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Prognostic value of CHA_2DS_2-VASc score in patients with 'non-valvular atrial fibrillation' and valvular heart disease: the Loire Valley Atrial Fibrillation Project

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Aims The CHA_2DS_2VASc score is a clinical risk stratification tool which estimates the risk of stroke and thromboembolism in non-valvular atrial fibrillation (AF). We aimed to establish the value of this score for risk evaluation in patients with non-valvular AF and valvular heart disease.

Methods and results Among 8053 patients with non-valvular AF (ESC guidelines definition), patients were categorized into Group 1 (no valve disease, $n = 6851$; 85%) and Group 2 (valve disease with neither rheumatic mitral stenosis nor valve prothesis, $n = 1202$; 15%). After follow-up of 868 $\pm$ 1043 days, 627 stroke/ thromboembolic (TE) events were recorded. Group 2 was significantly older, had a higher CHA_2DS_2VASc score and had a higher risk of thromboembolic events [hazard ratio (HR) 1.39; 95% CI 1.14–1.69, $P = 0.001$] compared with Group 1. Severe valve disease was not associated with worse prognosis for stroke/TE events. In the two groups, stroke/TE risk increased with a higher CHA_2DS_2VASc score. Factors independently associated with increased risk of stroke/TE events were older age (HR 1.25, 95% CI 1.14–1.36 per 10-year increase, $P < 0.0001$) and higher CHA_2DS_2VASc score (HR 1.33, 95% CI 1.23–1.45, $P < 0.0001$). The predictive value (c-statistic) of the CHA_2DS_2VASc score was similar in the two groups.

Conclusion In patients with non-valvular AF, left-sided valvular heart disease (excluding mitral stenosis and protheses) was associated with an increased risk of stroke/TE events. A higher CHA_2DS_2VASc score in these patients is likely to explain these results.

Keywords Atrial fibrillation • Valve disease • Stroke • CHA_2DS_2-VASc score

Introduction

The risk of stroke and thromboembolism (TE) is substantially increased in patients with atrial fibrillation (AF) but this risk is not homogeneous and can be estimated in individual patients using the CHA_2DS_2VASc score.[1–3] Patients with AF and CHA_2DS_2VASc score = 0 have a very low annual risk of stroke/TE events.[4,5] The studies which evaluated the CHA_2DS_2VASc score have largely studied patients with 'non-valvular AF' whether paroxysmal, persistent, or permanent.[6]

Current treatment guidelines have focused on 'non-valvular' AF, where patients with a CHA_2DS_2VASc score of ≥ 2 are recommended oral anticoagulation, whether as a Vitamin K antagonist (VKA) or a novel oral anticoagulant.[7,8] Patients with 'valvular' AF, as defined in the 2012 ESC guidelines (that is, those with a valvular prosthesis or rheumatic mitral disease) should receive anticoagulation regardless of the CHA_2DS_2VASc score, with VKA therapy being recommended.[8] The presence of a mechanical or biological mitral, but also aortic, valvular prosthesis is considered to be an independent risk factor of TE events in AF patients.[9,10] Similarly, patients with

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AF and a background of rheumatic fever and a mitral stenosis (MS) are also at high risk of TE.[9–11]

Nonetheless, there are limited data on the risk of stroke/thromboembolic complications in AF patients with valvular heart disease, other than those with valvular prosthesis or rheumatic mitral valve disease. However, these patients may account for 15–40% of all AF patients.[12] Such valve diseases may worsen left atrial dilation, contribute to a hypercoagulable state, and possibly increase the risk of stroke.[13]

In the present study, we aimed to establish the value of the CHA_2DS_2VASc score for stroke/TE risk evaluation in patients with 'non-valvular AF' and valvular heart disease. We tested the hypothesis that the CHA_2DS_2VASc score was a good risk stratification scheme even in AF patients with valvular heart disease.

Methods

Study population

Between January 2000 and December 2010, 8962 patients seen in the Cardiology department in our institution with a diagnosis of AF were identified. The regional university hospital of Tours serves ~400 000 inhabitants and is the only public institution in an area of about 4000 km^2. The information for each patient was extracted from computerized data of hospitalization and consultation of our institution. The local ethical committee of our institution was consulted and approved this study. The informed consent of patients was deemed unnecessary for our analyses since this is a retrospective analysis of a single centre cardiology department.

The CHA_2DS_2VASc score, which has been validated in non-valvular AF, was calculated for each patient: scoring 2 points for a past history of stroke/TE event and age $\geq$75 years ; 1 point for an age between 65 and 74 years, a history of high blood pressure, diabetes, heart failure, vascular disease (myocardial infarction, complex aortic plaque, and peripheral arterial disease), and female gender.[3,5] The HAS-BLED bleeding risk score was also calculated for each patient, which gave one point for the following items: high blood pressure, kidney and/or liver failure, stroke, haemorrhage, labile international normalized ratio, age $\geq$65 years, drugs and/or alcohol.[14]

Valvular disease and categorization of patients

Based on medical history and clinical presentation, the patients included in the registry had a transthoracic or transoesophageal echocardiography during their hospitalization. Our standardized echo lab with an imaging system allows us to consult each echo report easily. Echocardiographies were most often performed by trained seniors, with experience in valvular diseases. Patients with left-sided valvular heart disease were identified. Non-significant valve disease and right-sided valvular heart disease were not included in the present analysis. 'Significant' left-sided valvular heart diseases were then classified as 'severe' or 'non'severe' based on the European Society of Cardiology (ESC) guidelines.[10]

Severe mitral regurgitation (MR) was described by a vena contracta width $\geq$7 mm, effective regurgitant orifice area $\geq$40 mm^2 and/or regurgitant volume $\geq$60 mL/beat calculated on a PISA *(Proximal Isovelocity Surface Area)*. Mitral stenosis was considered severe if the valve area was $<$1.0 cm^2 or a mean trans-valvular gradient $>$10 mmHg. Aortic regurgitation (AR) was severe if vena contracta width $>$6 mm, effective regurgitant orifice area $\geq$30 mm^2 and/or regurgitant volume $\geq$60 mL/beat. An aortic stenosis (AS) was considered severe if valve area $<$1.0 cm^2 (or 0.6 cm^2/m^2 indexed to body surface area), mean trans-valvular gradient $>$40 mmHg, maximum jet velocity $>$4.0 m/s and/or velocity ratio $<$0.25. Mitral or aortic leaks described as minimal and mitral or aortic loose narrowings were considered non-significant. If the diagnosis was uncertain after echocardiography, some valvular heart diseases were graded using retrograde left heart catheterization and/or ventricular or aortic angiography.

Patients with 'valvular AF', that is, rheumatic MS and valvular prosthesis, as per the ESC guidelines, were excluded of the analysis.[8] Two patient groups were then established: (i) Group 1: patients without valve disease following investigations as above; and (ii) Group 2 : patients with so-called 'non-valvular AF' according to the definition of the ESC but with the presence of left-sided valve disease following investigations as above (AR, AS, or MR).

Stroke and thromboembolic events

Data on stroke/TE events during follow-up until December 2010 were obtained by searching in the medical database from consultation and hospitalization reports. Information on these events during the follow-up was recorded at each time it was documented within our institution, which includes a total of four hospitals covering all medical and surgical specialties. The incidence of stroke/TE events was calculated according to the CHA_2DS_2VASc score. From these results, we also calculated incidence of stroke/TE events in each group assuming if all patients had not been treated with anticoagulant, based on the assumption that administration of oral anticoagulation reduced the TE events risk by ~64%.[2]

Statistical analysis

The characteristics of the patients were given as percentages and means $\pm$ standard deviation. Comparisons between groups were made using χ^2 tests to compare categorical variables, and the Student's *t*-test or the non-parametric Kruskal–Wallis test where appropriate for continuous variables. A proportional hazard model was used to identify independent characteristics associated with the occurrence of an event during follow-up. Potential confounding factors were entered into the model for adjustment. The proportional hazard assumption was checked by plotting the log-log Kaplan–Meier curves. The results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Since the rate of patients treated with oral anticoagulation was not the same in the different groups of patients, we also considered the observed incidence of events in patients treated with anticoagulation and estimated the rate of events with no anticoagulation based on the assumption that effective anticoagulation was associated with a decrease of 64% in the risk of stroke/TE events.[2] We then calculated a ratio of these estimated incidences. We calculated Harrell's c-statistic with 95% CIs as a measure of model performance. C-statistics give a measure of how well the risk prediction scheme identifies patients who will have a future event. The c-statistics were calculated and then compared with others using the DeLong test. A *P*-value $<$0.05 was considered statistically significant. Statview 5.0 (Abacus, Berkeley CA, USA) and Medcalc 15.2 (MedCalc Software, Mariakerke, Belgium) were used for statistical analysis.

Results

The characteristics of the whole population (8962 patients, age 71 $\pm$ 15 years; 38% female and 39% with permanent AF) are described in *Table 1*. The mean CHA_2DS_2VASc score was 3.2 $\pm$ 1.8 and HAS-BLED score was 1.6 $\pm$ 1.1. Of these patients, 57% received warfarin and 35% were treated by an antiplatelet agent.

Among the 8962 patients, MR was diagnosed in 917 patients (10%), MS in 124 patients (1%), AR in 414 patients (5%), and AS in 555 patients (6%) (*Table 1*). Heart failure was commonly seen for patients with valve disease, particularly those with MR. Patients with AS and

Table 1 Characteristics of the patients with atrial fibrillation and/or with valve disease

Variable	No valve disease ($n = 7394$, 82.5%)	Isolated mitral regurgitation ($n = 656$, 7.3%)	Isolated mitral stenosis ($n = 44$, 0.5%)	Isolated aortic regurgitation ($n = 166$, 1.9%)	Isolated aortic stenosis ($n = 334$, 3.7%)	Combined valve disease ($n = 368$, 4.1%)	*P*-value
Age (years) (mean ± SD)	70 ± 15	74 ± 12	73 ± 15	73 ± 11	79 ± 9	75 ± 11	<0.0001
Women, *n* (%)	2775 (38)	289 (44)	31 (70)	61 (37)	134 (40)	177 (48)	<0.0001
Heart failure, *n* (%)	3715 (50)	524 (80)	31 (70)	119 (72)	234 (70)	289 (79)	<0.0001
Coronary artery disease, *n* (%)	2178 (29)	246 (38)	15 (34)	46 (28)	124 (37)	109 (30)	<0.0001
Previous myocardial infarction, *n* (%)	1017 (14)	149 (23)	3 (7)	22 (13)	59 (18)	48 (13)	<0.0001
Coronary artery bypass grafting, *n* (%)	375 (5)	44 (7)	3 (7)	9 (5)	21 (6)	14 (4)	0.33
Pacemaker or implantable cardioverter defibrillator, *n* (%)	1268 (17)	151 (23)	5 (11)	22 (13)	41 (12)	45 (12)	<0.0001
Hypertension, *n* (%)	3027 (41)	300 (46)	19 (43)	80 (48)	172 (51)	145 (39)	0.0003
Previous ischaemic stroke, *n* (%)	614 (8)	50 (8)	4 (9)	16 (10)	29 (9)	25 (7)	0.86
Renal insufficiency, *n* (%)	584 (8)	100 (15)	5 (11)	19 (11)	53 (16)	47 (13)	<0.0001
Diabetes mellitus, *n* (%)	1102 (15)	122 (19)	13 (30)	21 (13)	79 (24)	49 (13)	<0.0001
Chronic obstructive pulmonary disease, *n* (%)	764 (10)	70 (11)	4 (9)	20 (12)	46 (14)	47 (13)	0.27
Hyperlipidaemia, *n* (%)	1389 (19)	166 (25)	11 (25)	27 (16)	85 (25)	86 (23)	<0.0001
Permanent atrial fibrillation, *n* (%)	2727 (37)	317 (48)	23 (52)	79 (48)	165 (49)	184 (50)	<0.0001
CHA_2DS_2VASc score (mean)	2.9 ± 1.7	3.7 ± 1.6	3.8 ± 1.9	3.4 ± 1.5	4.0 ± 1.5	3.6 ± 1.7	<0.0001
HASBLED score (mean)	1.5 ± 1.1	1.8 ± 1.1	1.7 ± 1.1	1.8 ± 1.0	2.0 ± 1.0	1.7 ± 1.1	<0.0001
Left-ventricular ejection fraction (mean) ($n = 1934$)	47 ± 16	44 ± 16	54 ± 15	47 ± 14	50 ± 16	53 ± 14	<0.0001
Left-ventricular ejection fraction ≤45% ($n = 1934$), *n* (%)	610 (46)	166 (56)	5 (29)	19 (41)	38 (37)	48 (34)	0.0002
Medication during follow-up							
Oral anticoagulation ($n = 8120$), *n* (%)	3767 (56)	391 (65)	29 (67)	92 (62)	157 (52)	201 (60)	0.0003
Antiplatelet agent ($n = 7951$), *n* (%)	2256 (34)	234 (39)	18 (42)	37 (26)	117 (40)	100 (30)	0.003
ACE-inhibitor or angiotensin 2-blocker ($n = 4938$), *n* (%)	1475 (37)	251 (57)	12 (41)	44 (48)	83 (43)	110 (49)	<0.0001
Beta-blocker ($n = 4938$), *n* (%)	1726 (44)	232 (52)	16 (55)	40 (43)	73 (37)	87 (38)	0.001
Diuretic ($n = 4476$), *n* (%)	1490 (42)	292 (67)	21 (72)	54 (60)	112 (61)	156 (69)	<0.0001
Class III antiarrhythmic agent ($n = 5101$), *n* (%)	1994 (44)	227 (49)	17 (55)	49 (46)	93 (45)	96 (40)	0.24

ACE, angiotensin converting enzyme; CHADS(2), acronym for Congestive heart failure, Hypertension, Age >/ = 75, Diabetes mellitus, and prior Stroke or transient ischaemic attack; CHA_2DS_2VASc = acronym for Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes, Stroke/TIA/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65–74 years, Sex category (female).

MR were those with the highest CHA_2DS_2VASc scores, while those with MS and at a less extent those with MR were more likely to be treated with oral anticoagulation.

After exclusion of 909 patients with valvular AF (9%), 8053 patients were studied and categorized into Group 1 'no valve disease' ($n = 6851$; 85%) and Group 2 'valve disease' with neither rheumatic MS nor valve prothesis ($n = 1202$; 15%) (*Table 2*). In group 2, 61% of the patients had MR, 24% had AR, and 32% had AS (*Figure 1*).The number of patients with a history of stroke/TE event was very similar in the two patient groups. Patients in Group 2 were significantly older; more frequently had heart failure, coronary artery disease and renal failure, as well as a left-ventricular ejection fraction $\leq$45%.

Follow-up and TE events

After follow-up of 868 $\pm$ 1043 days, 627 stroke/TE events (521 strokes and 106 other systemic TE events) were recorded. *Figure 2* shows the event-free curves for stroke/TE events in the 2 groups. Compared with those in Group 1 with non-valvular AF, patients in Group 2 had a significantly higher risk of these events: HR 1.39 (95% CI 1.14–1.69, $P = 0.001$) in univariate analysis and after adjustment on oral anticoagulation (OAC) and antiplatelet agent (APA) use. Based on echocardiography, the severity of valve disease was not significantly associated with the occurrence of more stroke/TE events neither in univariate analysis (HR 1.12, 95% CI 0.78–1.61, $P = 0.53$) nor after adjustment on OAC and APA use (*Figure 3*).

Results of the univariate and multivariable analyses for the prediction of stroke/TE events in our cohort are in *Table 3*. In univariate analysis, the risk of stroke/TE events was particularly increased (with statistical significance) in AF patients with AR and in those with AS. Oral anticoagulation was significantly associated with a lower risk of stroke/TE events (HR 0.84, 95% CI 0.72–0.99). The model for adjustment in the multivariable analysis included (i) age and gender, (ii) CHA_2DS_2VASc score and HASBLED score, which both cover the main comorbidities considered to be relevant in AF patients for risk stratification of thromboembolic events (many possible confounders with significant differences in *Tables 1 and 2* being included in at least one these 2 scores), (iii) a set of parameters related to the type and severity of valve diseases, (iv) a set of parameters which were related to the type of atrial arrhythmia and pattern of AF, and (v) a set of parameters which were related to antithrombotic

Table 2 Characteristics of the patients with 'non-valvular AF' without valve disease and 'non-valvular AF' with valve disease (according to ESC definition)

Variable	Group 1 non-valvular AF, no valve disease ($n = 6851$, 85%)	Group 2 non-valvular AF, with valve disease ($n = 1202$, 15%)	*P*-value
Age (years) (mean $\pm$ SD)	70 $\pm$ 15	76 $\pm$ 12	<0.0001
Women, *n* ()	2565 (37)	513 (43)	0.0006
Heart failure, *n* (%)	3388 (49)	910 (76)	<0.0001
Coronary artery disease, *n* (%)	2023 (30)	419 (35)	0.0002
Previous myocardial infarction, *n* (%)	979 (14)	236 (20)	<0.0001
Coronary artery bypass grafting, *n* (%)	300 (4)	65 (5)	0.11
Pacemaker or implantable cardioverter defibrillator, *n* (%)	1092 (16)	209 (17)	0.44
Hypertension, *n* (%)	2861 (42)	581 (48)	<0.0001
Previous ischaemic stroke, *n* (%)	564 (8)	100 (8)	0.92
Renal insufficiency, *n* (%)	522 (8)	175 (15)	<0.0001
Diabetes mellitus, *n* (%)	1042 (15)	221 (18)	0.005
Chronic obstructive pulmonary disease, *n* (%)	703 (10)	152 (13)	0.01
Hyperlipidaemia, *n* (%)	1304 (19)	264 (22)	0.02
Permanent atrial fibrillation, *n* (%)	2440 (36)	566 (47)	<0.0001
CHA_2DS_2VASc score (mean)	3.1 $\pm$ 1.8	3.8 $\pm$ 1.6	<0.0001
HASBLED score (mean)	1.5 $\pm$ 1.1	1.9 $\pm$ 1.1	<0.0001
Left ventricular ejection fraction (mean) ($n = 1934$)	46 $\pm$ 16	46 $\pm$ 16	0.78
Left ventricular ejection fraction $\leq$45% ($n = 1934$), *n* (%)	552 (47)	230 (50)	0.47
Medication during follow-up			
Oral anticoagulation ($n = 7306$), *n* (%)	3408 (55)	657 (59)	0.01
Antiplatelet agent ($n = 7153$), *n* (%)	2141 (35)	421 (39)	0.03
Angiotensin-converting enzyme inhibitor or angiotensin 2-blocker ($n = 4382$), *n* (%)	1319 (37)	399 (52)	<0.0001
Beta-blocker ($n = 4382$), *n* (%)	1582 (44)	371 (48)	0.03
Diuretic ($n = 3957$)	1307 (41)	484 (65)	<0.0001
Class III antiarrhythmic agent ($n = 4544$), *n* (%)	1246 (33)	305 (39)	0.002

AF, atrial fibrillation; other abbreviations, see *Table 1*.

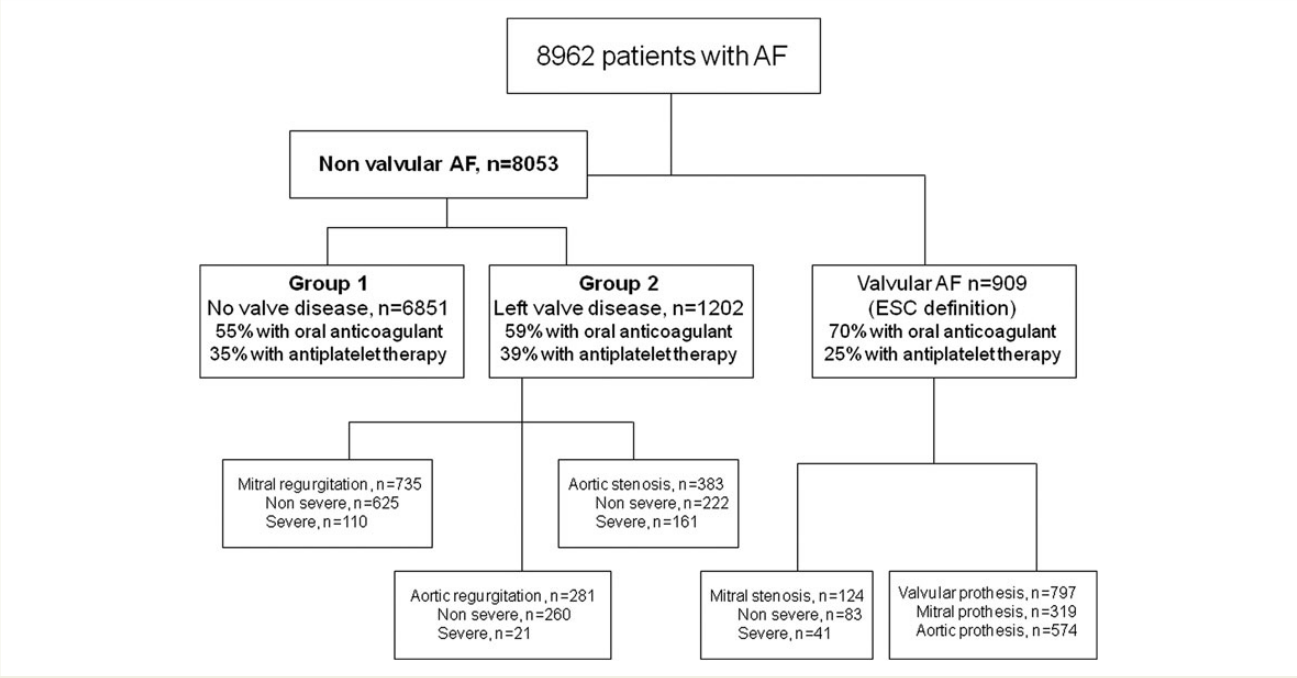

Figure 1 Study population by valve disease and therapy with oral anticoagulation.

therapy. In multivariable analysis, increasing age and increasing CHA_2DS_2VASc score were significantly associated with a higher risk of these events. The increased risk of stroke/TE events in patients from Group 2 (compared with those from Group 1) did not reach statistical significance (HR 1.24, 95% CI 0.84–1.83). The severity of valve disease was not independently associated with a higher risk of stroke/TE events.

CHA_2DS_2VASc score and rate of thromboembolism events

The rate of events per year increased with increasing CHA_2DS_2VASc score. For Group 1, the rate of events was 0.87%/year when CHA_2DS_2VASc score was 0–1, rising to 9.67%/year when score was $\geq$6. For patients in Group 2, similar finding were evident with a rate of stroke/TE events increasing from 0.90%/year with a CHA_2DS_2VASc score 0–1 to 11.07%/year when CHA_2DS_2VASc score was $\geq$6.

As rate of patients treated with oral anticoagulation was not the same in the two groups, we made the assumption that effective anticoagulation was associated with a decrease of 64% in the risk of stroke/TE events.[2] When annual incidence of embolism was estimated if none of the patients have been treated with oral anticoagulation, there was also an increase in the rates of events depending on CHA_2DS_2VASc score (*Table 4*). This increase ranged from 1.62 to 18.32%/year in Group 1 and from 0.90 to 21.22%/year in Group 2.

A comparison between Groups 1 and 2 found a similar risk of stroke/TE events for patients in when CHA_2DS_2VASc score was $<$6 and a higher risk (HR 1.30, 95% CI 1.05–1.61) when CHA_2DS_2VASc score was $\geq$6. Predictive values of CHA_2DS_2VASc in the two groups are in *Table 5*. There were no statistical differences for c-statistic neither in the two groups of AF patients nor in patients treated or untreated with VKAs.

Discussion

In this study, we have shown for the first time that there is an increased embolic risk in so called 'non-valvular AF' patients with valve disease compared with those without valve disease. Importantly, a higher CHA_2DS_2VASc score was likely to explain the increased risk in these patients and should remain the main reason to decide whether OAC is needed for stroke prevention. The CHA_2DS_2VASc score had a similar predictive value for TE in these two groups of non-valvular AF patients.

In this study, patients with left-valvular disease accounted for 22% of all AF patients. This figure is consistent with other international registries reporting rates of 21%.[12] We found that AF patients with a left valve condition (other than MS or valve prothesis) had a higher risk of stroke/TE events than those with no such condition, while these patients are all considered to have 'non-valvular AF' in most recent guidelines.

Our study is to our knowledge the first comprehensive analysis to report that patients with 'non-valvular AF and valve disease' significantly had an increased TE risk compared with other patients with 'non-valvular AF and no valve disease'. Many studies have suggested that the presence of MR with AF may play a role in the occurrence of TE events.[15,16] Mild and moderate MR might increase the TE risk[17] in contrast to severe MR which might have a putative protective effect.[18,19] The proposed mechanism would be an increase in atrial emptying and reduced intraatrial stasis, but these suggestions remain controversial. Our study does not allow do draw firm conclusion on this point although 61% of the AF patients in Group 1 with

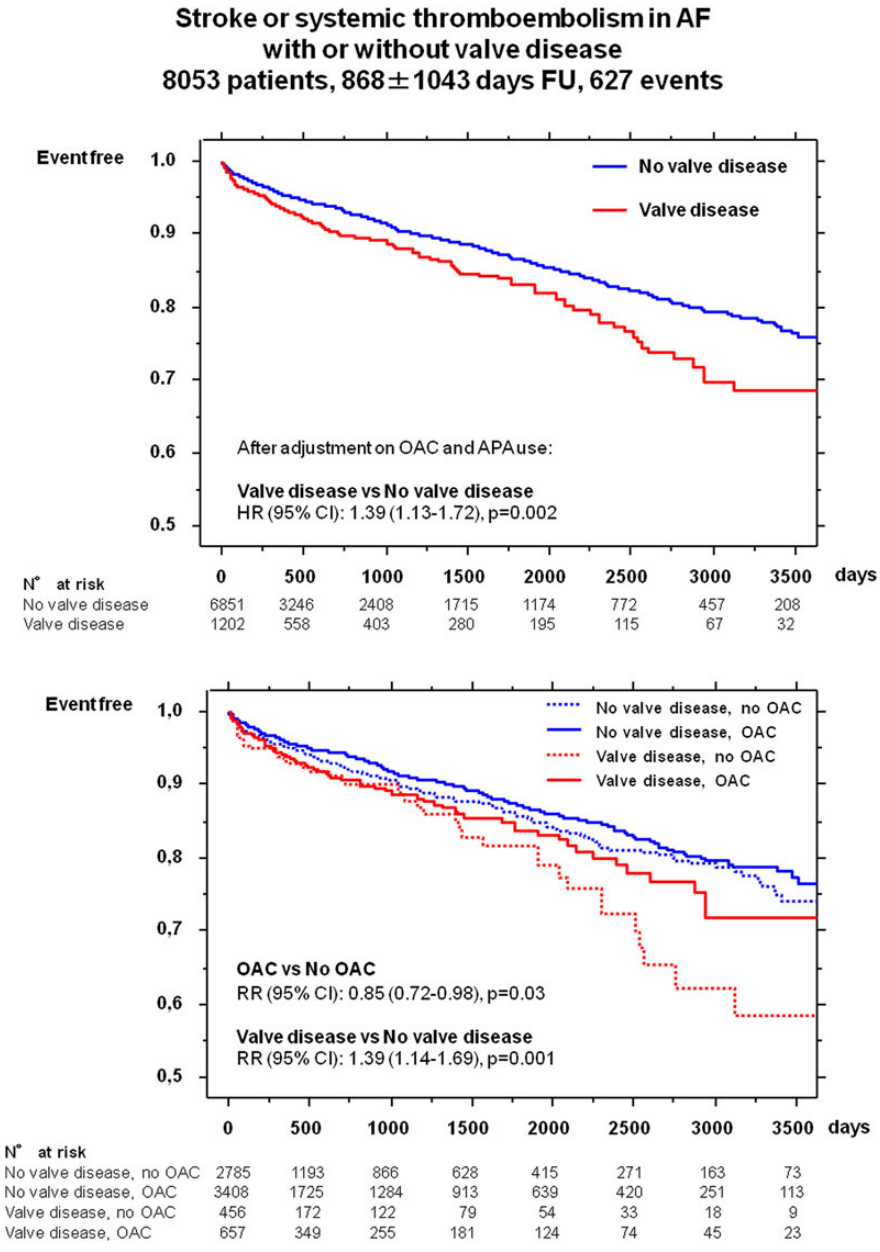

Figure 2 Kaplan–Meier estimates of the percentages of patients remaining free of stroke and/or thromboembolic events in patients with non-valvular atrial fibrillation. Top panel: event free curves in the two groups (Group 1 with no valve disease, Group 2 with valve disease) and adjustment of hazard ratio on oral anticoagulation (OAC) and antiplatelet agent (APA) use. Lower panel: event free curves in the two groups regarding the use or not of OAC.

valve disease had MR. However, neither MR nor severity of valve disease was associated with a higher risk of stroke/TE events on multivariable analysis.

Thromboembolism events related to aortic valve disease are less common than those associated with a mitral disease. The precise physiopathology of stroke in a patient with calcified AS is sometimes difficult to establish. There were 32% of the patients with AS in our group of AF patients with valve disease (18% with non-severe AS and 14% with severe AS). In current guidelines, anticoagulation is not indicated when there is no AF.[7,10] However, silent AF might be responsible for some TE events in addition to atherosclerosis or calcific microemboli in patients with valve diseases.[20] This may also explain the occurrence of acute cerebral injury within 2–3 days after a procedure of transcatheter aortic valve implantation.[20,21] In our study, patients with AS were older, more frequently had co-morbidities, and therefore had a higher CHA_2DS_2VASc risk score. This probably contributed to the increased risk of stroke/TE events for patients in the group with valve disease.

To our knowledge, there is no relationship between AR and the risk of TE events in patients with AF. In our study, this condition did

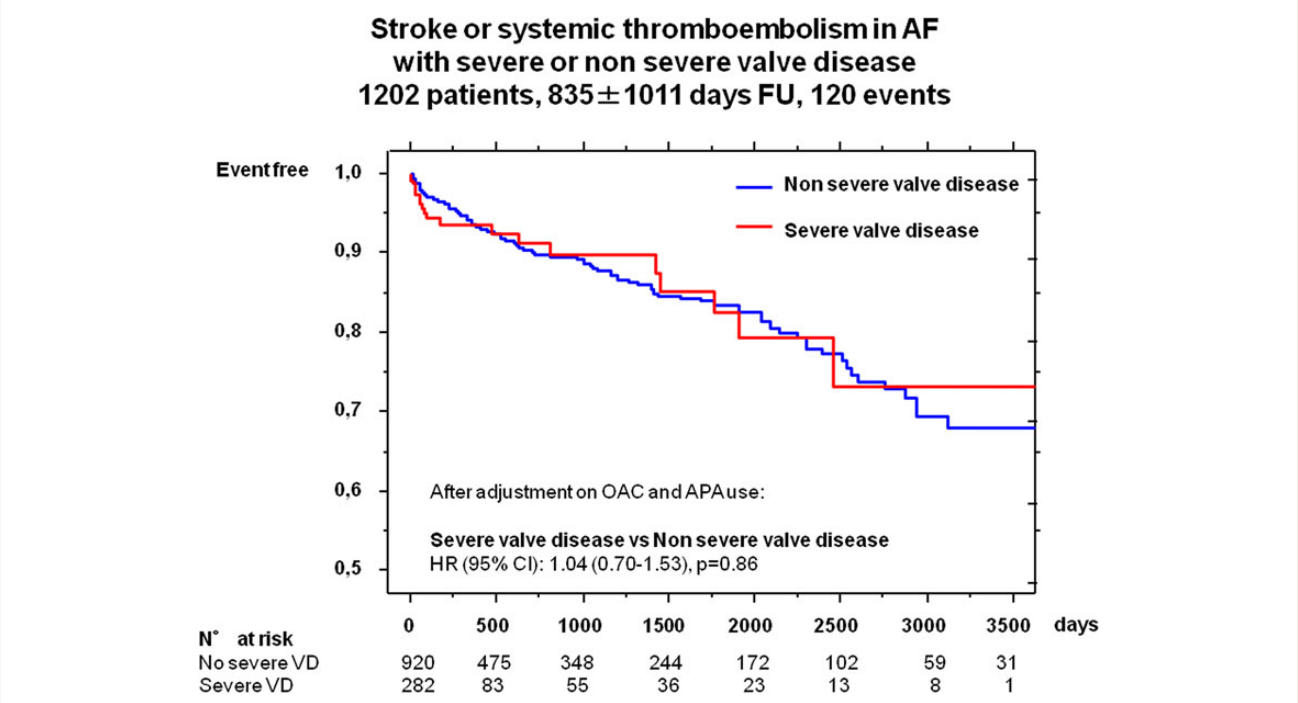

Figure 3 Kaplan–Meier estimates of the percentages of patients remaining free of stroke and/or thromboembolic events in atrial fibrillation patients with severe or non-severe valve disease and adjustment on oral anticoagulation (OAC) and antiplatelet agent (APA) use.

Table 3 Cox regression analysis for prediction of stroke/systemic thromboembolism

	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	***P*-value**	**Hazard Ratio (95% CI)**	***P*-value**
Age (per 10-year increase)	1.57 (1.47–1.68)	<0.0001	1.25 (1.14–1.36)	<0.0001
Female gender	0.80 (0.69–0.93)	0.004	0.77 (0.64–0.93)	0.01
CHA_2DS_2VASc score (as a continuous variable)	0.72 (0.69–0.75)	<0.0001	1.33 (1.23–1.45)	<0.0001
HASBLED score (as a continuous variable)	0.69 (0.65–0.73)	<0.0001	0.93 (0.82–1.05)	0.22
Non-valvular AF with valve disease (compared with non-valvular AF and no valve disease)	1.39 (1.14–1.69)	0.001	1.24 (0.84–1.83)	0.28
Mitral regurgitation (vs. no mitral regurgitation)	1.09 (0.87–1.36)	0.48	0.78 (0.54–1.13)	0.19
Aortic regurgitation (vs. no aortic regurgitation)	1.39 (1.02–1.90)	0.04	1.08 (0.74–1.58)	0.68
Aortic stenosis (vs. no aortic stenosis)	1.64 (1.24–2.15)	0.0005	1.04 (0.69–1.56)	0.86
Severe valve disease (compared with all other patients)	1.32 (0.95–1.85)	0.10	0.93 (0.60–1.43)	0.73
Atrial flutter and no documented AF (vs. AF and no atrial flutter)	0.41 (0.24–0.68)	0.0005	0.48 (0.28–0.84)	0.01
Atrial flutter with documented AF (vs. AF and no atrial flutter)	0.50 (0.30–0.84)	0.01	0.74 (0.44–1.27)	0.28
Permanent AF (vs. Non-permanent AF)	1.26 (1.09–1.47)	0.002	1.12 (0.95–1.32)	0.17
Vitamin K antagonist at discharge (vs. no vitamin K antagonist at discharge)	0.84 (0.72–0.99)	0.03	0.93 (0.77–1.11)	0.41
Antiplatelet agent at discharge (vs. no antiplatelet agent at discharge)	1.53 (1.30–1.79)	<0.0001	1.20 (0.99–1.46)	0.06

AF, atrial fibrillation.

not seem to be predictive of stroke/TE events. Finally, it is noteworthy that the severity of valvular disease was not predictive of stroke/TE events in our analysis, and this has not been previously reported on such a large scale.

Ourn study confirms both the low risk of stroke/TE events in patients with low CHA_2DS_2VASc score and the progressive increase in the risk with increasing score up to 11%/year for a score ≥6 in 'non-valvular AF' patients. These figures are consistent with those found in

Table 4 Incidence of stroke/thromboembolic events in patients with non-valvular AF with or with no valve disease, by CHA_2DS_2VASc score

	Group 1 non-valvular AF, no valve disease (n = 6851, 78%)			Group 2 non-valvular AF, with valve disease (n = 1202, 13%)			
CHA_2DS_2VASc score	Therapy with OAC, %	Observed rate of events, %/year	Estimated rate of events with no OAC, %/year	Therapy with OAC, %	Observed rate of events, %/year	Estimated rate of events with no OAC, %/year	Incidence ratio (95% CI) vs. group 1
0–1 (n = 1637, 20%)	48	0.87	1.62	63	0.90	1.90	1.19 (0.47–3.03)
2–3 (n = 2881, 36%)	60	3.01	6.19	66	2.76	5.98	0.98 (0.76–1.27)
4–5 (n = 2800, 35%)	56	4.60	9.18	56	5.67	11.29	1.12 (0.93–1.34)
≥6 (n = 735, 9%)	50	9.67	18.32	52	11.07	21.22	1.30 (1.05–1.61)

AF, atrial fibrillation.
*Based on a 64% reduction of thromboembolic events for the percentage of patients treated with warfarin in each stratum of risk.

Table 5 Comparison of c-statistics (95% confidence intervals) for CHA_2DS_2VASc score in patients with non-valvular AF and in patients with valve disease

	C statistic (95% CI)			
	All patients	Patients not on VKA	Patients on VKA	P-value[a]
All patients	(n = 8053) 0.655 (0.644–0.665)	(n = 3241) 0.655 (0.638–0.671)	(n = 4065) 0.654 (0.639–0.668)	0.96
Non-valvular AF and no valve disease (Group 1)	(n = 6851) 0.655 (0.643–0.666)	(n = 2785) 0.665 (0.647–0.683)	(n = 3408) 0.645 (0.628–0.661)	0.42
Non-valvular AF with valve disease (Group 2)	(n = 1202) 0.639 (0.611–0.666)[b]	(n = 456) 0.582 (0.535–0.628)[b]	(n = 657) 0.675 (0.637–0.710)[b]	0.10

C-statistic calculated as area-under-the-curve for the receiver-operator characteristic (ROC) for CHA_2DS_2VASc score as a continuous variable.
[a]For difference between patients on VKA and patients not on VKA.
[b]P = NS compared with patients with non-valvular AF and no valve disease (Group 1).

other cohorts.[22] It therefore seems valid to use the CHA_2DS_2VASc score in clinical practice for these AF patients since our findings may largely be explained by the more severe risk profile of patients in Group 2: older age, more heart failure with higher need of diuretics, more frequent hypertension, myocardial infarction, as well as a higher HAS-BLED score than in other groups. Considering our results of the comparison between predictive values, a major clinical implication of this work is that use of the CHA_2DS_2VASc score would significantly improve classification of patients at increasing risk of stroke in a similar way for non-valvular AF patients with or with no valve disease.

Limitations

This study based on a registry has the limitations of observational retrospective analysis. There were also many variables to be analysed and it is possible that remaining confounding factors interfered in the statistical analyses. Particularly, the risk and benefit associated with each antithrombotic therapy should be interpreted very cautiously in this context. A more precise comparison between the different valve diseases was not achieved because some patients belonged to several groups. Due to constant progress in echocardiographic methods to quantify valve disease severity since the early 2000s, some of the echocardiography criteria were not widely applied in the early 2000s and all the quantitative parameters were not available for each patient. Classification of the valve disease was done according to the reported parameters at the time of the echocardiography in our laboratory with standards methods but was not retrospectively reviewed. These limitations would most probably not affect the main results due to the large patient population and the clear differences in the outcomes in the different subgroups. Finally, the natural history and symptoms of a valvular disease may lead to a specific support with valvular surgery but without prosthesis or valve replacement, and this shortcoming in analysis may not allow us drawing definite conclusions.

Conclusion

This systematic analysis in 'real life' conditions reinforces the major interest of using the CHA_2DS_2VASc risk scores for clinical practice in AF patients. The CHA_2DS_2VASc score is valid for the risk evaluation of AF patients with left-valvular disease not included in the 'valvular AF' criteria as defined in the 2012 ESC guidelines. Also, our study found an increased embolic risk in these patients compared with those without valve disease. However, neither the valve disease *per se* nor its severity was clearly associated with this risk, while a

higher CHA_2DS_2VASc score in these patients was likely to explain these results.

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