Although all clinical scores have modest predictive value for high-risk patients who sustain events, the CHA2DS2-VASc score is clearly superior in identifying low-risk patients with thromboembolism rates <1%/y who do not need any antithrombotic therapy. Evidence of benefit from oral anticoagulation (OAC) treatment exists for reducing stroke and mortality even in the presence of 1 additional stroke risk factor (ie, CHA2DS2-VASc score 1 in men or 2 in women). After all, OAC significantly reduces strokes, thromboembolism, and death in patients with atrial fibrillation (AF).

Response by Savino and Halperin on p 1503

The risk of stroke is substantially increased in patients with AF, and stroke prevention with OAC is a pivotal part of the management of this common arrhythmia. OAC reduces the risk of stroke by 64% and all-cause mortality by 26% compared with control. Despite compelling evidence of benefit, OAC treatment in AF patients is still underused across different parts of the world.

The risk of stroke in AF is not homogeneous and varies with age and concomitant comorbidities. Comorbidities have been identified from non-OAC arms of the historical trial cohorts and large epidemiological cohorts. To aid clinicians in determining the risk of stroke, various stroke (and bleeding) risk stratification schemes have been proposed, essentially with the aim to answer the binary question, “Will my patient benefit from OAC treatment?” However, the drawback of OAC treatment is the potential to cause serious bleeding (particular intracranial hemorrhage); thus, the prescribing physician (and patient) has to carefully weigh the benefit and harm.

Comparing Stroke Risk Stratification Schemes

Some focus has been directed to various stroke risk stratification schemes, and we are often asked which is best. In 2008, the Stroke Risk in Atrial Fibrillation Working Group compared 12 risk stratification schemes and noted not only an overlap between risk factors but also clinically relevant differences. However, comparing stroke risk prediction across different schemes is not trivial. This statistical field has evolved from using area under the receiver-operating characteristics curve and C statistics to the more intuitive (interpretation wise) measures of net reclassification index and integrated discrimination improvement. Although C statistics and the net reclassification index (and other similar measures) are academic tools that are widely used in the literature to compare risk prediction, they are similarly highly debated among statistical experts.

An important perspective in terms of comparisons of risk stratification schemes is whether 1 scheme compared with another will put a patient at risk, that is, risk of either stroke or bleeding. Although a C statistic of 0.6 seems better than flipping a coin (50:50; ie, a C statistic of 0.5), not much clinical perspective can be put into that (statistical) number in conversations with a patient. Obsession with statistical significance needs to be balanced against practical clinical utility and ease of use.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From University of Birmingham Institute of Cardiovascular Sciences, City Hospital, UK (G.Y.H.L.); and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Denmark (G.Y.H.L., P.B.N.).

This article is Part I of a 2-part article. Part II appears on p 1504.

Correspondence to Gregory Y.H. Lip, MD, University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Dudley Rd, Birmingham, B18 7QH UK. E-mail g.y.h.lip@bham.ac.uk.

(Circulation. 2016;133:1498-1503. DOI: 10.1161/CIRCULATIONAHA.115.016713.)
© 2016 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.115.016713
The traditional approach was to use risk stratification schemes to focus on identifying high-risk patients to be targeted for OAC with an "inconvenient" drug, warfarin (a vitamin K antagonist [VKA] class of drugs). Thus, risk schemes artificially categorized patients with AF into low-, moderate-, or high-risk categories so that the high-risk subjects could be recommended for VKA. However, stroke risk is a continuum of risk, and patients did not conveniently fall into 3 neat categories of low, moderate, and high risk. In addition, the focus on identifying high-risk patients, who would be at risk of fatal and disabling strokes, was limited by the modest predictive value of existing stroke risk stratification schemes (CHA2DS2-VASc, CHADS2-VASc, etc) that were based on clinical features. Older risk scores such as CHADS2 were derived from clinical factors identified from the non-VKA arms of the historical trials of 2 decades ago in which <10% of patients screened were randomized and many common stroke risk factors were not recorded or consistently defined. The more recent CHA2DS2-VASc score extended the older CHADS2 score by giving 1 point to age of 65 to 74 years (and 2 points to age ≥75 years, recognizing that age was a powerful driver of stroke risk), vascular disease, and female sex (female sex as a stroke risk modifier, especially in older patients).

In 2016, the landscape for stroke prevention in AF has changed markedly. First, we are getting better at handling the VKAs, recognizing that we need to pay attention to quality of anticoagulation control, as reflected by the percentage of time in therapeutic range (TTR). Indeed, there is a close inverse relationship between TTR and thromboembolism and bleeding, and a TTR of >70% should be the goal. We also are aware of common clinical features that influence TTR, and such common factors can be incorporated into the SAME-TT R2 score (sex [female], age ≤60 years, medical history, treatment with interacting drugs [eg, amiodarone], tobacco use, race [nonwhite]) to help identify the patients likely to do well (or not) on a VKA. Second, we are now in the era of the non-VKA OACs (NOACs) that overcome some of the limitations of VKAs, particularly the interpatient and intrapatient variability in anticoagulation control and the necessity for regular monitoring in terms of international normalized ratios values.

Perhaps the use of risk stratification schemes would be better related to having a simple and practical checklist that merely highlights the important clinical manifestations (or risk factors) that patients may or may not have, with less emphasis on the exact risk prediction in 1 tool compared with another. Although all clinical scores had modest predictive value for high-risk patients who sustain events, the CHA2DS2-VASc score was clearly superior in identifying low-risk patients with thromboembolism rates <1%/y who did not need any antithrombotic therapy. Some comparisons between the older CHADS2 score and the CHA2DS2-VASc score have been published.7,17–20

In 2012, the focused update of the European Society of Cardiology guidelines recommended a practice shift so that the initial decision step was to identify these low-risk patients (defined as a CHA2DS2-VASc score of 0 in men and 1 in women) who did not require any antithrombotic therapy. The next step was to offer stroke prevention to those with ≥1 additional stroke risk factors. For a CHA2DS2-VASc score of ≥2, OAC is recommended (Class I recommendation), whereas for a CHA2DS2-VASc score of 1 in men, OAC should be considered, taking patient values and preferences into consideration (Class IIa recommendation).

In contrast, the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines still use a categorical approach, recommending OAC to high-risk patients with a CHA2DS2-VASc score of ≥2 and no antithrombotic therapy to low-risk patients with a CHA2DS2-VASc score of 0.22 For patients with a CHA2DS2-VASc score of 1, the recommendation is “nothing, aspirin or OAC.” In all guidelines, OAC is recommended for a CHA2DS2-VASc score of ≥2, regardless the absolute value of the CHA2DS2-VASc score (eg, 2, 3, 8, or 9).

The Interpretational Difficulties and Pitfalls
Although randomized, controlled trials are an ideal design to compare 2 strategies (ie, treatment versus no treatment), the inclusion and exclusion criteria may limit generalizability as a result of selection bias. Truly representative registries on AF populations enable the extension of knowledge of etiology, risk factors, and outcomes associations, as well as risk evaluation of different treatment strategies within different inception cohorts. These possibilities notwithstanding, observational studies investigating performances of risk scores predicting stroke outcomes are obligated to contend with competing risk of death. Hence, rates of stroke events are reported instead of the absolute risk of stroke.23,24 Arguing that, for example, a 2% 1-year event rate of thromboembolism equals a 1-year 2% absolute risk of thromboembolism is, at best, inaccurately formulated but, at worst, incorrect because of competing risk of death.

The next challenge arises when between-studies comparisons are made: Why does 1 observational study with low-risk AF patients report high event rates, whereas another study based on a seemingly similar population (but different cohort) reports relatively lower event rates? The reason may well be found in the details of the methodology and study designs. Different approaches to achieving an untreated population have been used. Studies based on the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort apply an algorithm using information from pharmacy and laboratory databases to establish person-time off warfarin.25 Nationwide cohorts such as the Danish, Swedish, and Taiwan cohorts lack data from laboratory testing (eg, the international normalized ratio values) and thus use prescription information only to determine whether patients are untreated.7,17,26 However, when outcomes related to thromboembolism are investigated, this may potentially bias the results toward null. One study based on data from the Danish nationwide cohort specifically reports results from the use of a continuous treatment
approach (assessing available tablets for included individuals) and the censoring approach, and the results were materially unaffected by the 2 different approaches. 27 In contrast, Friberg et al 28 attempted to establish a treatment-free population by excluding all patients who during follow-up initiated OAC treatment. This “conditioning on the future” approach could well lead to deflated or lowered event rates: AF patients who experience a thromboembolism are very likely to be started on OAC treatment, but these patients are excluded, causing events to be left out of the study. This may substantially bias the results away from the null hypothesis.

Altogether, different event rates from various cohorts may basically reflect study settings and design such as a hospitalized AF population versus a community-based population, a registry-based cohort versus randomized trial data, and a cohort with versus a cohort without healthcare plans rather than clinically important differences.

Net Clinical Benefit of Stroke Prophylactic Treatment Versus Alternative Treatment

Although stroke rates are not equal across study populations, within-study comparison of different treatment options is a valid approach to assess whether or not AF patients will benefit from treatment or not. As a result of the aforementioned discrepancies between European (stepwise approach to initially identify low-risk patients [ie, CHA2DS2-VASc score 0 in men and 1 in women] who do not need any antithrombotic therapy and then offer OAC to those with ≥1 additional stroke risk factors) and American (categorical approach) guidelines, recent analyses have focused on net clinical benefit, defined in various forms.

The main goal of this type of analysis is to approach the binary question with a binary answer put into a single measure that grasps both stroke risk and bleeding risks. However, it is important to accept the fact that a transient ischemic attack does not easily compare with a gastrointestinal bleeding event. Therefore, different weights have been proposed to capture (and compare) some of the adverse effects of OAC treatment.

The most simplistic comparison was proposed by Singer et al, 29 who proposed a weight of 1.5 for intracranial hemorrhage compared with a weight of 1 for ischemic stroke when offering patients antithrombotic treatment. A more embracing approach was published by Connolly et al, 30 who stratified bleeding events but also included other competing events such as myocardial infarction. A comprehensive analysis using these approaches yielded a positive net clinical benefit favoring warfarin treatment compared with no treatment but a positive net clinical benefit for warfarin compared with aspirin (Figure 1).

The overall trend regardless of net clinical benefit methodological approach is clear: Patients with 1 stroke risk factor (ie, CHA2DS2-VASc score of 1 in men or 2 in women) benefitted from OAC treatment, whereas low-risk patients with a CHA2DS2-VASc score 0 in men or 1 in women did not benefit from OAC or aspirin treatment compared with being untreated. 11 A different approach was made by Eckman et al, 32 who balanced ischemic stroke reduction with OAC against increased risk for intracranial hemorrhage. They estimated that the treatment threshold for VKA was a stroke rate of 1.7%/y (although TTR was not considered in the analysis), but for a newer, safer OAC such as dabigatran, the “tipping point” for treatment is shifted so that the threshold for initiating OAC is now a stroke rate of >0.9%/y.

Net clinical benefit (NCB) of antithrombotic treatment regimens vs no treatment. DC-1 indicates Danish cohort weights using 1 year of follow-up; and DC-5, Danish cohort weights using 5 years of follow-up. Adapted from Lip et al. 31

What Should Be Our Clinical Approach to Stroke Prevention?

To provide contemporary clinical guidance, a recent overview of stroke prevention in AF proposes an algorithm to address 2 questions 35: “Will my patient benefit from OAC treatment?” And if the answer is yes, then “What sort of OAC treatment should I offer?”

Step 1 is to identify low-risk patients (CHA2DS2-VASc score 0 in men and 1 in women). These patients do not need
any antithrombotic therapy. Step 2 is to offer stroke prevention, which is OAC to those with ≥1 additional stroke risk factors (ie, CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥1 in men and ≥2 in women). In Step 2, OAC is recommended for ≥1 stroke risk factors (excluding female sex as a lone risk factor), regardless of the absolute value of the CHA\textsubscript{2}DS\textsubscript{2}-VASc score (whether 2, 3, 8, or 9). Step 3 is then to decide on type of OAC, especially if a patient is previously anticoagulation naïve. By assessing the SAME-T\textsubscript{T2}R\textsubscript{2} score, the treating physician is provided with some guidance on whether a patient will (on probability) be able to obtain a sufficiently high TTR (>65%–70% of the time) when treated with a VKA.\textsuperscript{36–39} Of note, real-world studies show that good average individual TTR (ie, good-quality anticoagulation control, average TTR >70%) is associated with low stroke and bleeding risks.\textsuperscript{40,41}

This approach would avoid a trial of VKA (or warfarin stress test), which may put patients at risk of thromboembolism as a result of poor TTRs in the initial inception phase.\textsuperscript{42} Those patients with a SAME-T\textsubscript{T2}R\textsubscript{2} score >2 can be flagged for education and more regular review or follow-up to ensure good anticoagulation control or can be offered an NOAC (Figure 2).

The 3 individual steps suggested in this algorithm have been investigated independently with positive results but remain to be investigated in the full form (Figure 2). Although contemporary (European) guidelines recommend the use of NOACs in favor of VKA treatment, it is important to realize that choice of stroke prophylactic drugs is also affected by costs and reimbursement in different parts of the world, and VKA remains widely used.\textsuperscript{43} Hence, the suggested steps could aid prescribing physicians in recommending optimal treatment choices, acknowledging that the costs and effects of the drugs are different.

**Conclusion**

The risk of stroke in AF is not homogeneous. Risk assessments should be carefully evaluated in each patient, assessing clinical manifestations (also beyond risk factors in scores) and patient values and preferences. Obviously, a 64-year-old female patient with AF and documented hypertension has the same risk of stroke the day she turn 65 as the day before. However, because actual stroke risks vary in an individual patient, researchers should be less obsessed while trying to identify the exact stroke risk.

Indeed, stroke risk scores such as CHA\textsubscript{2}DS\textsubscript{2}-VASc are designed to be reductionist and simple to facilitate their broad practical use in everyday (and often busy) clinical settings. However, we should understand that a patient who gets 1 point for age of 74 years may be at higher absolute risk than a younger 65-year-old man who gets 1 point for mild, well-treated hypertension. This is not failure of any stroke risk prediction scheme, and it is not necessary for risk scores to identify the exact stroke risk. Rather, stroke risk prediction schemes should provide useful thresholds at which important dichotomous clinical decisions are made, for example, nonuse of antithrombotic therapy (in low-risk patients, ie, men with a CHA\textsubscript{2}DS\textsubscript{2}-VASc of 0 and women with a CHA\textsubscript{2}DS\textsubscript{2}-VASc of 1) versus anticoagulation for those with ≥1 additional stroke risk factor.

Finally, evidence of benefit from OAC treatment exists for reducing stroke and mortality even in the presence of 1 additional stroke risk factor (ie, CHA\textsubscript{2}DS\textsubscript{2}-VASc score 1 in men or 2 in women)\textsuperscript{44}; hence, this should trigger the prescribing physician to initiate a conversation with the AF patient about optimal stroke prevention. After all, OAC reduces strokes, thromboembolism, and death in AF, and OAC refers to NOAC or well-managed warfarin (with TTR >70%).

We should be less obsessed with identifying the exact stroke risk, which is not possible because the clinical status of a patient with AF (along with associated risk) does not remain static, given the elderly age, multiple comorbidities, and frequent hospitalizations associated with AF. Thus, in most patients with AF with at least 1 additional risk factor for stroke, we should be considering OAC given the elevated risk of AF-related stroke that is more likely to be fatal and disabling compared with non-AF related strokes.

**Disclosures**

Dr Lip reports guideline membership/reviewing for various guidelines and position statements from European Society of Cardiology,
European Heart Rhythm Association, The National Institute for Health and Care Excellence, etc; serving on steering committees for various phase II and III studies, Health Economics & Outcomes Research, etc; serving as an investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in AF, acute coronary syndrome, lipids, etc; serving as a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife; and Daiichi-Sankyo; and serving as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. Dr Nielsen has been serving as a speaker for Boehringer Ingelheim.

References


Response to Lip and Nielsen

John A. Savino III, MD; Jonathan L. Halperin, MD

Drs Lip and Nielsen provide a thoughtful discussion of the evidence supporting the value of oral anticoagulation, even for patients with atrial fibrillation near the lower portion of the stroke risk spectrum, citing the C statistic to support the predictive utility of the CHA2DS2-VASc score. Although the C statistic summarizes the positive and negative predictive values of the CHA2DS2-VASc score, it does not provide a robust estimate of the overall magnitude of risk, limiting its clinical applicability. It indicates the probability that a randomly selected patient with a stroke had a risk score higher than a randomly selected patient who did not. Although this is useful in assessing population-based data, it is not sufficient to guide the management of an individual patient, who presents in a specific clinical context. More often than not, other data that are not components of the risk score are available to influence therapeutic decisions. And just as the C statistic provides an important but limited assessment of its predictive performance, the CHA2DS2-VASc score is useful mainly as a first approximation of patients’ thromboembolic risk and the potential benefit of anticoagulation. Other factors, including their ability to tolerate anticoagulation, are crucial to consider and vary with the anticoagulant regimen prescribed. Most components of risk are not static variables. Like age, their impact fluctuates along continua of severity and may be influenced unequally by concurrent therapies in ways that have been incompletely defined.
Should Patients With Atrial Fibrillation and 1 Stroke Risk Factor (CHA₂DS₂-VASc Score 1 in Men, 2 in Women) Be Anticoagulated?: Yes: Even 1 Stroke Risk Factor Confers a Real Risk of Stroke

Gregory Y.H. Lip and Peter Brønnum Nielsen

_Circulation_. 2016;133:1498-1503
doi: 10.1161/CIRCULATIONAHA.115.016713
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/133/15/1498

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/