Atrial fibrillation (AF) increases the risk of morbidity and mortality because of a substantially increased risk of stroke and systemic thromboembolism. Overall, AF increases the stroke risk 5-fold; the attributable risk of ischemic stroke related to AF increases from 4.6% from the ages of 50 through 59 years to 20.2% from the ages of 80 through 89 years.1 Compared with non-AF–related strokes, strokes related to AF are associated with higher mortality, greater disability, longer hospital stays, and lower chance of being discharged home than strokes unrelated to AF.2

The risk of stroke in AF is reduced by anticoagulant therapy.3 Thromboprophylaxis can be obtained with vitamin K antagonists (VKA, eg, warfarin) or a non-VKA oral anticoagulant (NOAC). Major guidelines emphasize the important role of oral anticoagulation (OAC) for effective stroke prevention in AF.4,5 Initially, clinicians should identify low-risk AF patients who do not require antithrombotic therapy (ie, CHA2DS2-VASc score, 0 for men; 1 for women). Subsequently, patients with at least 1 stroke risk factor (except when the only risk is being a woman) should be offered OAC. A patient’s individual risk of bleeding from antithrombotic therapy should be assessed, and modifiable risk factors for bleeding should be addressed (blood pressure control, discontinuing unnecessary medications such as aspirin or nonsteroidal anti-inflammatory drugs). The international normalized ratio should be tightly controlled for patients receiving VKAs.

The objective of this article is to provide an overview of current concepts and recent developments in stroke prevention in AF, with suggestions for practical management.

A comprehensive structured literature search was performed using MEDLINE for studies published through March 11, 2015, that reported on AF and stroke, bleeding risk factors, and stroke prevention.

The risk of stroke in AF is reduced by anticoagulant therapy. Thromboprophylaxis can be obtained with vitamin K antagonists (VKA, eg, warfarin) or a non-VKA oral anticoagulant (NOAC). Major guidelines emphasize the important role of oral anticoagulation (OAC) for effective stroke prevention in AF.4,5 Initially, clinicians should identify low-risk AF patients who do not require antithrombotic therapy (ie, CHA2DS2-VASc score, 0 for men; 1 for women). Subsequently, patients with at least 1 stroke risk factor (except when the only risk is being a woman) should be offered OAC. A patient’s individual risk of bleeding from antithrombotic therapy should be assessed, and modifiable risk factors for bleeding should be addressed (blood pressure control, discontinuing unnecessary medications such as aspirin or nonsteroidal anti-inflammatory drugs). The international normalized ratio should be tightly controlled for patients receiving VKAs.

The risk of stroke in AF is reduced by anticoagulant therapy.3 Thromboprophylaxis can be obtained with vitamin K antagonists (VKA, eg, warfarin) or a non-VKA oral anticoagulant (NOAC). All the major guidelines emphasize the role of oral anticoagulation (OAC) use for stroke prevention in AF.4,5

The objective of this article is to provide an overview of current concepts and recent developments in stroke prevention in patients with nonvalvular AF.

**Search Strategy**

A comprehensive structured literature search was performed using MEDLINE for studies published through March 11, 2015, that reported on AF and stroke or bleeding risk factors, as well as on stroke prevention. The search terms included each of the following terms individually and in combination: atrial fibrillation, thromboembolism, stroke risk, risk stratification, oral anticoagulation, warfarin, aspirin, and thromboprophylaxis. We focused on primary published research articles and systematic reviews, as well as on clinical trials complemented by large observational cohorts.
Risk Factors for Stroke

Atrial fibrillation can cause stroke by several mechanisms consistent with the Virchow triad for thrombogenesis (thrombus formation): (1) stasis in the left atrium causing flow abnormalities; (2) structural heart and vascular disease (eg, mitral stenosis; fulfilling the abnormal vessel wall Virchow criterion); and (3) abnormal coagulation and fibrinolysis (eg, abnormal procoagulant hemostatic and platelet factors; fulfilling the abnormal blood constituents criterion).6 The prothrombotic state in AF has recently been comprehensively reviewed.6

The most common risk factors associated with stroke (eg, heart failure, hypertension, diabetes, age, prior stroke) were initially identified from the non-VKA cohorts of randomized trials conducted 2 decades ago.2 Although these trials provided information on patients treated with placebo, they have been criticized for randomizing fewer than 10% of patients screened and for not recording all the risk factors nor consistently defining them in the studies.7 Numerous systematic reviews have examined AF-related stroke risk factors.8,9 A study by the Stroke in AF Working Group8 reported that the strongest, most consistent independent risk factors for stroke were prior stroke or transient ischemic attack (TIA) (relative risk [RR], 2.5; 95% CI, 1.8-3.5), increasing age (RR, 1.5 per decade; 95% CI, 1.3-1.7), a history of hypertension (RR, 2.0; 95% CI, 1.6-2.5), and diabetes mellitus (RR, 1.7; 95% CI, 1.4-2.0). In this systematic review, female sex was inconsistently associated with stroke risk, and the evidence was inconclusive for heart failure or coronary artery disease as independent predictors of AF-related stroke.

Other systematic reviews that included large observational cohort studies also found evidence for vascular disease and female sex9 as risk factors for stroke. In a recent systematic review and meta-analysis of 17 studies, there was a 1.31-fold (95% CI, 1.18-1.46) elevated risk of stroke in women with AF.10 Even in populations that were entirely anticoagulated, stroke rates were higher in women, varying from 1.2% to 1.44% per patient-year for men and 2.08% to 2.43% per patient-year for women. The risk of stroke in women with AF is age dependent, with women younger than 65 and having no other risk factors being at low risk.11,12 In one European study involving AF patients younger than 65 years, female sex did not emerge as an independent risk factor13; however, female sex appears to still confer some stroke risk, especially in Asian cohorts.14,15

At a Glance

- The risk of stroke and mortality in AF is reduced by anticoagulant therapy, whether with vitamin K antagonists (VKA, eg, warfarin) or a non-VKA oral anticoagulant (NOAC).
- As an initial step, clinicians should identify low-risk AF patients who do not require antithrombotic therapy. Patients with at least 1 stroke risk factor (except when the only risk factor is being a woman) should be offered OAC.
- Clinicians also need to assess each patient’s individual risk of bleeding with antithrombotic therapy and correct modifiable bleeding risk factors: control blood pressure; remove unnecessary concomitant medication, such as aspirin, or NSAIDs; control INR and avoid labile INRs; counsel patient to reduce alcohol intake if excessive. Ultimately, the main priority is stroke prevention.

Risk Stratification Schemes

The various stroke risk factors in AF have been used to formulate several stroke risk prediction tools, to help risk stratify patients with AF (Table 1). The most common in use are the CHADS2 (congestive heart failure; hypertension; age ≥75 years; diabetes mellitus;1 point for each; stroke, 2 points) and CHA2DS2-VASc scores (see Table 3 for definition). All the risk stratification schemes based on clinical risk factors have weak or modest predictive value for identifying high-risk patients.5 However, the CHA2DS2-VASc score has particular value in identifying low-risk patients who do not need antithrombotic therapy.21,22 Hence, more recent guidelines have moved toward initial identification of low-risk patients first (because these patients do not need any antithrombotic therapy), rather than focus on identifying high-risk patients.6

CHADS2

The CHADS2 score was formulated and initially validated in a registry of hospitalized patients with AF.22 The CHADS2 score is relatively simple for identifying high-risk patients (score >2), whereas moderate risk was initially defined as a score of 1 to 2 and low risk as a score of 0.22 The CHADS2 had various limitations, and does not include many of the commonly accepted stroke risk factors (eg, age 65-74 years, vascular disease, female sex, asymptomatic left ventricular diastolic dysfunction, etc). Furthermore, according to the original validation study, those with a prior stroke and no other risk factor (which represented the highest risk category) would only score 2 and would be classified as moderate risk.33

AF atrial fibrillation
CHA2DS2-VASc CHA2DS2 criteria plus vascular disease, age 65-74 years, sex category
HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol
HEMORRHAGES hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke
INR international normalized ratio
LAA left atrial appendage
NOAC non-VKA oral anticoagulant
OAC oral anticoagulation
TIA transient ischemic attack
TRT time in therapeutic range
VKA vitamin K antagonists

In a recent systematic review, peripheral arterial disease was significantly associated with AF-related stroke risk in all 10 observational studies, with a reported risk range of 1.3- to 2.5-fold.16 Complex aortic plaque on the descending aorta, as identified by transesophageal echocardiography, was also a significant risk factor.17 Prior myocardial infarction was validated as a significant predictor of the primary end point in 5 of the 6 studies. There may be ethnic differences evident for peripheral arterial disease as a risk factor, with an RR of stroke approximately 1.22-fold higher in European populations,18 but 1.80-fold higher in Far Eastern populations.19

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### Table 1. Risk Factors Included in Various Clinical Stroke Risk Stratification Schema and Guidelines

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Risk Factors</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI,2,3 1994</td>
<td>65–75 &gt;75</td>
<td></td>
</tr>
<tr>
<td>Framingham,2,3 2003</td>
<td>≥75</td>
<td></td>
</tr>
<tr>
<td>van Walraven,2,4 2003</td>
<td>≥75</td>
<td></td>
</tr>
<tr>
<td>ATRIA,2,8 2013</td>
<td>≥75</td>
<td>Many others</td>
</tr>
<tr>
<td>CHADS2,22 2001</td>
<td>≥75</td>
<td></td>
</tr>
<tr>
<td>CCS,30 2014</td>
<td>≥65</td>
<td>Based on CHADS2-VASC</td>
</tr>
<tr>
<td>ESC,4 2012</td>
<td>≥75</td>
<td>CHADS2 score, 0, non-CHADS2 risk factors (similar to CHA2DS2-VASC) should be considered</td>
</tr>
<tr>
<td>ACCP,29 2012</td>
<td>65–74 &gt;75</td>
<td>Based on CHADS2-VASC</td>
</tr>
<tr>
<td>AHA/ACC/HRS,5 2014</td>
<td>65–74 &gt;75</td>
<td>Based on CHADS2-VASC</td>
</tr>
<tr>
<td>NICE,6 2014</td>
<td>65–74 ≥75</td>
<td>Based on CHADS2-VASC</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; AHA/ACC/HRS, American Heart Association, American College of Cardiology, and Heart Rhythm Society; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; SPAF, Stroke Prevention in Atrial Fibrillation; TE, thromboembolism.

**Footnote:** *Age and female sex combined are a single risk factor.*

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**CHA2DS2-VASC**

The CHA2DS2-VASC score (Table 2) was initially validated in the Euro-Heart survey cohort.26 This score included various non-CHA2DS2 risk factors such as age from 65 to 74 years, female sex, and vascular disease. For example, in contrast to CHADS2, the C in CHA2DS2-VASC refers to congestive heart failure, including moderate to severe left ventricular dysfunction (ejection fraction, <40%) and recent decompensated heart failure irrespective of ejection fraction, thus including both heart failure with reduced ejection fraction or heart failure with preserved ejection fraction.4 In the latter group, patients with cardiomyopathy (eg, restrictive or hypertrophic) could also be included under the C criterion, although robust data are limited.

The CHA2DS2-VASC score has been validated in numerous independent cohorts, including non-Western populations. In 2 Far Eastern studies, the CHA2DS2-VASC but not the CHADS2 score was significantly predictive of stroke.34,35 Most studies demonstrate that CHA2DS2-VASC is best at identifying “truly low-risk” patients for whom the absolute risks of stroke or systemic embolism were less than 1% per year and was as good as—possibly better than—the older CHADS2 score for predicting high-risk patients.31,32,36 The CHA2DS2-VASC score is now the recommended risk score by European,4 US,5 and National Institute for Health and Care Excellence (NICE)46 guidelines.

**Other Risk Stratification Schemes**

Clinical stroke risk prediction scores such as CHADS2 and CHA2DS2-VASC are based on common risk factors in patients with AF whom clinicians encounter in clinical practice. The CHA2DS2-VASC score does not include other rare factors that have been associated with stroke or systemic embolism in AF such as amyloid heart disease and end-stage renal failure. Large observational cohorts have clarified the effect of severe renal impairment on stroke and bleeding risks in AF, but renal impairment does not add predictive value to established scores, such as CHA2DS2-VASC.37

The other risk factor score schemes that have been developed, including the CHADS2 score,38 the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) stroke score,28 the CHA2DS2-VASC score,39,40 and the Qstroke27 score, all have limitations. All the major guidelines have continued to emphasize the use of the CHA2DS2-VASC score.

Most risk stratification schemes based on clinical criteria have weak predictive value for high-risk patients who sustain events (C statistic, approximately 0.6); thus, there has been much interest in the use of biomarkers to enhance the predictive value of clinical risk scores. Such biomarkers can include blood markers (eg, von Willebrand factor, D-dimer, natriuretic peptides),41-43 urine (eg, proteinuria, estimated glomerular filtration rate, or creatinine clearance),44 cardiac imaging (echocardiography, whether
transthoracic or transesophageal), or cerebral imaging (eg, computed tomography or magnetic resonance imaging), which would provide additional refinement to clinical risk stratification for the identification of high-risk individuals. The real practical value of measuring various biomarkers for stroke-risk prediction would require testing large cohorts of individuals who have not received anticoagulation treatment rather than testing highly selected cohorts of patients who have. Also, stroke risk scoring schemes must have simplicity and ease of use, for rapid application in everyday clinical practice. Although scoring systems incorporating complex multivariate analyses and modeling or addition of biomarkers may offer some improved predictive value, the resultant scores are less practical for everyday clinical use because of their complexity.

Any single stroke risk factor confers risk, and if left untreated, patients with AF may be exposed to a fatal or disabling stroke.45 Stroke risk stratification schemes have been formulated with assumptions that risk factors carry equal weight, but they do not.15 With the clinical practice change advocated by contemporary guidelines, the focus should be on the initial identification of truly low-risk patients who do not need antithrombotic therapy. All other AF patients who have 1 or more stroke risk factors can be offered stroke prevention therapy.

### Risk Factors for Bleeding

In addition to stroke risk assessment, it is important to evaluate bleeding risk in AF patients, especially cases in which thromboprophylaxis is being considered.46 Various bleeding risk stratification schemes have been proposed but until recently have not been widely used due to complexity and overlaps with stroke risk.47 Of the various bleeding risk scores,48-53 only 3 have been derived and validated in AF populations: HEMORR2HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke),50 HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly, drugs/alcohol),52 and ATRIA.53

### Table 2. Summary of Guideline Recommendations

<table>
<thead>
<tr>
<th>Stroke Risk Stratification</th>
<th>Treatment Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP,29 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS2 score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>OAC</td>
<td>Warfarin or dabigatran</td>
</tr>
<tr>
<td>1</td>
<td>OAC</td>
<td>Warfarin or dabigatran</td>
</tr>
<tr>
<td>0 plus additional non-CHADS2 risk factors (eg, age 65-74 y, woman, and vascular disease)</td>
<td>OAC</td>
<td>Warfarin or dabigatran</td>
</tr>
<tr>
<td>No risk factors</td>
<td>No antithrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>ESC,4 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial step: identify ‘low risk’ patients (CHA2DS2-VASc 0 in males, 1 in females)</td>
<td>No antithrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>Subsequent step: for patients with ≥1 additional stroke risk factors</td>
<td>OAC is recommended for CHA2DS2-VASc score ≥2 or should be considered for CHA2DS2-VASc score of 1 in men</td>
<td>OAC refers to a VKA (eg, warfarin) with TTR&gt;70%, or a NOAC (preferred); antiplatelet therapy with aspirin-clpidogrel combination therapy or—less effectively—aspirin monotherapy is recommended only when patients refuse any form of OAC</td>
</tr>
<tr>
<td>CCS,30 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algorithm: identify those aged ≥65 y and CHADS2 score risk factors</td>
<td>OAC</td>
<td>Warfarin or a NOAC, preferred</td>
</tr>
<tr>
<td>Algorithm: vascular disease</td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Algorithm: no risk factors, ie, age &lt;65 y with no CHADS2 risk factors nor vascular disease</td>
<td>No antithrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>AHA/ACC/HRS,5 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>OAC</td>
<td>OAC refers to warfarin or a NOAC as an alternative</td>
</tr>
<tr>
<td>1</td>
<td>Nothing, aspirin, or OAC</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No antithrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>NICE,4 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluative steps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial: identify low-risk patientsb</td>
<td>No antithrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>Subsequent: for AF patients with ≥1 additional stroke risk factors</td>
<td>OAC refers to warfarin or a NOAC as an alternative. Aspirin monotherapy should not be used for stroke prevention in AF.</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACCP, American College of Chest Physicians; AF, atrial fibrillation; AHA/ACC/HRS, American Heart Association, American College of Cardiology, Heart Rhythm Society; CCS, Canadian Cardiovascular Society; European Society of Cardiology; NICE, National Institute for Health and Care Excellence; NOAC, nonvitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TTR, time in therapeutic range; VKA, vitamin K antagonist.

*a* See Table 1 footnotes for CHADS2 and CHA2DS2-VASc expansions.

*b* Low-risk patients include men who have a CHA2DS2-VASc score of 0 and women 1.
Table 3. Assessment of Stroke and Bleeding Risk in Atrial Fibrillation Patients by Schema

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Age ≥ 75 y</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
</tr>
<tr>
<td>Age 65–74 y</td>
</tr>
<tr>
<td>Sex category (ie, female sex)</td>
</tr>
<tr>
<td>Maximum score</td>
</tr>
</tbody>
</table>

HAS-BLED<sup>b</sup>

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (systolic blood pressure &gt;160 mm Hg)</td>
</tr>
<tr>
<td>Abnormal renal and liver function (1 point each)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Bleeding tendency/predisposition&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Labile INRs (eg, TTR&lt;60%, applies only if the patient is taking warfarin)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Elderly (eg, age &gt;65 y, frail condition)</td>
</tr>
<tr>
<td>Drugs or alcohol excess (1 point each)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximum score</td>
</tr>
</tbody>
</table>

Abbreviations: INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack; TTR, time in therapeutic range.

<sup>a</sup> CHA2DS2-VASc is used to initially identify low-risk patients (CHA2DS2-VASc, 0 in males, 1 in females) who do not need any antithrombotic therapy.

<sup>b</sup> HAS-BLED categorizes those into low (score 0-2) or high (≥3) risk, where the latter can be identified for more regular review and follow-up.

<sup>c</sup> Abnormal liver function classified as the presence of long-term dialysis, renal transplant, or serum creatinine of 2.3 mg/dL (200 mmol/L) or higher. Abnormal liver function defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin 2 to 3× the upper limit of normal, in association with aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase 3× the upper limit normal); history of bleeding or predisposition (anemia); labile INR (ie, TTR>60%); concomitant antiplatelet drugs or nonsteroidal anti-inflammatory drugs; or alcohol excess.

Of the different scores, the simple HAS-BLED score (Table 3) has been validated in multiple independent cohorts and outperforms other bleeding risk scores in the prediction of serious bleeding.54-56 HAS-BLED has been validated in NOACs and in untreated and aspirin-treated patients.52,57 HAS-BLED is the only score predictive of intracranial hemorrhage risk and also has been shown to predict bleeding during bridging therapy<sup>58</sup> and during percutaneous coronary intervention.<sup>59</sup>

A high HAS-BLED score is not a reason to withhold OAC, but it can be used to highlight patients’ potential risk of bleeding and alert physicians to schedule more regular follow-up visits and provide straightforward warning about the necessity of avoiding falls and not engaging in other high-risk activities. A high HAS-BLED score suggests the need to focus on correcting the potentially reversible factors that contribute to bleeding, which include uncontrolled hypertension, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs with OAC, excessive alcohol intake, and labile INRs. Use of a decision support tool that integrates patient-specific stroke and bleeding risk would result in significant gains in quality-adjusted life expectancy.<sup>60</sup>

Falls are not an independent predictor of bleeding for those who are taking OAC medication.<sup>61</sup> A modeling exercise has suggested that a patient would need to fall 295 times a year for the benefit of stroke prevention with OAC to outweigh the risk of serious bleeding.62 Although a history of falls should not be a contraindication to OAC, AF patients who have actually sustained a fall remain at high risk of thromboembolism and morbidity.<sup>63</sup> Further investigation to ascertain the reasons for the fall and targeting interventions to reduce risk of falls—for example, treatment for correctable causes of falls (such as lowering blood pressure, vertigo, etc), polypharmacy, and the need for walking aids—should be paramount. Nevertheless, treatment decisions should be individualized.

Stroke and bleeding risk are closely related. Recent comparisons of HAS-BLED with the CHADS<sub>2</sub> and CHA2DS2-VASc scores showed an increase in bleeding rates among patients who have higher HAS-BLED, CHADS<sub>2</sub>, and CHA2DS2-VASc scores, but this was generally only significant for the HAS-BLED score; the latter score was also superior to CHADS<sub>2</sub> and CHA2DS2-VASc for bleeding risk prediction.<sup>54,55</sup> Other efforts have led to derivation and validation of a composite stroke and bleeding risk score.<sup>64,65</sup> Although there was a marginal improvement in the C statistic for predicting high-risk patients (C for composite score, 0.728 [95% CI, 0.659–0.798] compared with 0.706 [95% CI, 0.638–0.774] for HAS-BLED and 0.654 [95% CI, 0.574–0.733] for CHA2DS2-VASc scores), the discrimination compared with individual stroke and bleeding risk scores was nonsignificant. Thus, stroke risk should be assessed using a validated stroke score scheme and bleeding risk with a specific bleeding risk score scheme.

Net Clinical Benefit of Oral Anticoagulants

Effective stroke prevention for patients with AF requires the use of OACs, whether a VKA or a NOAC. NOACs fall into 2 broad classes, the oral direct thrombin inhibitors (eg, dabigatran) and oral factor Xa inhibitors (eg, rivaroxaban, apixaban, and edoxaban) (Table 4).

Stroke or systemic embolism is significantly reduced by VKAs in patients with AF (RR reduction, 64%; 95% CI, 49%-74%).66 Vitamin K antagonists are associated with an absolute RR of 2.7% per year (number needed to treat, 37) for embolism in patients with no history of prior stroke (primary prevention) and 8.4% per year (number needed to treat, 12) for patients with a history of prior stroke (secondary prevention). Compared with the control or placebo groups, the relative RR attributable to VKA is 26% (95% CI, 3%-43%; absolute RR 1.6% per year) for all-cause mortality.<sup>66</sup> A meta-analysis examining the efficacy of aspirin compared with either a control treatment or placebo for stroke or systemic embolism or mortality in AF found no benefit.66 A 19% reduction in stroke was observed with aspirin but that finding was attributable to the only positive study, the Stroke Prevention on Atrial Fibrillation (SPAF-I) trial, which reported a 42% reduction in stroke or systemic embolism with 325 mg/d of aspirin compared with a control treatment. However, the SPAF-I trial had major
internal heterogeneity of the aspirin effect. The study had 2 major groups: one group could not, or would not, take anticoagulation medicine. Of these, one subgroup of AF patients received placebo and the other aspirin. For the group that could take anticoagulation medication, one subgroup received placebo; another, aspirin; and a third group, warfarin. There was a significant, 94% reduction in stroke risk attributable to aspirin compared with placebo in the anticoagulation-eligible group. In the group that could not receive anticoagulation medication, there was no significant difference in stroke rates between aspirin and placebo. Indeed, aspirin is often considered for those deemed inappropriate for anticoagulation. In the SPAF-I trial, aspirin did not reduce stroke among those older than 75 years, nor did it prevent severe bleeding. Although the difference in stroke rates between aspirin and placebo was not marked, it has led many to conclude that aspirin is a reasonable alternative to warfarin for stroke prevention in elderly AF patients who were taking aspirin.

With VKAs, the quality of anticoagulation control is critical (as reflected by the time in therapeutic range [TTR], with a target INR of 2.0-3.0). Time in therapeutic ranges are closely related to efficacy and safety, with low rates of stroke and bleeding with high TTRs. With INRs persistently higher than 3.0, there is an increase in bleeding, especially in elderly patients, whereas the rate of thromboembolisms increase when INRs are less than 2.0. Even at an average INR of 1.7, the risk of stroke already increases 2-fold. Thus, VKAs require regular anticoagulation monitoring and are open to significant interpatient and intrapatient variability due to interactions with diet, drugs, and alcohol, among other factors.

In more recent years, the availability of the NOACs has changed the landscape of stroke prevention in AF. The NOACs offer efficacy, safety, and convenience for stroke prevention compared with the VKAs. The various phase 3 trials comparing NOACs against warfarin have been the subject of numerous reviews and meta-analyses. In a recent meta-analysis that included the RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy), ROCKET-AF (Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibitor), and ENGAGE-AF TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolyis in Myocardial Infarction study 48) trials, 42,411 participants received a NOAC and 29,272 participants received warfarin. NOACs significantly reduced stroke or systemic embolism events by 19% compared with warfarin (RR, 0.81; 95% CI, 0.73-0.91; P < .001) mainly related to a reduction in hemorrhagic stroke (RR, 0.49; 0.38-0.64; P < .001). NOACs also significantly reduced all-cause mortality (RR, 0.90; 0.85-0.95; P < .001) and intracranial hemorrhage (RR, 0.48; 0.39-0.59; P < .001) but increased gastrointestinal tract bleeding (RR, 1.25; 1.01-1.55; P = .04). Low-dose NOACs had similar overall reductions in stroke or systemic embolism events to warfarin (RR, 1.03; 0.84-1.27; P = .74) and had a more favorable bleeding profile (RR, 0.65; 0.43-1.00; P = .05), with significantly more ischemic strokes (RR, 1.28; 1.02-1.60; P = .045).

With the availability of 4 different NOACs as well as the VKAs, physicians now have a choice and can fit the drug to the patient. Various patient characteristics may influence the initial choice of one drug over another (Table 4). In the absence of head-to-head clinical trials, clinicians cannot directly compare one NOAC against another. Nevertheless, regulatory bodies and health economic analyses have performed indirect comparisons of one agent against another using warfarin as the comparator; such indirect comparisons (or network meta-analyses) should be interpreted with some caution given heterogeneity in trial inclusion-exclusion criteria, quality of INR control. Overall, there are few substantial differences in efficacy, although 150 mg of dabigatran twice daily may offer the greatest potency by reducing both ischemic and hemorrhagic stroke, and it has a similar risk of major bleeding as warfarin. For safety, the best bleeding profile is seen with 110 mg of dabigatran twice daily, apixaban, and edoxaban.

In some health care systems, there is a preference for a 3- to 6-month warfarin trial to determine if high TTRs (eg, >65%) can be achieved. NOACs are only used if the TTRs remain poor (<65%). This strategy may put patients at risk of stroke or systemic embolism because in the initial treatment stages, inadequate anticoagulation may result in an excess of thromboembolic events. Thus, VKAs remain the gold standard for the vast majority of AF patients, whereas NOACs are only used in those who cannot receive warfarin. In some health care systems, there is a preference for a 3- to 6-month warfarin trial to determine if high TTRs (eg, >65%) can be achieved. NOACs are only used if the TTRs remain poor (<65%). This strategy may put patients at risk of stroke or systemic embolism because in the initial treatment stages, inadequate anticoagulation may result in an excess of thromboembolic events. Thus, VKAs remain the gold standard for the vast majority of AF patients, whereas NOACs are only used in those who cannot receive warfarin.

Table 4. Optimal Selection of Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran 150 mg, 2/d</th>
<th>Direct Thrombin Inhibitors</th>
<th>Factor Xa Inhibitors</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke or TIA despite treatment VKA*</td>
<td>150 mg dabigatran, 2/d</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe renal impairmentb</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>GI tract symptoms or dyspepsia</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>High risk of bleedingd</td>
<td>75 mg dabigatran, 2/d (US); 110 mg dabigatran, 2/d (rest of world)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Preference for 1 dose per day</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; TIA, transient ischemic attack; VKA, vitamin K antagonist.

* Superior efficacy for preventing both stroke and hemorrhage.

b For creatinine clearance of <15 mL/min use VKA.

d High risk of bleeding is defined by a HAS-BLED score of 3 or higher. Use agent with the lowest incidence of bleeding, especially for GI tract bleeding.

e Awaiting approval.
Various clinical and pharmacogenetic factors have been proposed as determinants of warfarin dose or TTR. Recent randomized trials based on a pharmacogenetic testing as a means of predicting the response to warfarin have been disappointing.

Simple clinical risk factors have been incorporated into a new score, the SAMe-TT2R2 score (Table 5), which has been proposed as a means of identifying those newly diagnosed patients with AF who have not been treated with anticoagulation agents and who have a probability of doing well taking a VKA (SAMe-TT2R2 score, 0-2) and achieve a TTR greater than 65% or 70% (Figure). In contrast, a SAMe-TT2R2 score higher than 2 suggests that such patients are unlikely to achieve a good TTR by taking a VKA, so a NOAC should be used initially, without subjecting the patient to a "trial of warfarin" period. The SAMe-TT2R2 score has since been validated in independent studies to show it can discern those likely to achieve poor TTRs. A high SAMe-TT2R2 score translates to a greater chance of labile INRs, thromboembolism, death, and bleeding. This approach has been recommended in a position document from the European Society of Cardiology (ESC) Working Group on Thrombosis Anticoagulation Task Force.

Table 5. Definition of the SAMe-TT2R2 Score, Used to Aid Initial Decision Making Between Vitamin K Antagonist (With Good Quality Anticoagulation Control) and a Non–Vitamin K Antagonist Oral Anticoagulant

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>1</td>
</tr>
<tr>
<td>Age (&lt;60 y)</td>
<td>1</td>
</tr>
<tr>
<td>Medical history&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Treatment (interacting drugs, eg, amiodarone for rhythm control)</td>
<td>1</td>
</tr>
<tr>
<td>Tobacco use (within 2 y)</td>
<td>2</td>
</tr>
<tr>
<td>Race (not white)</td>
<td>2</td>
</tr>
<tr>
<td>Maximum points</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> The SAMe-TT2R2 score is proposed as a means to help with decision making, to identify those newly diagnosed nonanticoagulated AF patients who have a probability of doing well while taking a vitamin K antagonist (VKA) (with SAMe-TT2R2 score, 0-2) and achieve a TTR of at least 65% or 70%. In contrast, a SAMe-TT2R2 score of more than 2 suggests that such patients are unlikely to achieve a good TTR while taking a VKA, and a non-VKA oral anticoagulant should be used upfront, without a "trial of warfarin" period.

<sup>b</sup> Two of the following: hypertension, diabetes mellitus, coronary artery disease or myocardial infarctions, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, or hepatic or renal disease.

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**Figure. Algorithm for Risk Stratification and Selection of Anticoagulation Therapy for Stroke Prevention in Atrial Fibrillation**

- **Patient with newly diagnosed atrial fibrillation**
- **Calculate CHA2DS2-VASc score to determine stroke risk**
  - **High stroke risk?**
    - Male, CHA2DS2-VASc score ≥1
    - Female, CHA2DS2-VASc score ≥2
  - **Low stroke risk?**
    - No antithrombotic therapy

- **Calculate SAMe-TT2R2 score to determine initial anticoagulation treatment**
  - **SAMe-TT2R2 score >2?**
    - **Yes:** Vitamin K antagonist (VKA) therapy (eg, warfarin)
      - **Monitor anticoagulation control (goal: time in therapeutic range [TTR] >70%)**
        - **Inadequate anticoagulation control?**
          - **TTR <65% or within past 6 mo**
            - INR >5 twice
            - or INR >8 once
            - or INR <2 twice
          - **Yes:** Continue VKA therapy with regular monitoring
          - **No:** Non-VKA-oral anticoagulant therapy (oral direct thrombin inhibitors or oral factor Xa inhibitors)

- **No:** Vitamin K antagonist (VKA) therapy

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<sup>a</sup> Consider NOAC or VKA. If considering VKA, calculate SAMe-TT2R2 first before deciding on optimal OAC therapy.
Net Clinical Benefit

When making decisions about thromboprophylaxis, an important consideration is to balance ischemic stroke prevention against the potential risk of serious bleeding. The net clinical benefit of antithrombotic therapy can be determined in many ways, eg, by balancing the reduction in ischemic stroke against the risk of serious bleeding (ie, intracranial hemorrhage) weighted 1.5-fold.

Recent studies have found a positive net clinical benefit (balancing ischemic stroke reduction against the risk of intracranial hemorrhage weighted 1.5-fold) for OAC in patients with AF and at least 1 additional stroke risk factor. With the NOACs, the net clinical benefit was also generally positive for dabigatran and apixaban with CHA2DS2-VASc score of 1, and for all NOACs with CHA2DS2-VASc score of at least 2, and in a modeling analysis, could translate to an additional 65 000 cardiovascular events and deaths prevented in Europe. The threshold for initiating OAC treatment has been calculated as a stroke rate of 0.9% per year, based on the balance of ischemic stroke reduction vs intracranial hemorrhage with the availability of new safer OAC agents.

Guidelines for AF Treatment

When the only available oral anticoagulants were the VKAs, the focus was to identify high-risk patients to be targeted for this inconvenient drug, VKA (eg, warfarin), given the need for anticoagulation monitoring and other restrictions necessary with VKA use. Also, older guidelines, such as the 2006 ACC/AHA/ESC joint guidelines had divided patients using the CHADS2 score into low-, moderate-, and high-risk strata, for which low-risk patients were recommended aspirin; moderate-risk patients, aspirin or warfarin; and high-risk patients, warfarin. Such an approach did not work well, and numerous studies have shown that high-risk patients were undertreated, with OAC being used in approximately 50% of patients and with regional differences evident. Also, stroke risk is a continuum, and any 1 risk factor can confer risk if left untreated, exposing the patient with AF to a fatal or disabling stroke.

In 2010, and in a focused update in 2012, the ESC guidelines advocated a change in clinical practice highlighting the need to identify the low-risk patients (age <65 years and lone AF, including women) who do not need any antithrombotic therapy. Patients with 1 or more stroke risk factors should be offered OAC, with a preference for NOACs. If VKAs are used, a TTR higher than 70% was recommended. Only if patients refuse any form of OAC, then antiplatelet therapy with aspirin-clopidogrel combination therapy (if not at an unduly high bleeding risk) or—less effectively—aspirin monotherapy, may be considered. The HAS-BLED score is recommended for bleeding risk assessment.

In 2012, the American College of Chest Physicians (ACCP) published its consensus guidelines on antithrombotic therapy in AF patients. This was based on the CHADS2 score, where OAC was recommended for those with CHADS2 score of 1 or higher. In patients with a CHADS2 score of 0, additional non-CHADS2 risk factors should be considered, including age from 65 through 74 years, female sex, and vascular disease, whereby the presence of multiple non-CHADS2 risk factors would merit OAC treatment.

In 2014, the new AHA/ACC/HRS guidelines for AF advocated use of the CHA2DS2-VASc score for stroke risk stratification, but in a categorical approach whereby OAC was recommended for a CHA2DS2-VASc score of 2 or higher, and no therapy for a score of 0; however, for CHA2DS2-VASc score of 1, the recommendation was “no therapy, aspirin or OAC.” Oral anticoagulants could be either NOACs or VKAs. The value of the US guidelines approach for CHA2DS2-VASc score of 1 was recently tested in a nationwide cohort study of 12 935 men with AF and a CHA2DS2-VASc score of 1 but were not receiving antithrombotic therapy, where the annual stroke rate overall was 2.75%. The risk of ischemic stroke ranged from 1.96% per year for AF patients with vascular disease to 3.50% per year for those aged 65 through 74 years. For women with AF and a CHA2DS2-VASc score of 2 (ie, 1 additional risk factor), the annual stroke rate was 2.55%, with the risk of ischemic stroke increasing from 1.91% per year for patients with hypertension to 3.34% per year for those aged 65 through 74 years. Similar findings were observed from the Danish nationwide cohort study, where event rates in nontreated AF patients with 1 additional stroke risk factor increased stroke by 3.01-fold and death by 3.12-fold, at 1 year follow-up. Thus, OAC should still be considered for AF patients with 1 additional stroke risk factor given their high risk of ischemic stroke and death.

In 2014, NICE published its new AF guidelines. In contrast to some guidelines, the NICE guidelines are based on systematic reviews, evidence appraisal and cost-effectiveness. NICE guidelines advocate use of the CHA2DS2-VASc and HAS-BLED scores for stroke and bleeding risk assessment, respectively. The recommendations are to initially identify low-risk patients who do not need any antithrombotic therapy. Patients with a CHA2DS2-VASc score 2 or higher should be offered OAC, while men with a score of 1 should be considered for OAC. If VKAs are used, a TTR of higher than 65% was recommended. The guidelines clearly state that aspirin should not be used for stroke prevention in AF, due to its minimal efficacy, poor safety, and lack of cost-effectiveness.

The Canadian Cardiovascular Society (CCS) published its focused update in 2014, proposing a simplified algorithm-based approach to stroke risk stratification. The first step in the algorithm is to identify those aged 65 years or older who should be offered OAC. The second step is to identify those younger than 65 years with CHADS2 risk factors who should have OAC. Next, those younger than 65 years who have a CHADS2 score of 0 with “arterial disease, ie, coronary, aortic or peripheral” are recommended aspirin alone. Finally, those patients younger than 65 years with no CHADS2 risk factors nor vascular disease are recommended “no antithrombotic therapy.” This approach was tested in a nationwide cohort study, in which the overall rate of the combined end point of ischemic stroke, systemic embolism, or TIA was 4.32 per 100 person-years at 1 year, among the patients who would have had an indication for OAC therapy according to ESC guidelines but were not recommended for OAC according to the 2014 CCS algorithm; also, the subgroup of patients with prior vascular disease and a CHADS2 score of 0 (ie, only recommended aspirin treatment according to CCS algorithm) had an event rate
of 4.84 per 100-person-years at 1-year follow-up. Thus, based on the 2014 CCS algorithm, the subgroup not recommended for OAC were not low risk and use of the ESC guideline approach offered additional refinement of stroke risk stratification in such patients.

In summary, stroke risk stratification and treatment decisions can now be simplified, notwithstanding the various approaches advocated in guidelines. The initial step is to identify the low-risk patients who do not need any antithrombotic therapy, given their low absolute risk of stroke. Low-risk patients are those aged younger than 65 years with no stroke risk factors (a CHA2DS2-VASc score of 0 for males or 1 for females). Subsequently, patients with at least 1 additional stroke risk factor can be offered effective stroke prevention, which is OAC, either NOAC or VKA (Figure). Thus, this includes male AF patients with a CHA2DS2-VASc score of 1 and a score of 2 or higher for everyone else, irrespective of other risk stratification enhancements. In terms of clinical application and practicality, such an approach makes clinical decision making very simple and practical, without the necessity for complex investigations that may delay treatment decisions.

Does use of risk scores in guidelines to aid treatment decisions improve outcomes? As mentioned above, use of the CHA2DS2-VASc score enables refinement of stroke risk stratification and enables identification of those AF patients still at appreciable stroke risk who were previously considered at low risk when using other risk schemes. The net clinical benefit is also positive for patients with a CHA2DS2-VASc score of 1 or higher, whether from real-world cohorts or modeling analyses with the NOACs. Indeed, modeling analyses show that use of the ESC guidelines would translate to a reduction in additional thromboembolic, mortality, and bleeding events in Europe and Asia, compared with older guideline strategies. Finally, guideline adherent treatment is associated with improved efficacy and safety outcomes, whether from observational or trial-based cohorts.

Specific Considerations

Chronic Renal Failure

Atrial fibrillation patients with renal impairment represent a high-risk group, demonstrating a greater risk of stroke, myocardial infarction, and major bleeding. Approximately 20% of AF patients show a significant reduction in renal function over 2 years, and even normal or mild renal impairment at baseline did not preclude some patients from progressing to severe renal impairment.

Patients with severe renal impairment were largely excluded from randomized trials, and all NOACs do have some degree of renal excretion (the highest being with dabigatran, whereby the drug is also removed by hemodialysis). Initial observational studies were conflicting suggesting that stroke prevention with warfarin was offset by a high rate of major bleeding, especially in patients requiring dialysis. The most recent data from the Swedish AF cohort study suggests that warfarin is still associated with a positive net clinical benefit, balancing stroke reduction against bleeding risk, but emphasizes the importance of a high TTR to minimize adverse effects. Similar data have been published from the Danish nationwide cohort study.

Acute Coronary Syndrome and Percutaneous Coronary Intervention

Many patients with AF have associated coronary artery disease. Some may present with an acute coronary syndrome (ACS), be undergoing percutaneous coronary intervention, or both. Such patients are at high risk, so management is complex, having to use OAC plus antiplatelet therapy to balance between stroke prevention, recurrent cardiac ischemia, stent thrombosis, and risk of serious bleeding (especially intracranial hemorrhage). Observational and trial data have recently been reviewed by a European consensus group, which recommends an initial period of triple therapy (OAC, aspirin, clopidogrel) followed by OAC plus a single antiplatelet drug (preferably clopidogrel). After 1 year, the patients can receive OAC alone. In some patients at low thrombotic risk or high-bleeding risk, the initial triple therapy period could be substituted with OAC plus clopidogrel. In guidelines in which OAC is mentioned, this could refer to a NOAC or well-managed VKA (with TTR >70%). Third-generation drug eluting stents are also the preferred option, and with improvements in stent technology, the period during which additional dual antiplatelet drugs are needed can be shortened.

Bridging

Bridging refers to the use of a short-acting anticoagulants, eg, low-molecular-weight heparin, during the interruption of a longer-acting oral agent. Bridging anticoagulation is often used during anticoagulation interruptions for operative procedures and is associated with a higher risk of bleeding and adverse events. Indeed, observational and trial data do not support the use of routine bridging giving the higher bleeding risks and no difference in thromboembolism when compared with an uninterrupted OAC strategy; thus, the latter approach is used for most procedures. However, bridging may perhaps be considered for some very high-risk subgroups (eg, prosthetic mechanical heart valves); thus, risk stratification is important. NOACs may be beneficial based on promising data from post hoc analysis from randomized trials. Nevertheless, the use of NOACs requires understanding of their pharmacology, given their fast onset and offset of action, as well as the effect of renal function.

Left Atrial Appendage Occlusion

The concept of left atrial appendage (LAA) occlusion arises because most atrial thrombi arise from the LAA, in patients with AF. Thus, over the last decade, the LAA has been removed during cardiac surgery, or more recently subject to percutaneous occlusion with a variety of devices. For example, the WATCHMAN device has been tested in a randomized trial (PROTECT-AF), which showed that the LAA occlusion device was noninferior for safety and efficacy to standard therapy (warfarin). There was an initial excess of complications (eg, pericardial tamponade) in the device intervention group than in the control group (7.4 vs 4.4 per 100 patient-years; RR, 1.69, 95% CI, 1.01-3.19), but as operators became more experienced this diminished, as has been seen in subsequent registries. These findings were reinforced in the PREVAIL trial, which showed that LAA occlusion was noninferior to warfarin for ischemic stroke prevention or systemic embolism at more than 7 days after the procedure. Other methods of LAA occlusion are also available, but randomized trials are lacking. A recent position document from the European Heart Rhythm Association comprehensively reviews the literature.
and suggests practical points for its use.115 For now, LAA occlusion may be considered in patients with a high stroke risk and contraindications for long-term OAC.4

Cardioversion
Cardioversion of AF requires OAC for a minimum of 3 weeks before cardioversion, and OAC continued during and after cardioversion. Recent data on the NOACs may support their use to facilitate cardioversion and may be associated with less delay to the procedure, in contrast to using VKAs for which delays or cancellations were common pending a therapeutic INR.114-116 Irrespective of apparent successful rhythm control (whether by cardioversion or ablation), patients should continue taking OAC in the presence of stroke risk factors. Rhythm control should not be performed as a basis to stop OAC.

Patient Values and Preferences
Increasing awareness is evident on the importance of patient attitudes and preferences in deciding on managing strategies for AF, as well as treatment adherence.117 Particularly with NOACs (with their short half-life), poor adherence can be associated with a greater risk of stroke and mortality.118 Simply to avoid 1 stroke, patients are even prepared to sustain 4 major bleeding events.119 In contrast, physicians are more concerned with avoiding major bleeding, even at the expense of patients sustaining strokes.120,121

Conclusions
Substantial recent advances are evident in the area of stroke prevention in AF. Treatment has changed greatly, recognizing that stroke prevention is the cornerstone of AF management. Indeed, following the initial identification of low-risk patients using the CHA2DS2-VASc score, physicians can then offer effective thromboprophylaxis (which is OAC) to patients with at least 1 additional stroke risk factor. Clinicians should not offer aspirin for stroke prevention in AF. With this approach, clinicians can improve AF patient outcomes and reduce the huge burden of AF-related stroke.

ARTICLE INFORMATION
Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lip reported that he has served as a consultant for Bayer Healthcare, Merck, AstraZeneca, sanofi-aventis, Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, and sanofi-aventis. Dr Lane reported that she has received an investigator initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and has been on the speaker bureaus for Boehringer Ingelheim, Bayer, and Bristol-Myers Squibb/Pfizer.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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