Reviews

Can We Predict Stroke in Atrial Fibrillation?

Gregory Y.H. Lip, MD
Centre for Cardiovascular Sciences, University of Birmingham, City Hospital, Birmingham, United Kingdom

Address for correspondence:
Gregory Y.H. Lip, MD
Centre for Cardiovascular Sciences
University of Birmingham
City Hospital
Birmingham, B18 7QH,
United Kingdom
g.y.h.lip@bham.ac.uk

ABSTRACT

Stroke prevention with appropriate thromboprophylaxis still remains central to the management of atrial fibrillation (AF). Nonetheless, stroke risk in AF is not homogeneous, but despite stroke risk in AF being a continuum, prior stroke risk stratification schema have been used to 'artificially' categorise patients into low, moderate and high risk stroke strata, so that the patients at highest risk can be identified for warfarin therapy. Data from recent large cohort studies show that by being more inclusive, rather than exclusive, of common stroke risk factors in the assessment of the risk for stroke and thromboembolism in AF patients, we can be so much better in assessing stroke risk, and in optimising thromboprophylaxis with the resultant reduction in stroke and mortality. Thus, there has been a recent paradigm shift towards getting better at identifying the 'truly low risk' patients with AF who do not even need antithrombotic therapy, whilst those with one or more stroke risk factors can be treated with oral anticoagulation, whether as well-controlled warfarin or one or the new oral anticoagulant drugs.

The new European guidelines on AF have evolved to deemphasise the artificial low/moderate/high risk strata (as they were not very predictive of thromboembolism, anyway) and stressed a risk factor based approach (within the CHA_2DS_2-VASc score) given that stroke risk is a continuum. Those categorised as 'low risk' using the CHA_2DS_2-VASc score are 'truly low risk' for thromboembolism, and the CHA_2DS_2-VASc score performs as good as — and possibly better — - than the $CHADS_2$ score in predicting those at 'high risk'. Indeed, those patients with a CHA_2DS_2-VASc score = 0 are 'truly low risk' so that no antithrombotic therapy is preferred, whilst in those with a CHA_2DS_2-VASc score of 1 or more, oral anticoagulation is recommended or preferred.

Given that guidelines should be applicable for >80% of the time, for >80% of the patients, this stroke risk assessment approach covers the majority of the patients we commonly seen in everyday clinical practice, and considers the common stroke risk factors seen in these patients. The European guidelines also do stress that antithrombotic therapy is necessary in all patients with AF unless they are age <65 years and truly low risk. Indeed, some patients with 'female gender' only as a single risk factor (but still CHA_2DS_2-VASc score of 1, due to gender) do not need anticoagulation, especially if they fulfil the criterion of "age <65 and lone AF, and very low risk". In the European and Canadian guidelines, bleeding risk assessment is also emphasised, and the simple validated HAS-BLED score is recommended. A HAS-BLED score of ≥3 represents a sufficiently high risk such that caution and/or regular review of a patient is needed. It also makes the clinician think of correctable common bleeding risk factors, and the availability of such a score allows an informed assessment of bleeding risk in AF patients, when antithrombotic therapy is being initiated.

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder. AF commonly coexists with cardiovascular risk factors, and the presence of these adds to the development of new onset AF, especially if inadequately managed,[1] and to complications associated with AF, such as stroke.[2]

AF predisposes to stroke by its fulfillment of Virchow's triad of thrombogenesis,[3] whereby thrombus formation occurs in the presence of "vessel wall abnormalities" (now recognized as representing structural heart disease or vascular disease), "abnormal blood flow" (as evidenced by stasis in association with this arrhythmia), and "abnormal blood constituents" (given the abnormalities of clotting and platelets that are present in AF).

Strokes in AF are associated with greater mortality and morbidity, with more disability, longer hospital stays, and lower rates of discharge to the patient's own home. Clearly, AF represents a major public health problem, with a significant impact on healthcare costs.

Dr. Lip received an honorarium through an educational grant from Sanofi Aventis for his time and expertise spent writing this article. He has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis.

Received: July 10, 2011
Accepted with revision: August 15, 2011

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969

How Do We Reduce this Risk?

Compared with placebo, adjusted-dose oral anticoagulation (OAC) with warfarin reduces stroke risk by 64% (95% confidence interval [CI], 49%–74%) and all-cause mortality by 26% (95% CI, 3%–43%).[4]

In this meta-analysis, antiplatelet therapy reduced strokes by 22% (95% CI, 6%–35%) compared to control, which is a figure consistent with the reduction in stroke seen by use of antiplatelet therapy in non-AF patients with vascular disease.[5,6] When the analysis by Hart et al[4] is confined to the aspirin-only trials, aspirin showed a nonsignificant 19% (95% CI, −1% to 35%) reduction in the incidence of stroke, with no significant effect on mortality (relative risk reduction, 14% (−7 to 31).

Although there was no statistical heterogeneity among the trials, the stroke risk reduction with aspirin compared to placebo (−19% stroke risk reduction) was driven by the 1 single positive trial, the SPAF-1 trial,[7] which reported a 42% stroke risk reduction with 325 mg aspirin daily, compared to placebo. This single trial had internal heterogeneity between the anticoagulation-eligible and anticoagulation-ineligible arms of the trial (94% vs 8% stroke risk reduction, respectively); also, aspirin was ineffective in those aged >75 years and did not prevent severe strokes. The SPAF-1 trial was stopped at an interim stage and its result may be exaggerated.

In contrast, OAC was associated with a 39% (95% CI, 0.22–0.50) risk reduction compared with antiplatelet therapy.[4] More contemporary randomized trials very clearly confirm that aspirin is inferior to OAC for stroke prevention, and the risks of bleeding (including intracranial hemorrhage) with aspirin are not significantly different to OAC, especially in the elderly.[8–10]

In low-risk AF patients, 1 prospective randomized trial showed no difference between aspirin (150–200 mg daily; N = 426) and control for the primary endpoint of thromboembolism-related complications (cardiovascular death, symptomatic brain infarction, or transient ischemic attack), with a trend toward more major bleeding (and intracranial hemorrhage) in aspirin-treated patients.[11] In this trial, the Japanese AF trial, there were 27 primary endpoint events (3.1% per year; 95% CI, 2.1–4.6) in the aspirin group versus 23 (2.4% per year; 95% CI, 1.5–3.5) in the control group, and treatment with aspirin caused a nonsignificant trend for an increased risk of major bleeding (1.6%) (vs controls, 0.4%; $P = 0.101$).

Aspirin-clopidogrel combination therapy was compared to warfarin for stroke prevention in 1 trial, but this was stopped early due to a clear superiority of warfarin over aspirin-clopidogrel for stroke prevention.[12] When aspirin-clopidogrel was compared to aspirin alone in a trial of patients who had refused or were deemed inappropriate for warfarin,[13] there was a 28% reduction in ischemic stroke with aspirin-clopidogrel compared to aspirin alone. However, the risk of major bleeding with aspirin-clopidogrel was approximately 2% per year, which was >50% higher compared to aspirin alone, and broadly comparable to major bleeding rates seen with OAC.

As the patient gets older, the absolute beneficial effect of OAC increases, while the effect of aspirin declines markedly.[14] Of note, the risk of stroke (and vascular events) rises with increasing age, from age 65 years upward, but serious bleeding only showed a small rise with increasing age, with no marked difference between OAC and aspirin.

What Are the Risk Factors for Thromboembolism?

Whereas it is recognized that AF increases the risk of stroke and thromboembolism by 5-fold, we do increasingly appreciate that that this risk is not homogeneous and is altered by the presence of various stroke risk factors. Also, the risk profile changes over time. For example, in a 12-year follow-up study of patients with newly-diagnosed carefully-defined lone AF patients, the annual rate of thromboembolism and heart failure during follow-up was low (0.4% each), and 5 patients (1.4%) died; however, multivariate predictors of adverse outcomes, including thromboembolism, were arrhythmia progression (ie, from paroxysmal to permanent AF), development of cardiac diseases, and older age (all $P < 0.05$).[15]

Two comprehensive systematic reviews from the Stroke in AF Working Group and the UK National Institute for Health and Clinical Evidence (NICE) guidelines have summarized the published evidence for various risk factors on stroke, largely based on nonwarfarin arms of clinical trials and a few epidemiological cohorts.[16,17] These risk factors have been used to formulate stroke risk stratification schemes, such as the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or transient ischemic attack [doubled]) score,[18] as discussed further below.

These risk factors have been use to formulate and (perhaps artificially) categorize AF patients into low, moderate/intermediate, and high risk strata, so that the "high risk" subjects could at least be targeted for anticoagulation therapy with warfarin, which is an "inconvenient" (and sometimes dangerous) drug.

What are the common stroke risk factors in AF populations? The Stroke in AF Working Group analysis[16] identified previous stroke/transient ischemic attack (TIA) (adjusted relative risk [RR] 2.5), age (RR 1.5/decade), hypertension (RR 2.0), diabetes (RR 1.8), and female gender (RR 1.6) as risk factors. Interestingly, history of heart failure was not a significant risk factor, but moderate-systolic left ventricular dysfunction is still an independent predictor of thromboembolism. The NICE guideline systematic review[17] identified history of stroke or TIA, increasing age (from age 65 years upward), hypertension, and structural heart disease (left-ventricular dysfunction or hypertrophy) to be good predictors of stroke risk in AF patients. In this NICE review, the evidence regarding diabetes mellitus, gender, and other patient characteristics as stroke risk factors in AF was less consistent.

It is worth remembering that in many of the older trial datasets (and many of these trials only randomised <10% of AF patients who were screened), some common stroke risk factors have not been systematically looked for and/or recorded, and unsurprisingly, there are many inconsistencies in definition in the various different published studies. In addition, large epidemiological and cohort studies have provided much additional information on common stroke risk factors in everyday clinical practice,

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969

among AF populations, although some inconsistencies in definitions of stroke risk factors may still be evident.

In the Loire Valley AF Project, among nonanticoagulated AF patients with no $CHADS_2$ risk factors (N = 1035), the impact of age was clearly seen, because the stroke/thromboembolic event rate per 100 person-years was 0.23 (95% CI, 0.08–0.72), 2.05 (1.07–3.93), and 3.99 (2.63–6.06), in those aged <65, 65 to 74, and ≥ 75 years, respectively. In both univariate and multivariate analyses, heart failure, previous stroke, and vascular disease were significantly associated with increased risk of stroke/thromboembolism.[19]

In 1 recent nationwide cohort study from Taiwan, risk factors for ischemic stroke in AF patients on multivariate analysis were age (where stroke risk increased from age ≥65 years; odds ratio [OR] = 1.338 for age 65–74 years vs age 20–64 years, $P = 0.014$; OR = 1.652 for age ≥75 years vs age <65 years, $P < 0.001$), hypertension (OR = 2.656, $P < 0.001$), diabetes mellitus (OR = 1.341, $P = 0.005$), heart failure (OR = 1.611, $P < 0.001$), previous ischemic stroke or TIA (OR = 2.752, $P < 0.001$), and peripheral arterial disease (PAD) (OR = 1.814, $P = 0.006$).[20]

In another Danish nationwide cohort study, the presence of vascular disease also increased the risk of thromboembolism significantly at 5 and 10 years of follow-up, with hazard ratios (HRs) of 2.04 and 2.22, respectively.[21] In an epidemiological cohort, the Danish Diet, Cancer and Health (DCH) study, vascular disease (prior myocardial infarction [MI] and PAD) was an independent risk factor for the primary endpoint of "stroke or death" in patients with AF, even after adjustment for the commonly used $CHADS_2$ risk score.[22] There is no doubt that vascular disease is an important consideration in the risk assessment of stroke and cardiovascular events in AF patients.[23]

What Are the Different Scoring Systems for Stroke Prediction, How Do They Compare, and What Should We Use Now?

The $CHADS_2$ score[17] is the most commonly used and validated risk score for stroke in AF; this simple score was derived by amalgamation of the AF Investigators and SPAF-1 risk schema (both trial-based risk stratification schema, with the limitations associated with historical trial datasets mentioned above). The pros and cons of the $CHADS_2$ score have been recently discussed, particularly its noninclusion of many common stroke risk factors.[24] A recent systematic review and metaanalysis on validation of the CHADS2 clinical prediction rule to predict ischaemic stroke concluded that the pooled c statistic and calibration analysis suggested minimal clinical utility of the CHADS2 in predicting ischaemic stroke across all risk strata in AF.[25] The authors even suggested that further validation of CHADS2 should perhaps be undertaken.

For example, stroke risk in AF rises from age 65 years upward, and does increase stroke by 1.5-fold per decade,[15] as illustrated by other analyses described above. Thus, the age criterion in the $CHADS_2$ score needed to be re-examined, and given that age is a powerful driver for stroke (and mortality) in AF, extra weight was needed for the older subject (eg, age ≥75 years), who was likely to benefit more from OAC, given that aspirin is no safer than OAC and inferior to OAC for stroke prevention.[7,26]

Also, vascular disease is a risk factor for stroke, with AF patients with PAD being at very high risk for stroke and death.[20–22] As discussed above, OAC has a significant impact on reducing stroke and all-cause mortality in AF patients, compared to placebo or control.[4] In the Loire Valley AF Project, vascular disease significantly improved the predictive ability of the $CHADS_2$ score (net reclassification improvement [NRI] 0.40, integrated discrimination improvement [IDI] 0.031).[19] Female gender has also been associated with a higher risk of stroke in some studies,[27] but many of these studies have included much older female subjects, and clearly, young female subjects (eg, age <65 years) with lone AF would be considered at low risk.

To complement the $CHADS_2$ score, the new European Society of Cardiology guidelines[28] have deemphasized the low, moderate, and high risk stratification, given the poor predictive value of such artificial strata, and more emphasis was put on a risk factor–based approach. For example, in the 12-year follow-up analysis of lone AF (discussed above), the baseline $CHADS_2$ score was not predictive for thromboembolism (c-statistic 0.50; 95% CI, 0.31–0.69).[14]

After all, any stroke risk factor when present with AF causes a stroke, and with the improved knowledge on how to "handle" warfarin (ie, much lower risk of bleeding and improved stroke reduction with well-controlled warfarin, as reflected by high time in therapeutic range) and the imminent arrival (and regulatory approval) of new oral anticoagulant drugs, such as the oral direct thrombin inhibitors and oral Factor Xa inhibitors, the emphasis should focus instead on identifying 'truly low risk' patients with AF who do not even need any antithrombotic therapy, whilst those with one or more stroke risk factors can be considered for oral anticoagulation therapy.[24]

Thus, the European Society of Cardiology (ESC) guidelines recommended use of the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years [double points], Diabetes mellitus, previous thromboembolism [double points], Vascular disease, Age 65–74 years, and female gender) score (see Table 1) to complement the initial assessment with the $CHADS_2$ score.[28] The CHA_2DS_2-VASc score includes more of the common stroke risk factors seen in everyday clinical practice.

Given that guidelines should be applicable for >80% of the time, for >80% of the patients, the stroke risk assessment approach in the ESC guideline is applicable to most of the patients we commonly seen in everyday clinical practice, and considers the common stroke risk factors in such patients. The ESC guidelines do stress that antithrombotic therapy is necessary in all patients with AF unless they are age <65 and truly low risk. Indeed, some AF patients with 'female gender' only as a single risk factor (thus, still CHA2DS2-VASc score of 1) do not need anticoagulation, especially if they fulfil the criteria of "age <65 and lone AF, so very low risk of stroke".

The first derivation and validation of the CHA_2DS_2-VASc score was performed in an European cohort from the EuroHeart survey on AF,[29] to provide European data for the European guideline. This initial analysis had various

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969

Table 1. Assessment of Stroke (CHA_2DS_2-VASc) and Bleeding Risk (HAS-BLED) in Atrial Fibrillation Patients[28]

CHA_2DS_2-VASc[a]	Score	HAS-BLED[b]	Score
Congestive heart failure	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function (1 point each)	1 or 2
Age ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/ predisposition	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Elderly (eg, age >65 years)	1
Age 65–74 years	1	Drugs or alcohol (1 point each)	1 or 2
Sex category (ie, female gender)	1		
Maximum score	9	Maximum score	9

Abbreviations: CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (double points), Diabetes mellitus, previous thromboembolism (double points), Vascular disease, age 65–74 years, and female gender; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolic; TIA, transient ischemic attack. [a]CHA_2DS_2-VASc score = 0: recommend no antithrombotic therapy; CHA_2DS_2-VASc score = 1: recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy, but preferably oral anticoagulation; CHA_2DS_2-VASc score ≥2: recommend oral anticoagulation. [b]HAS-BLED score ≥3: indicates that caution is warranted when predicting oral anticoagulation and regular review is recommended.

limitations (including a proportion of patients lost to follow-up), but other validations of the CHA_2DS_2-VASc score have since been published.

In a nationwide Danish cohort study of 73,538 hospitalized nonanticoagulated patients with AF in Denmark reported that in "low risk" subjects (CHA_2DS_2-VASc score = 0), the 1-year rate of thromboembolism per 100 person-years was 0.78 (0.58–1.04), in contrast to an event rate with the $CHADS_2$ score of 1.67 (95% CI, 1.47–1.89).[21] The c-statistics (a statistical measure of the predictive value of a risk score) with the CHA_2DS_2-VASc score clearly outperform the $CHADS_2$ at 1, 5, and 10 years of follow-up (see Table 2).

These c-statistic data are consistent with another recent study investigating how AF burden improved clinical stroke risk assessment, which reported that the c-statistics of the $CHADS_2$ and CHA_2DS_2-VASc for predicting thromboembolism were 0.653 (95% CI, 0.50–0.81) and 0.898 (95% CI, 0.84–0.96), respectively, and that the c-statistic for the $CHADS_2$ score could be improved by the addition of AF burden data.[30]

A further large validation study was performed in a United Kingdom cohort of 79,884 AF patients aged ≥18 years in the UK General Practice Research Database, who were followed for an average of 4 years.[31] Again, low-risk subjects (CHA_2DS_2-VASc score = 0) were truly low risk (with annual stroke events <0.5%) with the CHA_2DS_2-VASc score.

In an analysis of the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trial population, an anticoagulated AF cohort (N = 7329 subjects),[32] the CHA_2DS_2-VASc scheme correctly identified the greatest proportion of AF patients at high risk, and the negative predictive value (ie, the percent categorized as "not high risk" actually being free from thromboembolism) for CHA_2DS_2-VASc was 99.5%. Finally, Poli et al[33] also reported a "real world" of 662 consecutive elderly anticoagulated AF patients, in which the $CHADS_2$ and CHA_2DS_2-VASc schemes had the best c-statistics (0.717 and 0.724, respectively).

Notwithstanding the above comments, all the published stroke risk scores (including $CHADS_2$ and CHA_2DS_2-VASc) are not very useful in the elderly, with only limited ability to predict the risk of stroke. Thus, the Birmingham Atrial Fibrillation in the Aged (BAFTA) Investigators recently concluded that given the systematic undertreatment of older people with anticoagulation, and the relative safety of warfarin versus aspirin in the elderly, there could be a pragmatic rationale for classifying all patients over 75 years of age as "high risk" until better tools are available.[34]

In summary, the CHA_2DS_2-VASc score clearly outperforms the $CHADS_2$ in identifying the "truly low risk" subjects with AF, and is at least as good as—and possibly better than—the $CHADS_2$ score in predicting the "high risk" subjects.

Do We Need to Take the Risk of Bleeding into Account, and How Is This Quantified?

Risk factors for bleeding on OAC have been identified from general anticoagulated cohorts, but few bleeding risk assessment tools have been derived and validated in AF populations.[35]

In the NICE guidelines systematic review, the following patient characteristics were identified as having supporting evidence for being risk factors for anticoagulation-related bleeding complications: advanced age; uncontrolled hypertension; history of myocardial infarction or ischemic heart disease; cerebrovascular disease, anemia, or a history of bleeding; and the concomitant use of other drugs such as antiplatelet agents.[36] The presence of diabetes mellitus, controlled hypertension, and gender were not identified as significant risk factors for bleeding.

Many risk factors for anticoagulation-related bleeding are also risk factors for stroke in AF patients. Older bleeding risk tools were also complicated and difficult to use in everyday clinical practice.[37] Thus, many prior guidelines have avoided formal recommendation of bleeding risk assessment using a specific bleeding risk score in AF patients.

More recently, the ESC guidelines[28] and Canadian guidelines[38] have recommended that bleeding risk assessment be done, and the simple HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969

Table 2. Event Rates and c-Statistics Comparing the $CHADS_2$ and CHA_2DS_2-VASc Scores at 1-, 5-, and 10-Year Follow-up[a]

Scale	Event Rates per 100 Person-Years			c-Statistic (95% CI)[b]
	Low Risk (Score 0)	Intermediate Risk (Score 1)	High Risk (Score >1)	
At 1 year				
$CHADS_2$	1.7	4.8	12	0.72 (0.69–0.75)
CHA_2DS_2-VASc	0.78	2.0	8.8	0.85 (0.83–0.87)
At 5 years				
$CHADS_2$	1.3	3.7	8.3	0.80 (0.78–0.81)
CHA_2DS_2-VASc	0.69	1.5	6.0	0.88 (0.87–0.89)
At 10 years				
$CHADS_2$	1.2	3.6	8.0	0.81 (0.80–0.83)
CHA_2DS_2-VASc	0.66	1.5	5.7	0.89 (0.88–0.90)

Abbreviations: $CHADS_2$, Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, and previous thromboembolism (double points); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age $\geq$75 years (double points), Diabetes mellitus, previous thromboembolism (double points), Vascular disease, age 65–74 years, and female gender; CI, confidence interval. [a]From Olesen et al.[21] [b]Based on Cox regression models using 3 risk groups and with covariates analyzed as categorical variables.

predisposition, Labile international normalized ratio [INR], Elderly, Drugs/alcohol concomitantly) score should be used.

The HAS-BLED score (see Table 1) was initially derived and validated in an AF population (N = 3978) from the EuroHeart survey, in which the predictive accuracy in the overall population (c-statistic 0.72) was consistent when applied in several subgroups.[39] Also, application of HAS-BLED had c-statistics of 0.91 and 0.85, in patients receiving antiplatelet agents alone or no antithrombotic therapy, respectively.

The HAS-BLED score has also been validated in a clinical trial population, as well as in a nationwide cohort study. In the analysis from the SPORTIF trial dataset,[40] multivariate analyses demonstrated that significant predictors of bleeding were concurrent aspirin use (HR 2.10; 95% CI, 1.59–2.77; $P < 0.001$); renal impairment (HR 1.98; 95% CI, 1.42–2.76; $P < 0.001$); age $\geq$75 years (HR 1.63; 95% CI, 1.23–2.17; $P = 0.0008$); diabetes (HR 1.47; 95% CI, 1.10–1.97; $P = 0.009$), and heart failure or left ventricular dysfunction (HR 1.32; 95% CI, 1.01–1.73; $P = 0.041$). Of the tested schemas, the new HAS-BLED score performed best, with a stepwise increase in rates of major bleeding with increasing HAS-BLED score (P-trend < 0.0001).

In the nationwide Danish cohort,[41] the c-statistics for the HAS-BLED and $HEMORR_2HAGES$ (Hepatic or renal failure, Ethanol abuse, Malignancy, Older [age >75 years], Reduced platelet count or function, 2 points for Rebleeding risk Hypertension [uncontrolled], Anemia, Genetic factors, Excessive fall risk [including neurodegenerative and psychiatric disorders] and history of Stroke) schemes were 0.795 (0.759–0.829) and 0.771 (0.733–0.806), respectively, with comparable results found in AF patients not receiving OAC. Thus, in this unselected nationwide cohort of hospitalized patients with AF, the HAS-BLED score performed similar to $HEMORR_2HAGES$ in predicting bleeding risk, but the HAS-BLED score is much simpler and easier to use in everyday clinical practice.

How should we use this bleeding risk score? In the ESC guidelines, a HAS-BLED score of $\geq$3 represents a sufficiently high risk such that caution and/or regular review of a patient is needed. It also makes the clinician think of correctable common bleeding risk factors; eg, improving blood pressure control and labile INRs would reduce points on the HAS-BLED score. The availability of such a score allows informed decisions when deciding whether to use a low-dose or high-dose regime of new OACs such as dabigatran.[28]

Bleeding risk is clearly multifactorial and apart from those with risk factors for bleeding, there are high-risk periods when OAC is initiated.[42] Given the importance of bleeding risk assessment and management in AF patients, the European Heart Rhythm Association recently published a position document, endorsed by the ESC Working Group on Thrombosis, with the objective of summarizing "best practice" when approaching antithrombotic therapy in AF patients.[44] This document addresses the epidemiology and size of the problem of bleeding risk in AF and reviews established bleeding risk factors. Patient values and preferences in balancing the risk of bleeding against thromboembolism are considered, and the prognostic implications of bleeding are discussed. The document also reviews bleeding risk stratification and currently published bleeding risk schema.

Conclusion

How should we approach stroke risk assessment in AF? By being more inclusive, rather than exclusive, of common stroke risk factors in AF, we can clearly do much better in reducing stroke and mortality in AF, which are the 2 main endpoints that are significantly reduced by oral anticoagulation, compared to placebo/control. Indeed, those categorized as "low risk" using CHA_2DS_2-VASc as

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969

recommended in the ESC guidelines were "truly low risk" for thromboembolism, and the CHA_2DS_2-VASc scheme performs as good as—and possibly better than—the $CHADS_2$ score in predicting those at "high risk."

The availability of the new OAC offers exciting new possibilities[43] so that once we identify the "truly low risk" patients (eg, CHA_2DS_2-VASc score = 0), OAC is recommended or preferred for AF patients with ≥1 stroke risk factors (CHA_2DS_2- VASc ≥1).[45]

Risk assessment must also consider bleeding risk when initiating OAC therapy. Thus, the HAS-BLED score is simple and is recommended as an informed assessment of bleeding risk in AF patients when antithrombotic therapy is being initiated.

References

1. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2011;123:1501–1508.
2. Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled 'Research Perspectives in Atrial Fibrillation'. *Europace.* 2009;11:860–885.
3. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet.* 2009;373:155–166.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857–867.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71–86. [Erratum in: *BMJ.* 2002;324:141.]
6. Soejima H, Morimoto T, Saito Y, et al. Aspirin for the primary prevention of cardiovascular events in patients with peripheral artery disease or diabetes mellitus. Analyses from the JPAD, POPADAD and AAA trials. *Thromb Haemost.* 2010;104:1085–1088.
7. Stroke Prevention in Atrial Fibrillation Investigators. A differential effect of aspirin in prevention of stroke on atrial fibrillation. *J Stroke Cerebrovasc Dis.* 1993;3:181–188.
8. Mant J, Hobbs FDR, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in atrial fibrillation in the elderly community population: the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), a randomised controlled trial. *Lancet.* 2007;370:493–503.
9. Rash A, Downes T, Portner R, et al. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing.* 2007;36:151–156.
10. Connolly S, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364:806–817.
11. Sato H, Ishikawa K, Kitabatake A, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. *Stroke.* 2006;37:447–451.
12. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet.* 2006;367:1903–1912.
13. ACTIVE Investigators, Connolly SJ, Pogue J, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med.* 2009;360:2066–2078.
14. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the Atrial Fibrillation Investigators. *Stroke.* 2009;40:1410–1416.
15. Potpara TS, Stankovic GR, Beleslin BD, et al. A 12-year follow-up study of patients with newly-diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation Study. *Chest.* (in press).
16. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology.* 2007;69:546–554.
17. Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost.* 2008;99:295–304.
18. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. *JAMA.* 2001;285:2864–2870.
19. Olesen JB, Fauchier L, Lane DA, et al. Risk factors for stroke and thromboembolism in relation to age amongst patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest.* (in press).
20. Lin LY, Lee CH, Yu CC, et al. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation—a nationwide database analysis. *Atherosclerosis.* 2011;217:292–295.
21. Olesen J, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: a nationwide cohort study. *BMJ.* 2011;342:d124.
22. Rasmussen LH, Larsen TB, Due KM, et al. Impact of vascular disease in predicting stroke, and death in patients with atrial fibrillation: the Danish Diet, Cancer and Health (DCH) cohort study. *J Thromb Haemost.* 2011;9:1301–1307.
23. Depta JP, Bhatt DL. Atherothrombosis and atrial fibrillation: important and often overlapping clinical syndromes. *Thromb Haemost.* 2010;104:657–663.
24. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation—friend or foe? *Thromb Haemost.* 2010;104:45–48.
25. Keogh C, Wallace E, Dillon C, Dimitrov BD, Fahey T. Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke. A systematic review and meta-analysis. *Thromb Haemost.* 2011 Aug 31;106(3):528–38. Epub 2011 Jul 28. PubMed PMID: 21800003.
26. Gorin L, Fauchier L, Nonin E, et al. Antithrombotic treatment and the risk of death and stroke in patients with atrial fibrillation and a CHADS2 score = 1. *Thromb Haemost.* 2010;103:833–840.
27. Lane DA, Lip GY. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. *Thromb Haemost.* 2009;101:802–805. [Erratum in: *Thromb Haemost.* 2010;104:653.]
28. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31:2369–2429.
29. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest.* 2010;137:263–272.
30. Boriani G, Botto G, Padeletti L, et al. Improving stroke risk stratification using the $CHADS_2$ and CHA_2DS_2-VASc risk scores in paroxysmal atrial fibrillation patients by continuous arrhythmia burden monitoring. *Stroke.* 2011;42:1768–1770.
31. Van Staa TP, Setakis E, Di Tanna GL, et al. A comparison of risk stratification schema for stroke in 79884 atrial fibrillation patients in general practice. *J Thromb Haemost.* 2011;9:39–48.
32. Lip GY, Frison L, Halperin JL, et al. Identifying patients at high risk for stroke despite anticoagulation. A comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke.* 2010;41:2731–2738.
33. Poli D, Lip GY, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a "real-world" elderly anticoagulated atrial fibrillation population. *J Cardiovasc Electrophysiol.* 2011;22:25–30.
34. Hobbs FD, Roalfe AK, Lip GY, et al.; on behalf of the Birmingham Atrial Fibrillation in the Aged (BAFTA) investigators and Midland Research Practices Consortium (MidReC) network. Performance of stroke risk scores in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial. *BMJ.* 2011;342:d3653.
35. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969

from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace.* 2011;13:723–746.
36. Hughes M, Lip GY; Guideline Development Group for the NICE National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM.* 2007;100:599–607.
37. Palareti G, Cosmi B. Bleeding with anticoagulation therapy—who is at risk, and how best to identify such patients. *Thromb Haemost.* 2009;102:268–278.
38. Cairns JA, Connolly S, McMurtry S, et al.; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol.* 2011;27:74–90.
39. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138:1093–1100.
40. Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol.* 2011;57:173–180.
41. Olesen JB, Lip GY, Hansen PR, et al. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. *J Thromb Haemost.* 2011;9:1460–1467.
42. Garcia DA, Lopes RD, Hylek EM. New-onset atrial fibrillation and warfarin initiation: high risk periods and implications for new antithrombotic drugs. *Thromb Haemost.* 2010;104:1099–1105.
43. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof P; Document reviewers:, Collet JP, Rubboli A, Poli D, Camm J. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace.* 2011 May;13(5):723–46.
44. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost.* 2010;104:49–60.
45. Lip GY. Anticoagulation therapy and the risk of stroke in patients with atrial fibrillation at 'moderate risk' [CHADS2 score = 1]: simplifying stroke risk assessment and thromboprophylaxis in real-life clinical practice. *Thromb Haemost.* 2010;103:683–685.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20969