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Stroke and bleeding risk co-distribution in real-word patients with atrial fibrillation: the Euro Heart Survey

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Author contribution:

M.M. – study concept, data analysis and interpretation, manuscript first draft, further revisions

G.Y.H.L. – study concept, data interpretation, manuscript drafting and revising

R.N. – data analysis and interpretation, manuscript revising

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Abstract

Background: The choice to recommend antithrombotic therapy to patients with atrial fibrillation should rely on cardio-embolic and bleeding risk stratification. Sharing some risk factors, schemes to predict thrombotic and bleeding risk are expected not to be independent, yet the degree of their association has never been clearly quantified.

Methods: We described the cardio-embolic ($CHADS_2$/CHA_2DS_2-VASc) and bleeding risk (HAS-BLED) co-distribution among patients of Euro Heart Survey on atrial fibrillation. We measured the within patient correlation (Spearman) and concordance between the two types of score and score-based risk categorization (low, intermediate, high). The score-based predicted risk co-classification was then related to the observed 1-year stroke and bleeding occurrence.

Results: In 3,920 patients, we found a between scores correlation of 0.416 ($p<0.001$) between HAS-BLED and $CHADS_2$, and 0.512 ($p<0.001$) between HAS-BLED and CHA_2DS_2-VASc. In 89% ($CHADS_2$/HAS-BLED) and 97% (CHA_2DS_2-VASc/HAS-BLED) of patients the bleeding risk category was equal or lower than their cardio-embolic risk category ($p<0.001$ for symmetry test). A complete concordance between risk categories was found in 39.6% ($CHADS_2$/HAS-BLED) and 21.7% (CHA_2DS_2-VASc/HAS-BLED); 4.4% ($CHADS_2$/HAS-BLED) and 7.7% (CHA_2DS_2-VASc/HAS-BLED) of patients had high cardio-embolic risk/low bleeding risk or vice-versa. A tendency of an increasing frequency of stroke was observed for increasing bleeding risk within cardio-embolic risk categories, and vice-versa.

Conclusion: In a real-world atrial fibrillation population, we confirmed that the cardio-embolic and bleeding risk classifications are correlated, but not exchangeable. It is then

worth verifying the advantages of a strategy adopting a combined risk assessment over a strategy relying only on the cardio-embolic risk evaluation.

Introduction

Patients with atrial fibrillation may differently benefit from long term anticoagulation according to the balance of their baseline risk for stroke and for bleeding. With the availability of newer anticoagulants, the choice might be not only to treat or not, but which treatment choice fits better the risk profile.

Strategies for treatment individualization, based on a trade-off between the treatment-related individual benefit and harm, are facilitated by the availability of clinical tools to predict the patient risk for the target and the adverse event. The $CHADS_2$ (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack)[1] and the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack, Vascular disease, Age 65-75, Sex category i.e. females)[2] scores are two clinical risk factor-based schemes to predict the risk of stroke in patients with atrial fibrillation, included in the guidelines for the antithrombotic therapy of major Scientific Societies.[3-5] Noticeably, the CHA_2DS_2-VASc was developed to better identify patients "truly at low risk" of stroke,[6] and this score is recommended in the ESC[3] and Asia Pacific Heart Rhythm Society (APHRS) guidelines.[7]

Several scores for the assessment of bleeding risk in patients with atrial fibrillation are also available in the literature.[8-11] The HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) score was shown to have a good predictive ability both in patients on and off oral

anticoagulants[12], and its use is recommended in the most recent European and Canadian guidelines.[3,4]

Schemes for thrombotic and bleeding risk assessment have some risk factors in common, and there is evidence that these scores are in fact associated with both the risk of stroke and the risk of bleeding.[13-16] Whether and to what extent the joint use of a score for the cardio-embolic risk and a score for the bleeding risk offers an advantage in making clinical decisions in clinical practice, in terms of risk stratification and treatment individualization, over a strategy relying only on the cardio-embolic risk assessment is not definitely clear. Surely it is affected by the co-distribution of the two scores, which needs to be assessed in a 'real-word' population.

With these objectives, we first described how a population of atrial fibrillation patients referred to the hospital was classified by a combined use of a score for cardio-embolic risk and a score for bleeding risk. Second, we measured the within patient correlation and concordance between the two types of score and score-based risk categorization. Third, we related outcomes of stroke and bleeding to the score-based risk co-classification.

Methods

Study population.

We analyzed the Euro Heart Survey (EHS) on atrial fibrillation database, which included data on 5,333 inpatients or outpatients, ≥ 18 years old, referred to 182 university, non-university, and specialized hospitals among 35 member countries of the European Society of Cardiology, with an ECG or Holter-proven diagnosis of atrial fibrillation during the

qualifying admission or in the preceding year.[17] Paper-based medical records and/or data from medical information systems were used to populate the database. We included in the present analysis only the EHS patients with nonvalvular atrial fibrillation (i.e. defined by the absence of a mitral valve stenosis or valvular surgery) and with data available for the calculation of the risk scores.

Risk scores.

The $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores were retrospectively calculated for each patient using the data on collected at discharge from the hospital or at the end of the index outpatient visit. A reduced version of the HAS-BLED score was used because of the unavailability of data for liver dysfunction and labile INR.

Statistical analysis.

Both the $CHADS_2$/HAS-BLED and CHA_2DS_2-VASc/HAS-BLED combinations of scores were considered. The co-classification of the study population according to each of those combinations was described, using either the raw scores or the score-based risk categories as defined in the literature[2,18] (for $CHADS_2$ and CHA_2DS_2-VASc: low risk = score 0; intermediate risk = score 1; high risk = score $\geq$ 2; for HAS-BLED: low risk = score 0; intermediate risk = score 1-2; high risk = score $\geq$ 3). Cross tabulation and box-plots were used to represent the co-distribution.

A Spearman rank correlation coefficient was calculated to express the extent of association/dependence between the patient cardio-embolic and bleeding risk score. We

then used two measures of concordance/exchangeability between the two risk categorizations (high, intermediate and low): a) the percentage agreement, i.e. percentage of patients classified into the same cardio-embolic and bleeding risk category; b) a weighted percentage agreement, taking into account also the "partial concordance", assigning a weight of 2 for perfect agreement, 1 for a 1-category disagreement, 0 for 2-category disagreement. Symmetry and marginal homogeneity (Stuart-Maxwell) tests were also performed to test, in case of discordance, if there was a statistically significant tendency for the cardio-embolic risk category to be higher than the bleeding risk category, or viceversa.

Secondary analyses

a) *Score co-distribution by antithrombotic therapy*. We described the score co-distribution also in subgroups of EHS patients defined according to the antithrombotic therapy they were prescribed at the time of the discharge from the hospital or at the end of the index outpatient visit, qualitatively comparing the degree of correlation in each group. The following subgroups of patients were defined: patients not receiving any antithrombotic treatment, patients receiving an antiplatelet agent and patients receiving a vitamin K antagonist (VKA - including patients receiving both a VKA and an antiplatelet agent). Patients receiving heparins were excluded from the current analyses. Our hypothesis for this secondary analysis was that the distribution of each risk score would be different in each by-treatment defined group (according to the Kruskal-Wallis rank-test), but that the level of within patients correlations between the two types of score would be similar in each treatment group as in the whole population.

b) *Score co-distribution and outcome.* We explored if there was any association between the score co-distribution and outcome. We did that investigating if, for each cardio-embolic risk category, there was a trend in the occurrence of adverse events according to the bleeding risk category, and vice-versa. Also, we investigated if, regardless of the level of risk, the concordance/discordance between cardio-embolic and bleeding risk categories was associated with a different outcome (considering stroke, bleeding or any); logistic regression analysis was used for this purpose. All analyses were stratified by or adjusted for antithrombotic treatment. Definitions used for the outcomes in the EHS on atrial fibrillation are provided elsewhere.[2]

Results

Of the 5,272 patients with atrial fibrillation in the EHS of atrial fibrillation who were discharged alive,[17] 3920 patients without mitral valve stenosis or valvular surgery and available data to calculate the risk scores, were included in this analysis. **Table 1** shows relevant characteristics of the study population.

Table 2 and **figure 1** (**panel A**) describe the co-distribution of $CHADS_2$ and HAS-BLED; **table 4** and **figure 1** (**panel C**) describe the co-distribution of CHA_2DS_2-VASc and HAS-BLED. The Spearman correlation coefficient was 0.416 ($p<0.001$) between $CHADS_2$ and HAS-BLED, and 0.512 ($p<0.001$) between CHA_2DS_2-VASc and HAS-BLED.

Those co-distributions translated into the joint score-based risk categorizations shown in **table 3**, **table 5** and in **figure 1** (**panel B** and **D**). The most prevalent risk group was the one at high cardio-embolic risk and intermediate bleeding risk (37.5% if $CHADS_2$, 60.8% if CHA_2DS_2-VASc was used), with 89% ($CHADS_2$/HAS-BLED) and 97% (CHA_2DS_2-VASc/HAS-BLED) of patients classified into a bleeding risk category equal or lower than their cardio-embolic risk category ($p<0.001$ for symmetry and marginal homogeneity tests). Using the $CHADS_2$ and HAS-BLED, 39.6% of patients were classified into the same cardio-embolic and bleeding risk category, while 21.7% was the agreement between CHA_2DS_2-VASc and HAS-BLED (16.3% were classified into the same cardio-embolic and bleeding risk category by both the $CHADS_2$/HAS-BLED and the CHA_2DS_2-VASc/HAS-BLED combination). Considering also the partial agreement, the weighted percentage agreement was 67.7% and 57.0%, respectively.

Score co-distribution and antithrombotic therapy

Table 1 describes frequencies and modalities of antithrombotic therapy prescribed at discharge. As expected, the distribution of each individual risk score significantly differed among the three by-treatment groups ($p<0.001$). When looking at the score co-distribution, positive Spearman correlation coefficients were obtained in each group similar to those found in the whole population (**supplementary table 1**). The score co-distribution across by-treatment groups is described in the **supplementary figure 1**.

Score co-distribution and outcome

Data on 1-year outcome were available for 2,934 out of 3,920 patients (74.8%). The score co-distribution and correlation in these patients resembled those of the initial population. **Table 6** shows, among patients on warfarin, the tendency for an increasing frequency of events (either stroke or bleedings, or both) as function of an increasing bleeding risk score, mainly evident within the high cardio-embolic risk category. Similarly, a tendency for an increasing frequency of events in accordance with an increasing cardio-embolic risk score was found within the intermediate and high bleeding risk categories. The same results for the entire population are provided in the **supplementary table 2**. Finally, a trend of an increasing frequency of stroke for a stronger concordance between cardio-embolic and bleeding risk category was observed (**table 7**), before and after accounting for the antithrombotic therapy, even if without reaching a statistical significance. The trend was not confirmed for the occurrence of major bleedings.

Discussion

We described the joint distribution of scores for the cardio-embolic risk ($CHADS_2$ or CHA_2DS_2-VASc) and scores for the bleeding risk (HAS-BLED) in patients with atrial fibrillation. We found a positive within patient correlation of moderate strength between the two types of scores (about 0.5), in the whole population and in subgroups defined by the prescribed antithrombotic therapy. A perfect concordance between cardio-embolic and bleeding risk category was found in largely less than 50% of patients, but only from 4.4% ($CHADS_2$/HAS-BLED) to 7.7% (CHA_2DS_2-VASc/HAS-BLED) of patients fell into the cells corresponding to a full discordance between the cardio-embolic and bleeding risk category (i.e. high cardio-embolic risk/low bleeding risk, or vice-versa). An

increasing bleeding risk score was associated with an increasing frequency of stroke events within the intermediate and high cardio-embolic risk score categories; the trend was less evident for bleeding events. A higher degree of within patient concordance between cardio-embolic and bleeding risk category appeared to be associated with a higher frequency of stroke.

The current literature has been focusing on verifying the predictive ability of proposed cardio-embolic and bleeding risk scores in real-word atrial fibrillation cohorts, but scarce attention has been paid to addressing the questions how those scores co-distribute and correlate, and so how the assumption of their independence is justifiable and their separate use necessary. For example, Friberg *et al.*[14] recently used the score-based co-stratification to assess the net benefit with warfarin associated to different $CHADS_2$ (or CHA_2DS_2-VASc) and HAS-BLED scores, in a large Swedish atrial fibrillation population; their cross-tabulations resemble ours (table 2 and 4), with empty cells at the top right and bottom left corners, and the highest concentration in the cells along the diagonal. Yet, they did not focus on how those strata were differently populated. Lopes *et al.*[19] reported the cardio-embolic and bleeding score-based categories co-distribution among the participants of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolism Events in Atrial Fibrillation) study. They calculated a weighted kappa (i.e. a measure of agreement adjusted for chance, which is usually used for evaluating the agreement between observers), but they did not report any measure of correlation between scores.

In fact, the relationship between cardio-embolic and bleeding risk scores has two important implications. First, if the two scores are used together (either in clinical

practice or in a risk-benefit analysis) their non-independence has to be accounted for.[20] Second, one type of score may be predicted from the other using appropriate statistics. Moreover, if there is not only an association but also a large degree of concordance, one score may be used as the surrogate for the other. In fact, according to our findings a patient at low, intermediate or high cardio-embolic risk would have about 30% chance of being either at low, intermediate or high bleeding risk. On the other hand, a generic patient would have a very low chance (less than 11% if $CHADS_2$ is used, or less than 2% if CHA_2DS_2-VASc is used) to have a predicted bleeding risk higher than the predicted cardio-embolic risk.

Therefore, what is the added value in clinical practice of using both scores instead of relying on their correlation or concordance? The added value lies in 1) improving the classification of those 70% of patients with incomplete concordance, also identifying those 2-10% patients with a bleeding risk higher that a cardio-embolic risk, and 2) facilitating the introduction, in an individualized decision making process, of different weights reflecting different patient's values, for a cardio-embolic and a bleeding event. Indeed, if the patient judges a major bleeding substantially more undesirable than a stroke, predicting accurately the patient's baseline risks of both events will be required to accommodate her values.

Limitations

To what extent our results are generalizable has to be established. Indeed though being a real-world population, the EHS cohort was a selected cohort (patients referred to the hospital) and mostly constituted by outpatients. This might have affected the distribution of each kind of score and, consequently, the type of relationship between

scores. In addition, it was an observational cohort; showing a significantly different distribution of risk scores across treatment groups we confirmed that treatment was not assigned randomly. However when the potential confounding by indication could play a role, we adjusted or stratified the analyses. Then, the small size of some subgroups limited the reliability of the estimates of the correlation coefficients. Likewise, the overall low number of events reduced the power of the analyses on the association between risk co-distribution and outcomes, and the high representation of intermediate-high risk categories limited their interpretation. Another limitation that deserves attention is the fact that we had to resort to a reduced version of the HAS-BLED score, possibly leading to an underestimation of the actual scores. Finally, we used the score-based risk categorizations described in the literature, which is something arbitrary and proposed for each type of score separately; thus, the definition of low/intermediate/high risk does not correspond exactly to the same annualized risk for every score.

Conclusions

The low concordance between the cardio-embolic and bleeding risk stratifications we found leaves room to the hypothesis that their separate assessment might be important. The impact on patient relevant outcomes of their combined assessment needs to be evaluated in a large implementation study of a decision model also accounting for the relative importance assigned to bleedings versus strokes.

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Figure legend

Figure 1. Cardio-embolic and bleeding risk scores co-distribution. A) $CHADS_2$ and HAS-BLED scores. B) $CHADS_2$ and HAS-BLED risk categories. C) CHA_2DS_2-VASc and HAS-BLED scores. D) CHA_2DS_2-VASc and HAS-BLED risk categories. Red line: median of HAS-BLED scores.

Tables

Table 1. Characteristics of the 3920* patients with atrial fibrillation from the Euro Heart Survey included in the current analyses

Characteristic	Description
Age, median (Q1, Q3)	68 (59, 75)
Women, n (%)	1,587 (40.5)
$CHADS_2$, median (Q1, Q3)	1 (1, 2)
CHA_2DS_2-VASc, median (Q1, Q3)	3 (2, 4)
HAS-BLED, median (Q1, Q3)	1 (1, 2)
Drugs prescribed at discharge, n (%)	
Warfarin	2,476 (63.2)
Aspirin	1,079 (27.5)
No antithrombotic therapy	365 (9.3)
Stroke at 1 year of follow up, n (%)	
Any patient	47 (1.6)
In patients on warfarin	27 (1.4)
In patients on aspirin	19 (2.5)
In patients off antithrombotic therapy	1 (0.4)
Major bleeding at 1 year of follow up, n (%)	
Any patient	44 (1.5)
In patients on warfarin	35 (1.8)
In patients on aspirin	8 (1.0)
In patients off antithrombotic therapy	1 (0.4)
Stroke and major bleeding at 1 year of follow up, n (%)	
Any patient	4 (0.1)
In patients on warfarin	4 (0.2)
In patients on aspirin	0 (0)
In patients off antithrombotic therapy	0 (0)

Legend: n, number. Q1, first quartile. Q3, third quartile. *Data on outcome at 1 year of follow up available for 2,934 out of 3,920 patients.

Table 2. $CHADS_2$ and HAS-BLED scores co-distribution

n (% of total)	HAS-BLED						
$CHADS_2$	**0**	**1**	**2**	**3**	**4**	**5**	**Any HAS-BLED**
0	331 (8.44)	264 (6.73)	83 (2.12)	6 (0.15)	0 (0.00)	0 (0.00)	684 (17.45)
1	314 (8.01)	641 (16.35)	318 (8.11)	64 (1.63)	5 (0.13)	0 (0.00)	1,342 (34.23)
2	129 (3.29)	472 (12.04)	369 (9.41)	83 (2.12)	7 (0.18)	0 (0.00)	1,060 (27.04)
3	28 (0.71)	213 (5.43)	196 (5.00)	60 (1.53)	5 (0.13)	0 (0.00)	502 (12.81)
4	4 (0.10)	71 (1.81)	77 (1.96)	52 (1.33)	10 (0.26)	1 (0.03)	215 (5.48)
5	0 (0.00)	17 (0.43)	42 (1.07)	25 (0.64)	9 (0.23)	2 (0.05)	95 (2.42)
6	0 (0.00)	5 (0.13)	8 (0.20)	6 (0.15)	3 (0.08)	0 (0.00)	22 0.56
Any $CHADS_2$	806 (20.56)	1,683 (42.93)	1,093 (27.88)	296 (7.55)	39 (0.99)	3 (0.08)	3,920

Legend: n, number. Grey cell = most prevalent cell.

Table 3. $CHADS_2$ and HAS-BLED co-distribution according to the score-based risk categories

	HAS-BLED risk category n (% of the total in each $CHADS_2$ risk category)			n (% of the total)
$CHADS_2$ risk category	**Low risk**	**Intermediate risk**	**High risk**	
Low risk	331 (48.4)	347 (50.7)	6 (0.9)	684 (17.5)
Intermediate risk	314 (23.4)	959 (71.5)	69 (5.1)	1,342 (34.2)
High risk	161 (8.5)	1,470 (77.6)	263 (13.9)	1,894 (48.3)
n (% of the total)	806 (20.6)	2,776 (70.8)	338 (8.6)	3,920

Legend: n, number. Grey cell = most prevalent cell

Table 4. CHA_2DS_2-VASc and HAS-BLED scores co-distribution

n (% of total)	HAS-BLED						
CHA_2DS_2-VASc	**0**	**1**	**2**	**3**	**4**	**5**	**Any HAS-BLED**
0	218 (5.56)	83 (2.12)	8 (0.20)	0 (0.00)	0 (0.00)	0 (0.00)	309 (7.88)
1	284 (7.24)	239 (6.10)	64 (1.63)	7 (0.18)	0 (0.00)	0 (0.00)	594 (15.15)
2	168 (4.29)	356 (9.08)	139 (3.55)	25 (0.64)	2 (0.05)	0 (0.00)	690 (17.60)
3	104 (2.65)	390 (9.95)	269 (6.86)	43 (1.10)	3 (0.08)	0 (0.00)	809 (20.64)
4	26 (0.66)	318 (8.11)	273 (6.96)	73 (1.86)	8 (0.20)	0 (0.00)	698 (17.81)
5	5 (0.13)	187 (4.77)	170 (4.34)	61 (1.56)	3 (0.08)	0 (0.00)	426 (10.87)
6	1 (0.03)	78 (1.99)	101 (2.58)	40 (1.02)	8 (0.20)	1 (0.03)	229 (5.84)
7	0 (0.00)	20 (0.51)	49 (1.25)	33 (0.84)	10 (0.26)	0 (0.00)	112 (2.86)
8	0 (0.00)	9 (0.23)	18 (0.46)	12 (0.31)	4 (0.10)	2 (0.05)	45 (1.15)
9	0 (0.00)	3 (0.08)	2 (0.05)	2 (0.05)	1 (0.03)	0 (0.00)	8 (0.20)
Any CHA_2DS_2-VASc	806 (20.56)	1,683 (42.93)	1,093 (27.88)	296 (7.55)	39 (0.99)	3 (0.08)	3,920

Legend: n, number. Grey cell = most prevalent cell.

Table 5. CHA_2DS_2-VASc and HAS-BLED co-distribution according to the score-based risk categories

	HAS-BLED risk category n (% of the total in each CHA_2DS_2-VASc risk category)			n (% of total)
CHA_2DS_2-VASc risk category	**Low risk**	**Intermediate risk**	**High risk**	
Low risk	218 (70.5)	91 (29.5)	0 (0.0)	309 (7.9)
Intermediate risk	284 (47.8)	303 (51.0)	7 (1.2)	594 (15.1)
High risk	304 (10.1)	2,382 (78.9)	331 (11.0)	3,017 (77.0)
n (% of total)	806 (20.6)	2,776 (70.8)	338 (8.6)	3,920

Legend: n, number. Grey cell = most prevalent cell

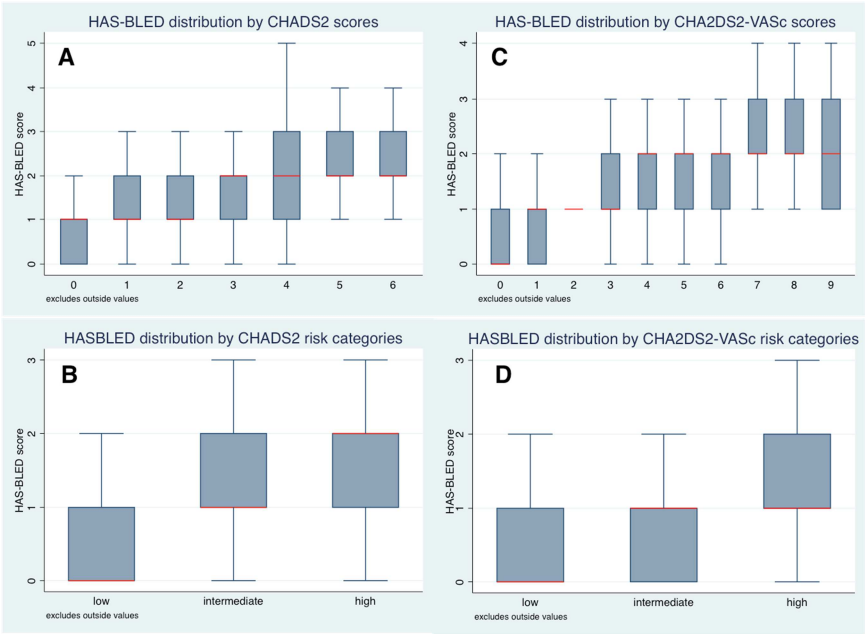
Table 6. Cardio-embolic and bleeding risk categories co-distribution and outcomes: patients prescribed with warfarin

Cardio-embolic risk category	HAS-BLED risk category	% of patients experiencing a stroke	% of patients experiencing a major bleeding	% of patients experiencing a stroke or a major bleeding
$CHADS_2$ Low risk	Low	1.0	0.5	1.0
	Intermediate	0.0	0.8	0.8
	High	0.0	0.0	0.0
$CHADS_2$ Intermediate risk	Low	1.5	1.0	2.0
	Intermediate	1.1	1.8	2.7
	High	0.0	9.1	9.1
$CHADS_2$ High risk	Low	0.9	1.8	2.6
	Intermediate	1.4	1.9	3.3
	High	6.5	6.5	12.0
CHA_2DS_2VASc Low risk	Low	0.7	0.0	0.7
	Intermediate	0.0	0.0	0.0
	High	-	-	-
CHA_2DS_2VASc Intermediate risk	Low	1.6	0.5	1.6
	Intermediate	0.9	0.9	1.8
	High	0.0	0.0	0.0
CHA_2DS_2VASc High risk	Low	1.0	2.0	2.5
	Intermediate	1.2	1.9	3.0
	High	5.8	6.7	11.5

Table 7. Within patient concordance between cardio-embolic and bleeding risk categories and outcomes

Cardio-embolic and bleeding risk scores	Concordance between cardio-embolic and bleeding risk category	% of patients experiencing a stroke [OR (95% CI)]*	% of patients experiencing a major bleeding [OR (95% CI)]*	% of patients experiencing a stroke or a major bleeding [OR (95% CI)]*
$CHADS_2$ /HAS-BLED	Discordance	0.8 [1.0]	1.7 [1.0]	2.5 [1.0]
	Partial Concordance†	1.5 [1.6 (0.2-11.9)]	1.4 [1.0 (0.2-4.2)]	2.8 [1.1 (0.3-3.7)]
	Concordance	1.8 [2.0 (0.3-14.9)]	1.7 [1.2 (0.3-5.3)]	3.2 [1.3 (0.4-4.3)]
CHA_2DS_2VASc/ HAS-BLED	Discordance	0.9 [1.0]	1.8 [1.0]	2.3 [1.0]
	Partial Concordance†	1.4 [1.3 (0.3-5.8)]	1.3 [0.8 (0.3-2.4)]	2.7 [1.1 (0.4-2.9)]
	Concordance	2.3 [2.1 (0.4-9.4)]	1.8 [1.2 (0.4-4.0)]	4.0 [1.7 (0.6-4.7)]

Legend: OR, odds ratio. CI, confidence interval.
*from logistic regressions adjusted for antithrombotic therapy
†1-category disagreement



Clinical Significance

- When deciding on antithrombotic therapy in patients with atrial fibrillation, the usefulness of a joint assessment of patient cardio-embolic and bleeding risks might be limited by the interdependence between the two risks
- The degree of correlation and concordance between validated cardio-embolic and bleeding risk schemes has never been explicitly described
- In a real-world population we confirmed that the available cardio-embolic and bleeding risk classifications are significantly correlated, but not exchangeable.

Supplementary Tables

Table 1. Correlation between cardio-embolic and bleeding scores in the whole population and in by-treatment defined groups

Cardio-embolic and bleeding risk scores	Treatment group	Trend for raw scores
		Spearman correlation coefficient (p value)*
$CHADS_2$/HAS-BLED	Any (whole population)	0.416 (<0.001)
	No antithrombotic therapy	0.603 (<0.001)
	On antiplatelet agent	0.420 (<0.001)
	On VKA	0.438 (<0.001)
CHA_2DS_2VASc/HAS-BLED	Any (whole population)	0.512 (<0.001)
	No antithrombotic therapy	0.673 (<0.001)
	On antiplatelet agent	0.563 (<0.001)
	On VKA	0.582 (<0.001)

Legend: VKA, vitamin K antagonists.
*P value for testing if Spearman correlation coefficient is statistically significantly different from 0

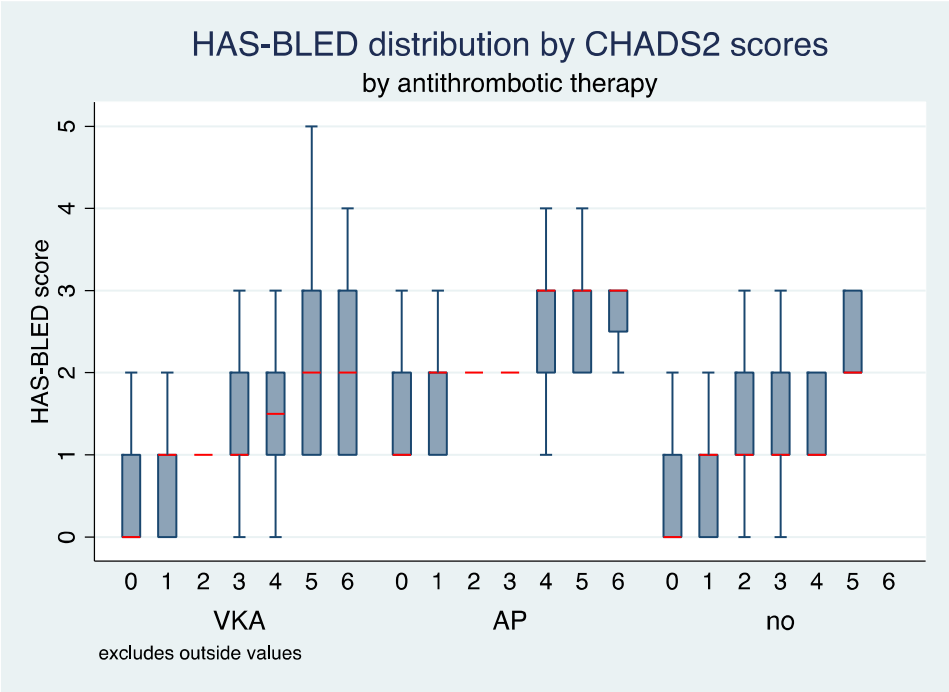
Table 2. Cardio-embolic and bleeding risk categories co-distribution and outcomes: all patients

Cardio-embolic risk category	HAS-BLED risk category	% of patients experiencing a stroke	% of patients experiencing a major bleeding	% of patients experiencing a stroke or a major bleeding
$CHADS_2$ Low risk	Low risk	0.7	0.4	0.7
	Intermediate risk	0.4	0.4	0.8
	High risk	0.0	0.0	0.0
$CHADS_2$ Intermediate risk	Low risk	1.3	0.8	1.7
	Intermediate risk	1.2	1.2	2.3
	High risk	4.3	2.1	6.4
$CHADS_2$ High risk	Low risk	0.9	1.7	2.6
	Intermediate risk	1.7	1.7	3.4
	High risk	5.6	5.1	10.2
CHA_2DS_2VASc Low risk	Low risk	0.6	0.0	0.6
	Intermediate risk	0.0	0.0	0.0
	High risk	-	-	-
CHA_2DS_2VASc Intermediate risk	Low risk	1.3	0.4	1.3
	Intermediate risk	0.4	0.4	0.9
	High risk	0.0	0.0	0.0
CHA_2DS_2VASc High risk	Low risk	0.9	1.8	2.3
	Intermediate risk	1.5	1.5	3.0
	High risk	5.3	4.5	9.4

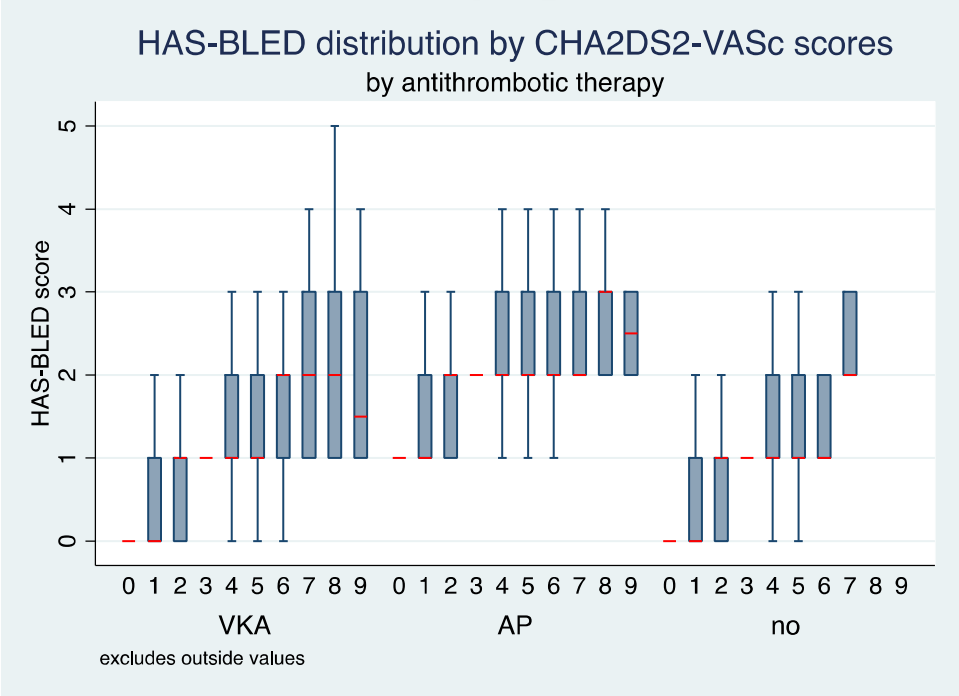
Supplementary figure

Cardio-embolic and bleeding risk scores co-distribution according to antithrombotic therapy prescribed at discharge

Panel A. $CHADS_2$ and HAS-BLED



Panel B. CHA_2DS_2-VASc and HAS-BLED



Legend: red line = median of HAS-BLED scores. VKA, vitamin K antagonists. AP, antiplatelet agents. No, no therapy