European Heart Journal (2013) **34**, 170–176
doi:10.1093/eurheartj/ehs314

The CHA_2DS_2-VASc score identifies those patients with atrial fibrillation and a $CHADS_2$ score of 1 who are unlikely to benefit from oral anticoagulant therapy

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Received 29 February 2012; revised 1 August 2012; accepted 6 September 2012; online publish-ahead-of-print 27 September 2012

See page 168 for the editorial comment on this article (doi:10.1093/eurheartj/ehs378)

Aims The CHA_2DS_2-VASc score is a modification of the $CHADS_2$ score that aims to improve stroke risk prediction in patients with atrial fibrillation (AF) by adding three risk factors: age 65–74, female sex, and history of vascular disease. Whereas previous evaluations of the CHA_2DS_2-VASc score included all AF patients, the aim of this analysis was to evaluate its discriminative ability only in those patients for whom recommendations on antithrombotic treatment are uncertain (i.e. $CHADS_2$ score of 1).

Methods and results We selected all patients with a $CHADS_2$ score of 1 from the AVERROES and ACTIVE trials who were treated with acetylsalicylic acid with or without clopidogrel and calculated the incidences of ischaemic or unspecified stroke or systemic embolus (SSE) according to their CHA_2DS_2-VASc score. Of 4670 patients with a baseline $CHADS_2$ score of 1, 26% had a CHA_2DS_2-VASc score of 1 and 74% had a score of $\geq$2. After 11 414 patient-years of follow-up, the annual incidence of SSE was 0.9% (95% CI: 0.6–1.3) and 2.1% (95% CI: 1.8–2.5) for patients with a CHA_2DS_2-VASc score of 1 and $\geq$2, respectively. The c-statistic of the CHA_2DS_2-VASc score was 0.587 (95% CI: 0.550–0.624). Age 65 to <75 years was the strongest of the three new risk factors in the CHA_2DS_2-VASc score.

Conclusion The CHA_2DS_2-VASc score reclassifies 26% of patients with a $CHADS_2$ score of 1 to a low annual risk of SSE of 1%. This risk seems low enough to consider withholding anticoagulant treatment.

Keywords Atrial fibrillation • Antithrombotic treatment • Stroke risk score

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that increases the risk of stroke five-fold.[1] Dose-adjusted vitamin K antagonists (VKAs) and acetylsalicylic acid (ASA) reduce the risk of stroke by 64 and 19%, respectively.[2] Although VKA therapy is more effective than ASA at preventing ischaemic stroke, its benefit is offset by an increased haemorrhage risk.[2] Therefore, the key to deciding to initiate VKA therapy requires identifying those patients in whom the risk of ischaemic stroke without anticoagulants is sufficiently high to outweigh the increased risks of intracranial and major extracranial haemorrhage associated with VKA therapy. Several stroke risk stratification schemes have been proposed for patients with AF.[3] Of these, the $CHADS_2$ score is most widely used as it does not require costly additional tests, is easily applied and remembered by physicians, and has been validated to provide significant risk discrimination.[3] The $CHADS_2$ score assigns 1 point for heart failure, hypertension, age $\geq$75 years, and diabetes mellitus and 2 points for prior stroke or transient ischaemic attack. All guidelines recommend

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that patients with a $CHADS_2$ score of 2 or higher should be treated with VKA therapy because the risk of ischaemic stroke outweighs the increased risk of bleeding induced by VKA therapy.[4–6] However, guidelines are less firm in their recommendations concerning patients with a $CHADS_2$ score of 1, reflecting uncertainty about the benefits of VKA therapy in this population.[4–6]

The CHA_2DS_2-VASc score has been proposed as an improvement to the $CHADS_2$ score specifically for risk discrimination of lower risk patients.[7] Compared with the $CHADS_2$ score, the CHA_2DS_2-VASc score includes three additional risk factors for ischaemic stroke: age 65–74 years, female sex, and vascular disease, the latter defined as previous myocardial infarction or peripheral arterial disease.[7] The CHA_2DS_2-VASc score has been validated in several cohorts of patients with AF and was shown to provide a modest, but significant discrimination of stroke risk.[7–10] However, as most of the patients in those validation cohorts had a $CHADS_2$ score of 2 or higher, treatment recommendations were unchanged irrespective of the CHA_2DS_2-VASc score. The important unresolved issue is whether the CHA_2DS_2-VASc score improves risk discrimination in patients in whom it is unclear if treatment with anticoagulants is beneficial (i.e. those with a $CHADS_2$ score of 1). Furthermore, in some of the previous validation cohorts, patients were receiving anticoagulant therapy with a VKA.[7,8] This is problematic because risk discrimination in patients already receiving a VKA is not relevant to the decision whether or not to treat with a VKA. So it is ideal to validate a risk score for stroke in patients treated with no therapy or, more practically, with antiplatelet therapy because it is deemed unethical to withhold all antithrombotic therapies from patients with AF who have an additional risk factor for stroke.

The aim of the present study was to determine the ability of the CHA_2DS_2-VASc score to discriminate stroke risk in AF patients with a $CHADS_2$ score of 1 and thereby identify those patients for whom anticoagulant therapy may not be of benefit.

Methods

Patients

For the present analyses, we selected patients with AF and a $CHADS_2$ score of 1, who were treated either with ASA only or with ASA and clopidogrel from three previously published trials: AVERROES, ACTIVE-W, and ACTIVE-A.[11–13] The AVERROES trial (Apixaban vs. Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) was designed to determine the efficacy and safety of apixaban compared with ASA for the treatment of patients with AF for whom VKA therapy was considered unsuitable.[11] The ACTIVE trials (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) were initiated to evaluate the role of clopidogrel plus ASA for the prevention of stroke and other vascular events in patients with AF. The ACTIVE-W trial compared clopidogrel plus ASA with VKA therapy, and the ACTIVE-A trial compared clopidogrel plus ASA with ASA alone in patients for whom therapy with a VKA was considered unsuitable.[12,13]

The inclusion criteria for the AVERROES and ACTIVE trials were similar and are described in detail elsewhere.[11–13] In short, patients were eligible if they had documented AF (in the 6 months before enrolment or at baseline) and one of the following risk factors for stroke: prior stroke or transient ischaemic attack, an age of 75 years or older, hypertension, diabetes mellitus, documented peripheral arterial disease, or a left ventricle ejection fraction (LVEF) of 35–45% or less. Patients with congestive heart failure (New York Heart Association class 2 or higher) and a LVEF $>$ 45% were eligible for the AVERROES trials, but not for the ACTIVE trial. Patients with non-central nervous system (CNS) systemic emboli, or with coronary artery disease (CAD) and an age of 55–74 years as the only risk factor for stroke were eligible for the ACTIVE trials, but not for the AVERROES trial.

Key exclusion criteria for the three trials were an indication for VKAs other than AF (e.g. mechanical heart valves), or an indication for clopidogrel (ACTIVE trials only, e.g. recent coronary artery stents), valvular disease requiring surgery, or a high risk of bleeding (defined slightly different between the AVERROES and ACTIVE trials, but including active peptic ulcer disease or serious bleeding in the preceding 6 months, a history of intracranial haemorrhage, ongoing alcohol or drug abuse, thrombocytopenia of $<$50–100 $\times$ 10^9/L, or known documented haemorrhagic tendencies). The AVERROES trial also excluded patients with severe renal failure or liver transaminases levels greater than two times the upper limit of normal.

The daily dose of ASA in the ACTIVE and AVERROES trials ranged from 75 to 324 mg. Clopidogrel was given at a fixed dose of 75 mg once daily in the ACTIVE trials.

The AVERROES and ACTIVE trials complied with the Declaration of Helsinki. The study protocols were approved by institutional ethics boards and all participants provided written informed consent.

Outcomes and statistical analysis

The outcome of this analysis was the composite of ischaemic or non-specified stroke and non-CNS systemic embolus. Stroke was a clinical diagnosis that was made on the basis of typical symptoms lasting at least 24 h. Brain imaging, which was available in the vast majority of patients, was not required but was recommended for the general diagnosis of stroke. In the three trials, strokes were sub-classified into those that were ischaemic, primary haemorrhagic, or of uncertain type. In this analysis, primary haemorrhagic stroke was disregarded because the focus was on the prediction of ischaemic stroke. Non-CNS systemic embolus was defined as an acute loss of blood flow to a peripheral artery supported by evidence of embolism from surgical specimens, angiography, or other objective testing. All study outcomes were adjudicated by adjudication committees blinded to assigned treatments. Information on documented cardiovascular events prior to enrolment in the study was collected at the beginning of the study.

The CHA_2DS_2-VASc score was calculated with the relevant variables collected at baseline. No information on prior CAD or myocardial infarction was collected for patients in the AVERROES trial. Proportions of participants with CHA_2DS_2-VASc scores of 1, 2, 3, and 4 were calculated. Incidence rates were calculated by dividing the number of events by the number of patient-years of follow-up. The time to first event was time from enrolment until earliest occurrence of ischaemic or non-specified stroke or non-CNS systemic embolus. Patients were censored at either death, loss to follow-up, or end of study, whichever occurred first. Incidence rates were calculated for patients with CHA_2DS_2-VASc scores of 1, 2, 3, 4, and 2–4. Incidence rates were calculated for all patients (i.e. patients treated either with ASA only or with combined ASA and clopidogrel) and for patients treated with ASA only. Kaplan–Meier cumulative hazard rates over time were plotted for all patients and patients with the CHA_2DS_2-VASc scores of 1 and 2–4. Cox proportional hazard

regression models were used to assess the relative increase in hazard associated with the CHA_2DS_2-VASc scores of 2, 3, or 4, and 2–4 vs. 1.

The ability of the CHA_2DS_2-VASc score to discriminate between high and low risk patients was assessed with the Harrell's c-statistic and net reclassification improvement (NRI) for time-to-event data as described by Pencina and colleagues.[14–16] In calculation of the NRI, Kaplan–Meier estimates of 1-year risk were used. Patients with a CHA_2DS_2-VASc score of 1 were regarded as 'reclassified down', and patients with a CHA_2DS_2-VASc score of 2–4 were regarded as 'reclassified up'. The 95% confidence interval (CI) limits for NRI were the 2.5th and 97.5th percentiles obtained with 1000 bootstrap samples.

In order to assess the relative contributions of the new CHA_2DS_2-VASc risk factors (i.e. age category 65 to <75 years, the extra point for age over 75 years, peripheral arterial disease or prior myocardial infarction, and female sex), univariate Cox regression models and a multivariate model to adjust the factors for each other were fitted. The analyses were done using Statistical Analysis Software, version 9.2 of the SAS System for SunOS (SAS Institute Inc., Cary, NC, USA).

Results

Of the 13 673 patients who were randomized to antiplatelet therapy in the three trials, 4670 had a $CHADS_2$ score of 1 and were used in the present analysis. Of those, 48% (2240 patients) was randomized to receive ASA only, and 52% (2430 patients) was randomized to receive the combined ASA and clopidogrel treatment. Mean follow-up time was 2.5 years [standard deviation (SD) 1.4 years]. Patients from the two ACTIVE trials had a longer follow-up time than patients from the AVERROES trial [means of 2.9 years (SD 1.4 years) and 1.1 years (0.5 years), respectively]. Baseline characteristics are shown in *Table 1*. A total of 1924 patients (41%) were younger than 65 years, 2241 patients (48%) were aged 65 to <75 years, and 505 patients (11%) were 75 years or older. Most patients had permanent AF (52%), 19% had persistent AF, and 28% had paroxysmal AF. Apart from age, hypertension was the most common risk factor for stroke (present in 79% of patients, *Table 1*).

Of the 4670 patients with a $CHADS_2$ score of 1, the CHA_2DS_2-VASc score was 1 in 26% of patients and 42%, 26%, and 3% of patients had CHA_2DS_2-VASc scores of 2, 3, and 4, respectively (*Table 2*).

Table 3 shows the incidence rates of the composite outcome of ischaemic or non-specified stroke or non-CNS systemic embolus. Of the 4670 patients with 11 414 patient-years, 205 patients had experienced an outcome event, amounting to an incidence of 1.8

Table 1 Baseline characteristics of patients with a $CHADS_2$ score of 1 treated with ASA only or with combined ASA and clopidogrel

Characteristic	All (*N* = 4670)	CHA_2DS_2-VASc score 0 or 1 (*N* = 1224)	CHA_2DS_2-VASc score ≥2 (*N* = 3446)
Mean age, years (SD)	65.5 (9.0)	56.5 (6.4)	68.9 (7.3)
Female sex, *n* (%)	1589 (34)	0 (0)	1589 (46)
Antiplatelet treatment, *n* (%)			
ASA	2240 (48)	602 (49)	1638 (48)
ASA and clopidogrel	2430 (52)	622 (51)	1808 (53)
Classification of atrial fibrillation, *n* (%)[a]			
Permanent	2439 (52)	567 (46)	1872 (54)
Paroxysmal	1324 (28)	374 (31)	950 (28)
Persistent	899 (19)	280 (23)	619 (18)
Presence of CHA_2DS_2-VASc variables, *n* (%)			
Heart failure	282 (6)	98 (8)	184 (5)
Hypertension, receiving treatment	3710 (79)	1063 (87)	2647 (77)
Age <65 years	1924 (41)	1224 (100)	700 (20)
Age 65 to <74 years	2241 (48)	0 (0)	2241 (65)
Age ≥75 years	505 (11)	0 (0)	505 (15)
Diabetes mellitus, receiving treatment	119 (3)	45 (4)	74 (2)
Peripheral arterial disease	88 (2)	0 (0)	88 (3)
Myocardial infarction[b]	337 (9)	0 (0)	337 (12)
Coronary artery disease[b]	646 (18)	43 (5)	603 (22)
Ischaemic stroke or transient ischaemic attack	0 (0)	0 (0)	0 (0)

ASA, acetyl salicylic acid; SD, standard deviation.
[a]Available for 4662 patients.
[b]Available only for 3658 patients from ACTIVE A and ACTIVE W.[12,13]

per 100 patient-years (95% CI: 1.6–2.1). Patients with a CHA_2DS_2-VASc score of 1 had an incidence rate of 0.9 per 100 patient-years (95% CI: 0.6–1.3) and patients with a CHA_2DS_2-VASc score of ≥2 had a more than two-fold increased rate of 2.1 per 100 patient-years (95% CI: 1.8–2.5; hazard ratio: 2.45, 95% CI: 1.66–3.75). The incidence rates in patients with CHA_2DS_2-VASc scores of 2 and 3 or 4 were 2.0 per 100 patient-years (95% CI: 1.6–2.4) and 2.4 per 100 patient-years (95% CI: 1.9–2.9), respectively (*Table 3*). The incidence for patients treated with ASA only was higher than for patients treated with ASA and clopidogrel combined (2.3 vs. 1.3 per 100 patient-years, *Table 4*). The relative risk increase with increasing CHA_2DS_2-VASc score was similar regardless of the type of antiplatelet treatment.

In this group of patients with a $CHADS_2$ score of 1 treated with ASA only or combined ASA and clopidogrel, the Harrell's c-statistic was 0.587 (95% CI: 0.550–0.624; *Table 3*). The NRI for 1-year risk prediction calculated assuming the patients with the CHA_2DS_2-VASc score of 1 were reclassified down and patients with a score of 2 or higher were reclassified up was 0.74 (95% CI: 0.58–0.88) for events and −0.47 (95% CI: −0.50 to −0.45) for non-events, leading to an overall NRI of 0.27 (95% CI: 0.11–0.41; *Table 3*). When regarded as a dichotomized risk score (CHA_2DS_2-VASc score of 1 is test-negative and 2–4 is test-positive), the positive likelihood ratio of the CHA_2DS_2-VASc score was 1.18 (95% CI: 1.08–1.28) and the negative likelihood ratio was 0.49 (95% CI: 0.23–0.79).

Figure 1 shows the Kaplan–Meier cumulative hazard curves for all patients, and for those with CHA_2DS_2-VASc scores of 1 and 2 or higher. The rates of stroke or non-CNS systemic embolus are fairly constant over the first 5 years (*Figure 1*).

Table 5 shows the hazard ratios for the three new risk factors that are introduced by the CHA_2DS_2-VASc score. Age 65 to <74 years and age ≥75 years were associated with a two-fold increased risk of the composite outcome. Female sex was a weaker risk factor (adjusted hazard ratio: 1.32) and a personal history of peripheral arterial disease or myocardial infarction was not a risk factor in this cohort (hazard ratio: 0.97).

Table 2 Distribution of the CHA_2DS_2-VASc score in patients with a $CHADS_2$ score of 1

CHA_2DS_2-VASc score	*N* (%)
All	4670 (100)
1	1224 (26)
2	1984 (42)
3	1338 (29)
4	124 (3)

Discussion

This is the first study to show that in patients with AF in whom there is a real clinical question about the decision to anticoagulate, the CHA_2DS_2-VASc score adds potentially valuable information. Previous evaluations of the CHA_2DS_2-VASc score have studied AF patients across the whole range of stroke risk and have thereby included many patients in whom there is no real potential for improved risk stratification because they will anyway benefit from anticoagulation (i.e. $CHADS_2$ score ≥2).[7–10] Unlike most previous analyses, all patients in this cohort had a $CHADS_2$ score of 1 and were treated only with antiplatelet therapy. The results show that the CHA_2DS_2-VASc score separates a very low risk group (i.e. 1% per year stroke risk) from the other patients. The very low risk patients with a CHA_2DS_2-VASc score of 1 were men aged <65 years with either hypertension (87%), heart failure (8%), or diabetes mellitus (4%). Given the risks of bleeding associated with VKA treatment and the 1% per year

Table 3 Incidence rates of ischaemic or unspecified stroke or systemic non-CNS embolus in patients with a $CHADS_2$ score of 1, treated with ASA only or combined ASA and clopidogrel

	Number of events[a]/patients	Patient-years of follow-up	Incidence rate, per 100 patient-years	Hazard ratio (95%CI)[b]	Harrell's c-statistic (95%CI)[c]	NRI (95% CI)[d]
All	205/4670	11414	1.8 (1.6–2.1)			
CHA_2DS_2-VASc						
1	27/1224	3074	0.9 (0.6–1.3)	1	0.587 (0.550–0.624)	
2	92/1984	4729	2.0 (1.6–2.4)	2.2 (1.5–3.5)		
3–4	86/1462	3610	2.4 (1.9–2.9)	2.7 (1.8–4.3)		
1	27/1224	3074	0.9 (0.6–1.3)	1	0.567 (0.541–0.592)	0.27 (0.11–0.41)
2–4	178/3446	8340	2.1 (1.8–2.5)	2.5 (1.7–3.8)		

ASA, acetylsalicylic acid; CI, confidence interval; NRI, net reclassification improvement.
[a]An event is the first occurrence of ischaemic or unspecified stroke or non-CNS systemic embolus. Time to event is the time between randomization and event first occurrence.
[b]Cox proportional hazards regression model. 95% CI limits for hazard ratio are profile likelihood limits.
[c]Harrell's c-statistic and its 95% CI were estimated using the SAS macro %survcstd.[15]
[d]NRI for time-to-event data using Kaplan–Meier estimated of 1-year risk.[16] Patients with a CHA_2DS_2-VASc score of 1 were regarded as 'reclassified down' and patients with a score of ≥2 were regarded as 'reclassified down'. The 95% CI limits for NRI were the 2.5th and 97.5th percentiles obtained with 1000 bootstrap samples.

Table 4 Incidence rates of ischaemic or unspecified stroke or systemic non-CNS embolus according to type of antiplatelet treatment

	Number of events[a]/patients	Patient-years of follow-up	Incidence rate, per 100 patient-years	Hazard ratio (95%CI)[b]
Combined ASA and clopidogrel				
All	79/2430	5950	1.3 (1.1–1.7)	
CHA_2DS_2-VASc				
1	11/622	1609	0.7 (0.3–1.2)	1
2	38/1020	2421	1.6 (1.1–2.2)	2.4 (1.2–4.8)
3–4	30/788	1921	1.6 (1.1–2.2)	2.3 (1.2–4.8)
1	11/622	1609	0.7 (0.3–1.2)	1
2–4	68/1808	4341	1.6 (1.2–2.0)	2.3 (1.3–4.6)
ASA only				
All	126/2240	5463	2.3 (1.9–2.8)	
CHA_2DS_2-VASc				
1	16/602	1465	1.1 (0.6–1.8)	1
2	54/964	2309	2.3 (1.8–3.1)	2.2 (1.3–3.9)
3–4	56/674	1689	3.3 (2.5–4.3)	3.0 (1.8–5.5)
1	16/602	1465	1.1 (0.6–1.8)	1
2–4	110/1638	3998	2.8 (2.3–3.3)	2.5 (1.5–4.4)

ASA, acetylsalicylic acid; CI, confidence interval.
[a]An event is the first occurrence of ischaemic or unspecified stroke or non-CNS systemic embolus. Time to event is the time between randomization and event first occurrence.
[b]Cox proportional hazards regression model. 95% CI limits for hazard ratio are profile likelihood limits.

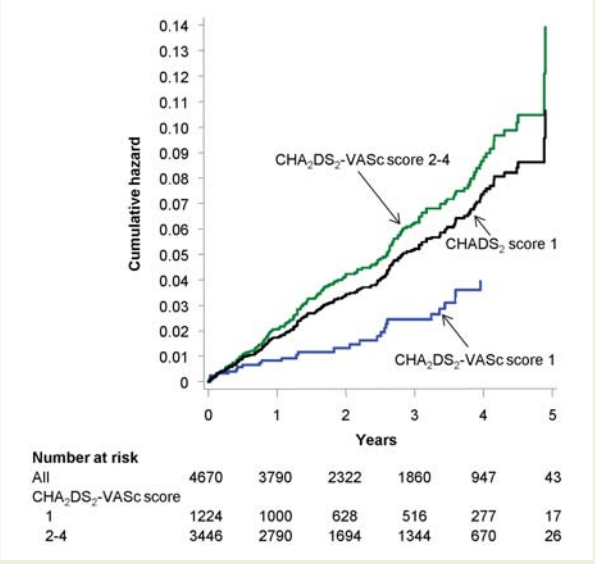

Figure 1 Kaplan–Meier cumulative hazard rates of the composite outcome of ischaemic or unspecified stroke and non-CNS systemic embolus in patients treated with acetylsalicylic acid (ASA) only or with combined ASA and clopidogrel. Black line represents all patients with a $CHADS_2$ score of 1; blue line represents patients with a CHA_2DS_2-VASc score of 1; green line represents patients with a CHA_2DS_2-VASc score of 2–4.

Table 5 Relative risk of the composite outcome of ischaemic or unspecified stroke and non-CNS systemic embolus associated with the additional risk factors introduced by the CHA_2DS_2-VASc score

Characteristic	Hazard ratio (95%CI)[a]	Adjusted hazard ratio (95%CI)[b]
Age		
<65 years	1	1
65 to <74 years	1.97 (1.44–2.74)	1.90 (1.38–2.64)
≥75 years	2.31 (1.47–3.58)	2.24 (1.42–3.48)
Previous peripheral arterial disease or myocardial infarction		
No	1	1
Yes	0.99 (0.66–1.42)	0.97 (0.65–1.41)
Sex		
Male	1	1
Female	1.45 (1.10–1.91)	1.32 (1.00–1.75)

CI, confidence interval.
[a]Univariate Cox proportional hazard models fitted to all patients with a $CHADS_2$ score of 1 treated with acetylsalicylic acid (ASA) only or with combined ASA and clopidogrel. 95% CI limits for hazard ratio are profile likelihood limits.
[b]Age, previous peripheral arterial disease or myocardial infarction, and sex were included in the multivariate Cox model.

stroke risk in patients with a CHA_2DS_2-VASc score of 1, we think it is unlikely that these patients will benefit from treatment with VKA therapy. This is partially in contrast with the 2010 guidelines of the European Society of Cardiology that recommends either ASA or oral anticoagulant therapy for patients with a CHA_2DS_2-VASc score of 1.[4]

Within this group of patients with a $CHADS_2$ score of 1, the CHA_2DS_2-VASc score significantly improves risk stratification. However, the improvement by the CHA_2DS_2-VASc score is modest, as expressed by the c-statistic of 0.587 (95% CI: 0.550–0.624). This is likely due to the selection of patients with a $CHADS_2$ score of 1 (all at moderate risk of stroke) and probably also due to the fact that the CHA_2DS_2-VASc shares four risk factors with the CHADS2 score. Despite the modest degree of the risk discrimination improvement, the clinical consequence of this reclassification is substantial. Whereas most guidelines suggest that oral anticoagulant therapy preferred in patients with a $CHADS_2$ score of 1, reclassification using the CHA_2DS_2-VASc score means that 26% of patients (1224 of 4670 patients, *Table 2*) are reclassified as low risk and can be treated with ASA rather than VKA. Conversely, if patients with a $CHADS_2$ score of 1 would normally be treated with ASA only, the CHA_2DS_2-VASc score reclassifies 74% into a higher risk category that may benefit from VKA therapy.

Ideally, a risk score aimed to guide treatment of patients with AF should take into account both the risk of stroke without anticoagulants and the risk of bleeding with anticoagulants. The aim of our analyses was, however, to explore the discriminative ability of the CHA_2DS_2-VASc score for stroke risk prediction in patients with a $CHADS_2$ score of 1 and we have not examined bleeding risks in an anticoagulated population.

The major strength of the present study is that the analysis is restricted to the group of patients for whom current guidelines provide conflicting recommendations.[5,6] Despite this restriction, this study included a large number of patients ($n = 4670$) enrolled in large randomized trials with rigorous patient follow-up and all events were carefully adjudicated.

Several points of this study merit discussion. First, information on prior myocardial infarction or CAD, one of the components of the CHA_2DS_2-VASc score, was not collected in the 1012 patients from the AVERROES trial (22% of patients). However, when the results of the AVERROES and ACTIVE trials were analysed separately, the results were consistent (results not shown). Second, half of the patients in this cohort were treated with clopidogrel in addition to ASA. The incidence of the primary outcome was higher in patients treated with ASA only compared with patients treated with combined ASA and clopidogrel (2.3 and 1.3% per year, respectively). However, even in the group treated with ASA only, the risk of patients with a CHA_2DS_2-VASc score of 1 was still sufficiently low (1.1% per year, *Table 4*) to argue that they may not benefit from VKA therapy.[17] This threshold incidence to prefer anticoagulants over ASA may be different with the new oral anticoagulants. Dabigatran, apixaban, and rivaroxaban had a 30–70% lower risk of intracranial haemorrhage compared with VKA therapy and apixaban did not increase major or intracranial bleeding compared with aspirin.[11,18–20] These data suggest that the threshold for the use of the new anticoagulants, although likely subject to heavy debate, may be as low as 1% per year.[17,19]

The stroke risk of 0.9% per year for patients with a CHA_2DS_2-VASc score of 1 without VKA therapy in this study is in line with the risk of 0.6–1.5% per year found in other evaluations of the CHA_2DS_2-VASc score.[7,9,10] The risk found in these studies, however, was derived from registries with less accurate outcome adjudication and varying proportions of patients treated with antiplatelet drugs.

The added points for age (1 additional point for age $\geq$75 years and 1 point for age 65–74 years) were the most important of the three new factors in the CHA_2DS_2-VASc score. Female sex was a weaker risk factor and previous vascular disease was not a significant predictor of stroke in our cohort. Of note, only 2% of patients in this cohort had documented peripheral arterial disease, which is substantially lower than a cohort that did show an effect of previous vascular disease on stroke risk.[21] This can be regarded as an argument to generate a new stroke risk scheme without vascular disease, but this would require new validations and given the acceptance of the CHA_2DS_2-VASc score, it would be less helpful to propose yet another clinical score.[4]

In conclusion, the CHA_2DS_2-VASc score reclassifies 26% of patients with a $CHADS_2$ score of 1 to a low risk of stroke of around 1% per year. This risk may be considered sufficiently low to refrain from oral anticoagulant therapy.

Funding

The ACTIVE and AVERROES trials were supported by Sanofi-Aventis; Bristol-Myers Squibb; and Pfizer.

Conflict of interest: none declared.

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