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Physician's Fear of Anticoagulant Therapy in Nonvalvular Atrial Fibrillation

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Abstract: Despite the availability of predictive tools and treatment guidelines, anticoagulant therapies are underprescribed and many patients are undertreated for conditions that predispose to thromboembolic complications, including stroke. This review explores reasons for which physicians fear that the risks of anticoagulation may be greater than the potential benefit. The results of numerous clinical trials confirm that patients benefit from judiciously managed anticoagulation and that physicians can take various approaches to minimize risk. Use of stratification scores for patient selection and accurate estimation of stroke risk may improve outcomes; bleeding risk is less important than stroke risk. Adoption of newer anticoagulants with simpler regimens may help physicians allay their fears of anticoagulant use in patients with atrial fibrillation. These fears, although not groundless, should not overtake caution and hinder the delivery of appropriate evidence-based care.

Key Indexing Terms Atrial fibrillation; Stroke; Oral anticoagulants. [Am J Med Sci 2014;348(6):513–521.]

THE LANDSCAPE: ANTICOAGULATION INDICATIONS AND USE

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 2.4 million Americans and predisposing to a risk for ischemic stroke that is 2 to 5 times greater than that of age-matched controls.^{1–3} Stroke is the leading cause of adult disability, affecting 795,000 Americans annually.⁴ An estimated 69,165 of these strokes are attributable to AF.^{5,6} Every hour, approximately 8 Americans suffer from an ischemic stroke arising from AF.^{5,6} Currently, validated risk stratification schemes such as CHADS₂ and CHA₂DS₂-VASc, based on other predisposing conditions, facilitate stroke prediction in patients with AF (Table 1).^{7,8} Oral anticoagulation can make a significant dent in this stroke risk in AF and is backed by evidence-based stroke prevention guidelines.^{8–10} Recently, schemes such as HAS-BLED (Table 2) have been developed to evaluate the risk of bleeding, the feared complication of oral anticoagulation therapy.^{11–13} Despite guidelines and tools, anticoagulation is underprescribed, which exposes patients with AF to the risk of debilitating strokes.³

Several studies have evaluated the prevalence of oral anticoagulation use in patients with AF.^{14–20} The rate of oral anticoagulation prescribing in patients with AF with a moderate-to-high risk of stroke ranged from 41% to 65%.^{14,21,22} Even after the elimination of patients with contraindications to anticoagulation,

the rate of oral anticoagulation use did not increase.^{14,21,22} Among these studies, the National Anticoagulation Benchmark Outcomes Report (NABOR), a performance improvement program, investigated treatment gaps and predictors of warfarin use in a nationally representative AF population sample in the United States.¹⁴ Although risk factors indicated that 86% of patients had a high risk for stroke, only 55% of those at high risk received warfarin.¹⁴ High-risk stratification was not a positive predictor for warfarin use, and contraindications to warfarin did not account for the marked level of underuse.¹⁴ Another study examined Medicare Part D claims data for warfarin use among beneficiaries with nonvalvular AF (NVAF) in the context of current treatment guidelines.²¹ Among those at moderate-to-high stroke risk but not at high bleeding risk, 41.3% did not receive warfarin within 12 months of the index diagnosis.²¹ These real-world results showed that a significant proportion of Medicare beneficiaries in need of anticoagulation were not treated according to clinical guidelines, which led to an excessive rate of ischemic stroke in an at-risk population.²¹

The underuse of warfarin may stem from the drug's well-known limitations; however, compliance with guidelines may also be influenced by variables at system, physician, and patient levels.²² Newer oral anticoagulants may reduce the risk of stroke with a lower risk of adverse events than warfarin, but the need to understand why physicians deviate from anticoagulation guidelines "has implications that transcend therapeutic class."²² This review explores possible explanations for withholding anticoagulant therapy. Such explanations frequently are based on fears that the risks are greater than any potential benefit of anticoagulants.²³ Although it is undeniable that anticoagulant therapy may be associated with risk of bleeding, it is also evident from long experience, confirmed by objective analysis, that patients benefit from anticoagulation and that there are ways to minimize their bleeding risk. The choice of new oral anticoagulants with different mechanisms of action and simpler regimens may help persuade physicians and patients alike. It should be noted that the majority of studies to date with newer oral anticoagulants have focused on stroke risk factors in patients with NVAF. Although not as common, patients with valvular AF (VAF, ie, those with AF and rheumatic mitral stenosis or a prosthetic mitral valve) are also at risk for ischemic stroke.²⁴ Although warfarin therapy (based on target International normalized ratio [INR]) has been reported as an effective means for stroke prevention,⁸ the role that newer anticoagulants might play in stroke prevention in patients with VAF has not been evaluated.

BARRIERS TO ADEQUATE ANTICOAGULATION: REAL AND PERCEIVED REASONS FOR UNDERTREATMENT

Physicians' Fears

Many physicians associate anticoagulant use with a heightened risk of bleeding.²⁵ Death certificate data in 2003 and 2004 ranked anticoagulants first in the number of mentions of "deaths from drugs causing adverse effects in therapeutic use."²⁶ For a retrospective analysis of health care claims within

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TABLE 1. Risk scores to stratify candidates for anticoagulant therapy^{7,8}

CHADS ₂ risk criteria	Value	CHADS ₂ score	Adjusted stroke risk (%/yr)
Congestive heart failure	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 yr	1	2	4.0
Diabetes	1	3	5.9
Stroke/TIA/TE	2	4	8.5
		5	12.5
Maximum	6	6	18.2

CHA ₂ DS ₂ -VASC risk criteria	Value	CHA ₂ DS ₂ -VASC score	Adjusted stroke risk (%/yr)
Congestive heart failure/LV dysfunction	1	0	0
Hypertension	1	1	0.7
Age ≥75 yr	2	2	1.9
Diabetes	1	3	4.7
Stroke/TIA/TE	2	4	2.3
Vascular disease (prior MI, PAD and aortic plaque)	1		
Age, 65–74 yr	1	5	3.9
Sex, female	1	6	4.5
Maximum	9	7	10.1
		8	14.2
		9	100.0

LV, left ventricular; MI, myocardial infarction; PAD, peripheral arterial disease; TE, thromboembolism; TIA, transient ischemic attack.

a 4 million member managed care organization, patients diagnosed with AF were stratified into 2 cohorts: warfarin therapy (patients initiating warfarin) or warfarin candidates (eligible according to American College of Cardiology/American Heart Association/European Society of Cardiology guidelines but not receiving warfarin).²⁷ During 2 years of follow-up, 4.7% experienced a hemorrhagic event.²⁷ The incidence of intracranial hemorrhage was identical in both cohorts.²⁷ There was no significant increase in risk for hemorrhage within the warfarin therapy group after adjustment for age, sex, and additional risk factors for hemorrhage.²⁷ Although the study was not designed to determine why warfarin was underused despite indications for its use, the perceived risk of bleeding complications may have been a contributing factor.²⁷ The investigators acknowl-

edged that use of nonprescription antiplatelet agents may have contributed to the similarity in rates of hemorrhage and suggested that such similarity might also have resulted from conservative dosing and management of warfarin therapy, possibly with attainment of a lower INR than achieved in clinical trials.²⁷ Earlier investigators noted that physicians treating patients with AF were more averse to cause harm in the form of warfarin-related hemorrhage than harm due to stroke resulting from failure to treat with warfarin.²⁸ If physicians' treatment decisions are driven predominantly by historical concerns regarding an increased bleeding risk, conservative use and cautious dosing may deprive patients of the full benefit of anticoagulation.²⁷

An Australian group randomly selected 1,000 family physicians, of whom 596 responded to a survey aimed at

TABLE 2. Clinical criteria for HAS-BLED bleeding risk score

Clinical criteria ^a	Score	HAS-BLED score	Bleeds/100 patient-yr ^b
Hypertension	1	0	1.13
Abnormal renal or liver function (1 pt each)	1 or 2	1	1.02
Stroke	1	2	1.88
Bleeding	1	3	3.74
Labile INR	1	4	8.70
Elderly	1		
Drug or alcohol use (1 pt each)	1 or 2		
Maximum	9		

^a Hypertension: systolic blood pressure >160 mm Hg; abnormal renal function: chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L; abnormal liver function: chronic hepatic disease or biochemical evidence of significant hepatic derangement (eg, bilirubin >2 times upper limit of normal associated with liver enzymes >3 times upper limit of normal); bleeding: history of or predisposition to bleeding; labile INR: unstable/high INR or poor time in therapeutic range; drug or alcohol use: concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs.

^b Based on initial cohort reported by Pisters et al¹¹ with insufficient events at HAS-BLED score ≥5 to provide rates; actual stroke rates in contemporary cohorts may vary from these estimates.

INR, international normalized ratio.

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