromboembolism.[7–9]

Novel oral anticoagulants have the potential to reduce the burden of stroke by providing effective, safe, and more convenient alternatives to warfarin.[7–9] This article will review current strategies for stroke prevention in AF, describe the assessment of stroke and bleeding risk, and discuss evidence supporting the use of novel oral anticoagulants. Content in this paper, including a discussion of dosing, mechanisms, side effects, interactions, and bleeding risks, will prepare clinicians to anticipate and address clinical and educational needs of self, patients, and families. Evidence-based knowledge of the risks and benefits associated with novel oral anticoagulants will promote the optimal prescribing and use of these agents.

Stroke and bleeding prevention in atrial fibrillation

In 2009, 1 million people were hospitalized for stroke in the United States, of whom 12% were diagnosed with AF as a comorbid condition.[10] Historically, oral antithrombotic therapy with warfarin was considered the evidence-based, best-practice treatment for

Abbreviations: AF, atrial fibrillation; $CHADS_2$, cardiac failure, hypertension, age, diabetes, stroke (doubled); CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, previous stroke or transient ischemic attack (doubled), vascular disease, sex category; CI, confidence interval; CrCl, creatinine clearance; GI, gastrointestinal; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol; ICH, intracranial hemorrhage; INR, international normalized ratio; MI, myocardial infarction; RR, relative risk; TTR, time in therapeutic range.

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patients with 2 or more risk factors for stroke.[11,12] Antiplatelet therapy with aspirin was considered an alternative to warfarin for stroke prevention in some patients, such as those with contraindications to warfarin or those with 1 clinically relevant nonmajor risk factor (such as female sex, age 65–74 years, or vascular disease)[11,12]; however, warfarin offers greater efficacy. In a meta-analysis of trials investigating antithrombotic prevention of stroke in AF, warfarin reduced stroke by 62% and aspirin reduced stroke by 22%.[13]

Thromboprophylaxis with anticoagulant or antiplatelet agents reduces the risk of stroke; however, the risk of bleeding remains a primary concern with these agents. Decisions about using antithrombotic therapy should be based on the absolute risks of stroke and bleeding, and the clinical benefits for individual patients.[1,6,14] Clinicians must accurately assess stroke and bleeding risks using risk assessment scales that facilitate systematic evaluation of such risks. Risk scales should be used to prevent under- or overestimation of risk, because both scenarios may influence treatment decisions that impact quality of life and clinical outcomes.[15]

Risk assessment of stroke

The $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke [doubled]) risk index is used to quantify stroke risk in patients with AF and can help determine the need for anticoagulant therapy.[1,6,14,16] The $CHADS_2$ score is based on the sum score of points that are assigned to each of 5 risk factors for stroke; and higher $CHADS_2$ scores are associated with increased stroke risk (Table 1).[16]

Although straightforward, the $CHADS_2$ score does not account for all known stroke risk factors for patients with AF. The CHA_2DS_2-VASc index incorporates additional risk factors, assigning additional points for age ≥75 years (2 points), history of vascular disease (1 point), age 65–74 years (1 point), and female gender (1 point).[17] When validated and compared with $CHADS_2$, CHA_2DS_2-VASc showed a modest improvement in predictive value.[17] However, when applied in clinical practice, conclusions were mixed on whether the CHA_2DS_2-VASc risk index was superior to the well-validated and simpler $CHADS_2$.[1,6,14]

Risk assessment of bleeding

Bleeding risk during anticoagulant therapy for AF varies and is influenced by factors such as age, comorbidities, alcohol intake, and genetics. Although bleeding risk stratification schemes attempted to account for the most important risk factors, many scoring systems were difficult to apply in clinical practice or were not studied in patients with AF.[18–20] Furthermore, the availability of multiple bleeding risk assessment tools may create uncertainty over which to use. Of 5 tools previously described in the literature,[18,19,21–23] the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly, drugs/alcohol concomitantly; see Table 2[22]) performed best in a comparative validation analysis, demonstrating a stepwise increase in rates of major bleeding with higher HAS-BLED scores ($P < 0.0001$).[20,24] In addition to confirming the association between increased HAS-BLED scores and bleeding, a study of 965 anticoagulated outpatients also found that higher HAS-BLED scores predicted a 51% increased risk of adverse cardiovascular events and a 68% increased risk of mortality.[25] However, in patients with AF, risk factors for bleeding with anticoagulant treatment overlapped with risk factors for stroke.[1,6,14] Use of criteria from the HAS-BLED scale (Table 2) will assist clinicians with care planning and anticoagulation treatment decisions.[22]

Table 1
Stroke risk in patients with nonvalvular atrial fibrillation not treated with anticoagulant, according to $CHADS_2$ index.

$CHADS_2$ risk criteria		Score
Prior stroke or TIA		2
Age >75 y		1
Hypertension		1
Diabetes		1
Recent exacerbation of CHF		1
$CHADS_2$ score	Patients ($n = 1733$)	Adjusted stroke rate, %/y (95% CI)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

CHF, congestive heart failure; CI, confidence interval; TIA, transient ischemic attack.
Adapted from Gage et al.[16]

Challenges of thromboprophylaxis with warfarin and antiplatelet agents

Warfarin, a vitamin K antagonist, acts by inhibiting the synthesis of vitamin K-dependent clotting factors, including factors II, VII, IX, and X, and the anticoagulant proteins C and S (Fig. 1). Although it has several food and drug interactions and a narrow therapeutic window, warfarin is highly effective, inexpensive, and has been widely researched and used for several decades.[26,27]

Despite its widespread use, prescription of warfarin and management of stroke in patients with AF are often suboptimal.[28–30] Warfarin dosing must be adjusted to ensure that a therapeutic INR range (2.0–3.0) is strictly maintained to minimize the risks of bleeding and stroke. An INR <2.0 places patients with AF at greater risk for stroke, and an INR >3.0 increases the risk for major or minor bleeding and/or intracranial hemorrhage (ICH).[31,32]

Warfarin is associated with a variable response and therefore maintenance of therapeutic INR levels is a challenge for health care providers, patients, and families. Regular monitoring to guide dose adjustment is necessary because warfarin has drug, food, and pharmacogenomic interactions that may increase or decrease anticoagulant effects (Table 3[7–9,31,33–35]).[31,36,37] Further, many patients receiving warfarin therapy do not achieve optimal INR control.[29,38] For example, in a prospective study of the registry of the Canadian Stroke Network, 74.2% of 597 patients with ischemic stroke and known AF treated with warfarin had a subtherapeutic INR.[29] Many patient characteristics were associated with poor control, such as older age, female gender, non-Caucasian race, current smoking status, current amiodarone use, no prior warfarin use, medical history of alcohol and substance abuse, heart failure, diabetes, and dementia.[39]

The quality of INR control can be measured by time in therapeutic range (TTR), and effective INR control is defined as a minimum TTR between 60% and 65%.[40] A large, multicenter study found that patients at centers where TTR was less than 65% did not benefit from anticoagulant therapy.[40] In a separate analysis of patients taking warfarin for stroke prevention in AF, the TTR varied by centers and countries from 54% to 73%, and adherence with warfarin treatment algorithms was associated with higher TTR.[38]

Another reason for suboptimal warfarin use is clinicians' concerns about the risk of bleeding complications, particularly a major bleeding event such as ICH.[41–43] When surveyed, physicians reported not prescribing warfarin due to risk of falls, dementia, short life expectancy, and history of bleeding.[44] Older age, higher bleeding risk, comorbidities, and limited ability to adhere to