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.

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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%.14–17,21–22 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 undertreatment.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.22 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.23

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.24 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,25 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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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). During 2 years of follow-up, 4.7% experienced a hemorrhagic event. The incidence of intracranial hemorrhage was identical in both cohorts. 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. 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. 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. 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.

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

| TABLE 1. Risk scores to stratify candidates for anticoagulant therapy |
|------------------------------------------------|
| **CHA**<sub>2</sub>S<sub>D</sub>-VASC risk criteria | Value | **CHA**<sub>2</sub>S<sub>D</sub>-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 |
| Diabtes | 1 | 3 | 4.7 |
| Stroke/TIA/TE | 2 | 4 | 2.3 |
| Vascular disease (prior MI, PAD and aortic plaque) | 1 | 5 | 3.9 |
| Age, 65–74 yr | 1 | 6 | 4.5 |
| Sex, female | 9 | 7 | 10.1 |
| Maximum | 9 | 8 | 14.2 |
| | | 9 | 100.0 |

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

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

| TABLE 2. Clinical criteria for HAS-BLED bleeding risk score |
|------------------------------------------------|
| **Clinical criteria**<sup>a</sup> | Score | HAS-BLED score | Bleeds/100 patient-yr<sup>b</sup> |
|------------------------------------------------|
| 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 | 5 | 5.83 |
| Drug or alcohol use (1 pt each) | 1 or 2 | 6 | 100.0 |
| Maximum | 9 | 7 | 100.0 |

<sup>a</sup> 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); 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.

<sup>b</sup> Based on initial cohort reported by Pisters et al<sup>11</sup> 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.
identifying barriers to the use of anticoagulation. Offered a choice of strategies for AF management, a minority (45.6%) of respondents selected warfarin in the presence of a minor risk for falls; even fewer (17.1%) said they would prescribe warfarin for a patient receiving treatment for a peptic ulcer. Prescribing patterns were influenced by physicians’ experience and fear of bleeding events. For example, among the physicians surveyed, 15.8% reported having a patient with AF experience an intracranial hemorrhage while on anticoagulation, whereas 45.8% reported having patients who experienced ischemic stroke in the absence of anticoagulant therapy. The experience of intracranial hemorrhage in an anticoagulated patient with AF appeared to condition family physicians to feel responsible for this outcome, whereas they admitted to no such responsibility when presented with the more common experience of stroke in a patient with AF not receiving anticoagulation. The inculcation to “first do no harm” may condition physicians to feel more responsible for harm resulting from “omission” rather than “commission,” and this sense of culpability may lead them to shun therapies they associate with a risk of adverse events, even when the potential benefits are shown to be greater than the risks.

Strikingly, similar results emerged from a population-based matched-pair analysis of 530 Canadian physicians’ warfarin-prescribing patterns before and after adverse bleeding events in patients with AF. Warfarin-associated bleeding events negatively influenced warfarin prescribing throughout the 90-day study, whereas adverse events possibly related to underuse of warfarin seemed not to affect subsequent prescribing.

Fear of bleeding is the factor common to clinicians providing warfarin therapy across countries and continents. Warfarin anticoagulation to conventional intensities increases the risk of intracranial hemorrhage 7-10-fold to an absolute rate of 1% annually for many stroke-prone patients. Most such hemorhages (70%) are intracerebral hematomas, with patient-related risk factors (advanced age, prior stroke, hypertension and intensity of anticoagulation) overlapping those for stroke. Although intracranial bleeding is the most feared complication of anticoagulation, more common sites of bleeding are in fact the gastrointestinal (GI) tract, the genitourinary tract, and the soft tissues.

After analyzing studies published between 1966 and 2002, Man-Son-Hing and Laupacis concluded that physicians’ fears of the risk of bleeding associated with anticoagulant therapy are often exaggerated and unfound. Studies pursued when the intensity of anticoagulation was higher than current levels (target INR 3.0–4.5 versus 2.0–3.0) showed higher than expected rates of intracerebral hemorrhage in anticoagulated patients with a history of stroke, whereas recent studies based on the current less aggressive INR target have not confirmed those early findings. The salient issue is careful selection of patients and accurate estimation of stroke risk; anticoagulant-associated bleeding risk needs to be considered relevant to relatively few patients.

Specific Fears: Falling, Upper GI Tract Bleeding and Stroke

Investigators and clinicians agree that there is an increased risk of potentially life-threatening bleeding complications associated with anticoagulant therapy, including bleeding into specific sites such as the GI tract or intracranial bleeding in patients with head trauma or uncontrolled hypertension. However, after a 1999 decision analysis, Man-Son-Hing et al asserted that a predisposition to falling, with the possibility of head trauma, is not a contraindication to the use of anticoagulant therapy in older patients with AF. They calculated that for the person with an average risk of AF-related stroke, the 5% annual risk of subdural hematoma from falling is so small that the person would have to fall 295 times in the course of a year to accrue greater risk than benefit from anticoagulant therapy. Similarly, systematic review by Man-Son-Hing and Laupacis demonstrated that in the era of routine testing and treatment for Helicobacter pylori infection, patients with a history of resolved upper GI tract bleeding seem to be at no higher risk of upper GI bleeding than those with a negative history.

However, it should be noted that GI bleeding is one of the feared complications of anticoagulant therapy in patients who are frequently taking NSAIDs. Pooled results of a systematic analysis of 18 case-control and cohort studies performed between 1990 and 1999 demonstrated that persons taking nonsteroidal anti-inflammatory drugs (NSAIDs) without cytoprotection had a relative risk (RR) of 3.8 (95% confidence interval [CI], 3.6–4.1) for GI tract bleeding. The increased risk was maintained during treatment and returned to baseline on cessation of treatment. Results of randomized comparative trials showed that concomitant use of an NSAID with misoprostol or a proton pump inhibitor reduced the upper GI bleeding risk by approximately one half. Use of a cyclooxygenase-2 inhibitor-specific NSAID reduced the risk of upper GI tract bleeding to about half the rate associated with conventional NSAIDs. To determine how factors that increase the risk of major upper GI tract hemorrhage influence the choice of antithrombotic treatment for older patients with AF and an elevated risk for stroke, Man-Son-Hing and Laupacis conducted a systematic literature search of studies published between January 1966 and December 2000 in developing a decision-analytic model based on the risk of upper GI tract bleeding and stroke. The investigators determined the risk of anticoagulant-related bleeding in the presence of defined risk factors; that is, 3.8 times baseline for a patient taking a noncytoprotective NSAID and 2.4 times baseline for a patient taking warfarin, which resulted in a risk of 9.1 times baseline (3.8 × 2.4) for a patient taking both medications. Across several clinical scenarios, anticoagulation was the best therapy in terms of gain in quality-adjusted life-years for most of the older patients with AF. The main exception was patients with a low risk of AF-related stroke (because of an absence of clinical risk factors for stroke) combined with a high risk of upper GI tract bleeding (because of concomitant use of noncytoprotective NSAIDs). For such patients, acetylsalicylic acid (ASA) or no antithrombotic therapy appeared appropriate. For older patients with AF and a higher than average risk for upper GI tract bleeding, the choice of antithrombotic therapy for stroke prevention varied according to the magnitude of bleeding risk. The authors concluded that warfarin was no longer clearly the optimal antithrombotic therapy for older persons with a significantly higher risk of upper GI tract bleeding and/or lower risk for stroke who were concurrently taking a conventional NSAID.

Lowering the Barriers to Effective Anticoagulation

In a 2011 editorial, Goldhaber addressed practical issues confronting physicians who provided day-to-day care of patients on anticoagulant therapy. Faced with a surfeit of information, clinicians lack a “unifying and reliable” source of information about developments in anticoagulant therapy. Goldhaber noted, for instance, important differences among 3 apparently authoritative sets of practice guidelines. There are also clinically important differences among various schemes for stratifying stroke risk in patients with AF. Experts fail to...
agree which tool is the most reliable for scoring bleeding risk during anticoagulant therapy. Not surprisingly, clinicians are uncertain how to balance the risk of thromboembolic events against the risk of bleeding and consequently, for fear of causing harm, err on the side of caution. Other stratification schemes are available that can help clinicians estimate patients’ who fall risk and make better selection of candidates for anticoagulation even when a risk for falls is present.47,48

A positive direction for future therapy emerged from a study by Banerjee et al49 who modeled differing scenarios using a real-world cohort derived from the Danish National Patient Registry. In patients with a CHADS2 score ≥1 or CHA2DS2-VASc score ≥2, warfarin offered a net clinical benefit in preventing stroke, but the newer Food and Drug Administration (FDA)–approved agents, dabigatran, rivaroxaban and apixaban, offered greater net clinical benefit than warfarin.49 The authors suggest that their findings may encourage physicians to use anticoagulation in patients stratified by a relatively simple risk-scoring system (Figure 1) and raise awareness of the advantages of a new generation of anticoagulants compared with warfarin.49

Primary care physicians may overlook hypertension as a powerful determinant of intracerebral hemorrhage risk, whereas hypertensive patients are often unaware of symptoms until they suffer a catastrophic complication, such as ischemic stroke or intracerebral hemorrhage.34,50 Providing effective antihypertensive therapy by the physician, and close adherence to therapy by the patient, are essential to reduce the risk of intracerebral hemorrhage associated with anticoagulation in patients with hypertension patients.34,50 Advances in neuroimaging with magnetic resonance are allowing unprecedented insights into brain pathology and predictive factors for intracerebral hemorrhage risk, but such techniques are not yet fully developed for routine clinical use.34,50 The impact of

![FIGURE 1. Algorithm for choice of anticoagulant in patients with nonvalvular AF. Relative effectiveness based on post hoc modeling using the Danish National Registry. AF, atrial fibrillation; ASA, acetylsalicylic acid; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.](image-url)
hypertension control in reducing the incidence of intracerebral hemorrhage has been demonstrated in a number of trials, notably the Perindopril Protection against Recurrent Stroke Study (PROGRESS). In patients at high risk for recurrent stroke (N = 6105, mean age 64 years), absolute rates of intracerebral hemorrhage dropped from 2% to 1% (RR reduction, 50%; 95% CI, 26–67), when mean blood pressure was reduced by 12/5 mm Hg from baseline.51

A history of stroke should not be considered a contraindication to anticoagulant treatment: a prior stroke increases the risk of another stroke for a patient with AF. For most patients, nonfatal and extracranial bleeds are far less clinically significant than strokes of any severity, and patients at risk who are not adequately anticoagulated may be more likely to have embolic strokes. The American Hospital Association/American Stroke Association’s 2012 science advisory on the use of oral antithrombotic agents for stroke prevention in NVAF did not directly address physicians’ fears regarding anticoagulation. However, in reiterating the FDA’s rationale for approving a higher but not a lower dose of a new oral anticoagulant, dabigatran etexilate, the advisory alluded to a prior observation that “the irreversible effects of strokes and systemic emboli have greater clinical significance than nonfatal bleeding.” Superior stroke prevention with the higher dose, as the FDA’s approval indicates, is a more desirable outcome than a lower rate of nonfatal bleeding with the lower dose.

A recent analysis of outcomes in a retrospective cohort study helps to illuminate the RRs, benefits and optimal timing for reinitiating warfarin therapy after a major gastrointestinal bleeding (GIB) event. Anticoagulation therapy with warfarin was reinitiated in 653/1,329 (49.1%) of the patients, which was associated with a decreased risk of thromboembolism (hazard ratio [HR], 0.71; and 95% CI, 0.54–0.93; P = 0.01), and decreased mortality (HR, 0.67; 95% CI, 0.56–0.81; P < 0.0001). Of note, the recurrence rate of major GIB events was not affected by the reinitiation of warfarin anticoagulation therapy, with an HR of 1.18 (95% CI, 0.94–1.10). Although limited by the retrospective design of this study, this analysis suggests that restarting warfarin anticoagulant therapy 7 days or later after a major GIB event is associated with lower rates of thromboembolism and increased survival, with no increase in GIB event rates. Physicians may be hesitant to treat with anticoagulants if they lack confidence in the patient’s ability to adhere to a medication regimen. The many challenges of warfarin use, a lengthy dose-adjustment period, the need for frequent sampling and regular anticoagulation monitoring, the difficulty of maintaining the INR within the therapeutic range, dietary restrictions, raise barriers to optimal anticoagulation in at-risk populations.

Although treatment with the newer oral anticoagulants is more expensive than with older therapy, such as warfarin, these agents may offer adherence advantages because they have simpler dosing regimens and fewer requirements for dose adjustment, anticoagulation monitoring, or dietary restrictions. Because there are no available reversal agents for these newer therapies, patients and prescribers should be aware that optimal protocols to address bleeding event complications are still under development, whereas new and specific reversal therapies are currently in clinical trials.

### Conventional Anticoagulation

#### Warfarin

Warfarin received FDA approval in 1954 and is the most widely prescribed oral anticoagulant drug in North America. It induces anticoagulant activity by antagonizing vitamin K-dependent synthesis of clotting factors in the liver. Although the antiplatelet agent ASA has been found to reduce the risk of stroke by 21%, long-term therapy with warfarin is associated with a stroke risk reduction of 68%. Warfarin, slow to take

| TABLE 3. Fifteen key points for patient education about oral anticoagulant therapy |
| --- |
| 1. Indicate the reason for initiating anticoagulant therapy and how it relates to clot formation |
| 2. Review the names of the patient’s medications, both trade and generic names, explain why they are indicated and discuss how they work for the purpose they are prescribed |
| 3. Discuss how long therapy is likely to be needed |
| 4. If the patient is taking warfarin, explain the importance of regular monitoring, target values and what the INR indicates |
| 5. If the patient is taking warfarin, explain the importance of dietary precautions, including restrictions on alcohol and green leafy vegetables |
| 6. Describe common signs and symptoms of bleeding and what to do if they occur |
| 7. Describe common signs and symptoms of clotting complications and what to do if they occur |
| 8. Outline precautions the patient should take to minimize the risk of trauma or bleeding |
| 9. Discuss potential drug interactions and how to manage medication changes |
| 10. For women of child-bearing age, explain the importance of contraception |
| 11. Explain the importance of informing all health care providers (eg, dentists, optometrists) of the use of anticoagulant medication |
| 12. Emphasize the importance of notifying the anticoagulation provider when dental, surgical or other interventional procedures are scheduled |
| 13. Explain when and how to take anticoagulant medications and how to manage a missed dose |
| 14. Discuss the utility of carrying identification (identification card, medical alert bracelet) |
| 15. Document the education imparted to the patient |

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effect and difficult to dose, has been the only available oral anticoagulant for the last half century.25-58-61 The response to warfarin is subject to genetic variations and drug–drug interactions,61-62 and the therapeutic effect is susceptible to dietary variations.61 some of which, such as consumption of green and leafy vegetables, might otherwise be considered positive behaviors for stroke risk reduction. Warfarin is also a leading cause of emergency department visits and preventable costs.63,64 The low acquisition cost of warfarin may be counterbalanced by the costs of laboratory monitoring to ensure that the anticoagulant effect remains within the narrow safe range and by the costs of managing potentially catastrophic complications of therapy.34,62 Despite its shortcomings, warfarin remains an important drug for long-term anticoagulant therapy worldwide.66 An estimated 7 million people in the United States and Europe have either paroxysmal or persistent AF, for which anticoagulant therapy is indicated to reduce the risk of stroke.66 However, the recent approval of new oral anticoagulants offers therapeutic alternatives that are at least as effective as warfarin and offer a potential for safer and more easily managed anticoagulation.67-71

New Oral Anticoagulants

Three new oral anticoagulants have recently been approved in the United States for the reduction of stroke risk in patients with AF: dabigatran, rivaroxaban and apixaban.10,32-69-71 These agents have been compared with warfarin; to date, head-to-head comparisons are lacking.72

Dabigatran Etxelate

Dabigatran etxelate, an oral direct thrombin inhibitor, was approved by the FDA in 2010 to reduce the risk of stroke and systemic embolism (SSE) in patients with NVAF.72,73 Dabigatran etxelate is administered in a fixed dose of 150 mg twice daily for most patients, with a dose of 75 mg twice daily recommended for patients with creatinine clearance (CrCl) of 15 to 30 mL/min.73 The phase 3 Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared open-label dose-adjusted warfarin with 2 blinded doses (150 mg twice a day or 110 mg twice a day) of dabigatran etxelate for the primary outcome of SSE in 18,113 patients with NVAF.72,73 For warfarin-treated patients (n = 6022), the INR was within therapeutic range (2.0-3.0) a mean 64% of the study period.72 Updated results adjudicated in a blinded fashion according to the study protocol demonstrated that the dose of 150 mg twice daily of dabigatran etxelate was superior to warfarin for the prevention of SSE (HR, 0.66; 95% CI, 0.53-0.82; P < 0.001 for superiority), with a similar risk of the primary safety end point of major bleeding (3.1% and 3.4% per year, respectively; P = 0.31).72,73 Lower rates of intracranial hemorrhage were reported for dabigatran 110 mg twice daily and 150 mg twice daily than for warfarin (0.2%, 0.3%, and 0.7%, respectively; P < 0.001 for either dabigatran dose versus warfarin).73 Similar rates of SSE were recorded in the dabigatran etxelate 110 mg twice daily and warfarin groups (1.54% and 1.71% a year, respectively; P = 0.30); dabigatran etxelate 110 mg twice daily was associated with a lower rate of major bleeding than warfarin (2.9% versus 3.6% per year, respectively; P = 0.003).72,73 The FDA did not approve the 110 mg twice daily dose; hence, it is not available for clinical use in the United States.53,69 The concomitant use of dabigatran etxelate with P-glycoprotein (P-gp) inducers (eg, rifampin) reduces exposure to dabigatran and should generally be avoided.75 In patients with moderate renal impairment, concomitant administration of dabigatran etxelate with P-gp inhibitors (eg, dronedarone and systemic ketoconazole) is not recommended, as coadministration is expected to increase exposure to dabigatran.75 No drug–food interactions are reported. Routine blood coagulation monitoring is not required during dabigatran etxelate therapy, but when necessary, the extent of anticoagulation may be estimated by measuring the activated partial prothrombin time or the ecarin clotting time.75

Rivaroxaban

An oral factor Xa inhibitor, rivaroxaban, was approved by the FDA in 2011 to reduce the risk of SSE in patients with NVAF and subsequently for additional indications.10,70 To reduce the risk of SSE in patients with NVAF, rivaroxaban is administered at a dose of 20 mg/d to patients with CrCl ≥50 mL/min; for patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg/d.10,75-76 Rivaroxaban and warfarin were compared for efficacy in 14,264 patients with NVAF in the phase 3 Rivaroxaban Once-daily oral direct Factor Xa inhibi- tion compared with vitamin K antagonism for the prevention of stroke and Embolism Trial in AF (ROCKET-AF).76,77 The results suggest that rivaroxaban may be an alternative to warfarin for patients with AF with a moderate-to-high risk of stroke.72 Rivaroxaban was noninferior to warfarin for preventing SSE both in the intent-to-treat population (2.1% and 2.4% a year, respectively; P < 0.0001 for noninferiority) and the per-protocol population (HR, 0.88; 95% CI, 0.74-1.03; P < 0.001 for noninferiority and P = 0.12 for superiority).76 Among patients treated with warfarin, INR values were within therapeutic range (2.0-3.0) for 55% of the time.76 The incidence of the primary safety end point, major and clinically relevant nonmajor bleeding, was similar in the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively; P = 0.44).76 The reported rate of intracranial hemorrhage for rivaroxaban (0.5%) was lower than that for warfarin (0.7%). Major GIB was more common in the rivarox- aban group: 224 bleeding events (3.2%) compared with 154 in the warfarin group (2.2%, P < 0.001).76 As with dabigatran, routine blood coagulation monitoring is not required.77 Rivarox- aban should not be used concurrently with other anticoagulants or combined P-gp and strong cytochrome P450 3A4 (CYP3A4) inhibitors and inducers.78

Apixaban

In 2012, this orally administered factor Xa inhibitor received FDA approval to reduce the risk of SSE in patients with NVAF.71 In clinical trials, apixaban was given as a fixed dose of 2.5 mg or 5 mg twice daily without routine coagulation monitoring.32,77-78 The recommended dose is 5 mg twice daily; for patients with ≥2 of the following characteristics: age, 80 years or older, body weight ≤60 kg and serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg twice daily.75 The utility of apixaban for stroke prevention in NVAF was evaluated in 2 large, randomized, double-blind trials: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)77 and Apixaban Versus Ace- tylsalylic Acid to Prevent Strokes (AVERROES).78 The ARISTOTLE trial compared apixaban with warfarin for the prevention of SSE in patients with NVAF and ≥1 additional risk factor for stroke.77 Apixaban reduced SSE by 21% com- pared with warfarin (HR, 0.79; 95% CI, 0.66-0.95; P = 0.01).77 Apixaban treatment compared with warfarin resulted in less major bleeding (2.1% and 3.1%, respectively; P < 0.001) and intracranial hemorrhage (0.33% and 0.8%, respectively). Apixaban was better tolerated than warfarin, and fewer patients were withdrawn from therapy.77 In AVERROES, the
efficacy of apixaban 5 mg twice daily was compared with ASA (81–325 mg once daily) for the prevention of SSE in 5,599 patients with NVAF who were not candidates for warfarin treatment. The trial was stopped early on the recommendation of the Data and Safety Monitoring Board when clear benefits favoring apixaban became evident regarding stroke reduction (HR, 0.45; 95% CI, 0.32–0.62; P < 0.001). Rates of major bleeding (1.4% versus 1.2%) and intracranial hemorrhage (0.4% versus 0.4%) noted with apixaban were similar to those observed with ASA. Apixaban was better tolerated than ASA, with significantly fewer discontinuations of study drug. Simultaneous use of strong inducers of CYP3A4 and P-gp reduces blood levels of apixaban, and concurrent use should be avoided. Concurrent use of an anticoagulant with an anti-platelet agent or an NSAID generally increases bleeding risk, and clopidogrel, in particular, should be used with caution if coadministered with apixaban.

CONCLUSIONS

Fear of bleeding is a widely acknowledged reason that many physicians do not prescribe, and many patients at risk do not receive, the requisite preventative anticoagulant therapy. Although all anticoagulant therapies necessarily involve some degree of bleeding risk, anticoagulation-related bleeding risk may be lowered by consistent use of evidence-based stratification schemes designed to help physicians identify patients who require anticoagulation to reduce the risk of stroke, predict the risk of bleeding during anticoagulant therapy and take preventive measures accordingly. Medication adherence may be fostered with the use of one of the new fixed-dose anticoagulants rather than warfarin, which requires dose adjustment and monitoring to maintain anticoagulant effect within a narrow therapeutic window. Education plays a key role in minimizing patient susceptibility, helping patients understand the importance of lifelong anticoagulation and the need for consistent lifestyle measures and raising awareness of signs and symptoms of adverse events including bleeding. As more evidence emerges from clinical trials, clinical guidelines may be expected to converge and clarify optimal approaches to long-term anticoagulant care.

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