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Original article

Joint use of cardio-embolic and bleeding risk scores in elderly patients with atrial fibrillation

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ABSTRACT

Background: Scores for cardio-embolic and bleeding risk in patients with atrial fibrillation are described in the literature. However, it is not clear how they co-classify elderly patients with multimorbidity, nor whether and how they affect the physician's decision on thromboprophylaxis.
Methods: Four scores for cardio-embolic and bleeding risks were retrospectively calculated for ≥65 year old patients with atrial fibrillation enrolled in the REPOSI registry. The co-classification of patients according to risk categories based on different score combinations was described and the relationship between risk categories tested. The association between the antithrombotic therapy received and the scores was investigated by logistic regressions and CART analyses.
Results: At admission, among 543 patients the median scores (range) were: $CHADS_2$ 2 (0–6), CHA_2DS_2–VASc 4 (1–9), $HEMORR_2HAGES$ 3 (0–7), HAS-BLED 2 (1–6). Most of the patients were at high cardio-embolic/high-intermediate bleeding risk (70.5% combining $CHADS_2$ and $HEMORR_2HAGES$, 98.3% combining CHA_2DS_2–VASc and HAS-BLED). 50–60% of patients were classified in a cardio-embolic risk category higher than the bleeding risk category. In univariate and multivariable analyses, a higher bleeding score was negatively associated with warfarin prescription, and positively associated with aspirin prescription. The cardio-embolic scores were associated with the therapeutic choice only after adjusting for bleeding score or age.
Conclusion: REPOSI patients represented a population at high cardio-embolic and bleeding risks, but most of them were classified by the scores as having a higher cardio-embolic than bleeding risk. Yet, prescription and type of antithrombotic therapy appeared to be primarily dictated by the bleeding risk.

1. Introduction

The underuse of vitamin K antagonists (VKAs) among elderly patients with atrial fibrillation (AF) has been confirmed in different settings [1–6]. Indeed, the CHA_2DS_2–VASc [6,7], that assigns 2 points (and not 1 as $CHADS_2$ [8]) to age ≥75 years, and 1 point to age ≥65 years would qualify all patients older than 75 years as candidates for long term anticoagulation, and all patients older than 65 years for aspirin treatment, even in the absence of other risk factors [9–11].

Since the fear of treatment-related bleeding is the most likely reason for the under-prescription of anticoagulants, tools for the prediction of the risk of bleeding in patients with AF on VKAs have been proposed [12–15]. All the available scores for bleeding risk include older age among risk factors. The different therapeutic guidelines frame their recommendations on the degree of cardio-embolic risk based upon $CHADS_2$ or CHA_2DS_2–VASc, but fail to express uniform agreement on the use and usefulness of bleeding scores, although suggesting of considering the patient bleeding risk to decide on the long-term antithrombotic therapy [9–11]. Moreover, it is still controversial whether and to which extent the decisions on cardio-embolic prophylaxis in the most common population of patients with AF (the oldest old with

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[1] REPOSI denotes REgistro POliterapie Società Italiana di Medicina Interna.

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multimorbidity) currently rely upon a joint assessment of both cardio-embolic and bleeding risks.

With this background, we analyze retrospectively patients older than 65 years with atrial fibrillation or flutter (AFF) enrolled in REPOSI [16] during the first (2008) and the second (2010) collection waves of this registry, with the aims to describe: i) the stratification of patients according to the different scores for cardio-embolic and bleeding risks; ii) the within-patient relationship between cardio-embolic and bleeding risks as defined by these scores; iii) whether or not the prescription of antithrombotic therapy was related to the score-based assessment of cardio-embolic and bleeding risks.

2. Materials and methods

2.1. Study population

Patients analyzed in this study were recruited in the frame of the 'REgistro POliterapie SIMI' (REPOSI) [16]. The REPOSI is a collaborative and independent Registry organized by the Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute of Pharmacological Research in Milan with the purpose to create a network of internal medicine and geriatric wards in order to evaluate hospitalized patients older than 65 years affected by multiple diseases and prescribed with polypharmacy. Patients recruited for REPOSI in 2008 and 2010, and admitted to the participating Italian wards with a known diagnosis of AFF (International Classification of Diseases — Ninth Revision [ICD-9] codes 427.31 or 427.32) were analyzed in this study. Patients newly diagnosed with AFF during the index hospitalization were not included.

2.2. Cardio-embolic and bleeding risk stratification

The patient population was retrospectively classified according to the cardio-embolic risk as predicted by $CHADS_2$ and CHA_2DS_2–VASc scores [6,7], and according to the bleeding risk as predicted by $HEMORR_2HAGES$ and HAS-BLED scores [12,14]. The components of each score, the annual event rates associated with the risk categories as reported in the literature, as well as the corresponding absolute risk reduction or increase with VKAs are summarized in online Appendix A. The scores were retrospectively calculated for each patient using the data collected at admission on socio-demographic characteristics, clinical history and drug use before the hospitalization and the reason for hospitalization. A modified $HEMORR_2HAGES$ score not including genetic risk factors, and a modified HAS-BLED score, not including the labile INR factor were used, because the corresponding data were not available in REPOSI; both these modified versions of the scores have already been used and validated [12,14,17]. The resulting risks were reported both as continuous scores and as categories (low, intermediate, high), using for the latter the originally proposed score-based stratifications [6,12,14,17,18] (online Appendix A). Classification of patients' cardio-embolic risk was compared using both scores, and the classification of patients' bleeding risk using both scores. We then described the co-stratification of the study population using both a scheme for the cardio-embolic risk and one for the bleeding risk, testing different combinations. Correlation between scores, as a measure for trend, was tested by the Spearman test. Concordance/discordance between risk categories was expressed as percentage of patients classified into the same/different risk category. Although risk categories are categorical ordinal variables, linear regression analyses were used to show the average association between the risk categories as defined using the different scores. For this purpose the low, intermediate and high risk categories were coded as 0, 1 and 2, respectively.

2.3. Antithrombotic therapy and risk scores

The study population was characterized according to the antithrombotic therapy recorded at hospital admission, considering as long-term therapy VKAs and antiplatelet drugs (aspirin, clopidogrel, ticlopidine and aspirin plus dypyridamole). To evaluate retrospectively the association between the cardio-embolic/bleeding risk scores and the prescribed antithrombotic therapy, two sets of analyses were performed.

a. *Risk scores as predictors of VKA prescription*. A classic logistic regression was used to evaluate this relationship, in simple and multivariable analyses (including both cardio-embolic and bleeding score as predictors). CART (Classification and Regression Trees analysis) [19] was also used as a multivariable approach to further explore how the scores were hierarchically associated with VKA prescription. The program automatically selected for each score the best-splitting value for the therapeutic choice, i.e. that value above or below which VKAs were more likely to be prescribed or not.
b. *Risk scores as predictors of antithrombotic therapy type*. With the aim of taking into account all the possible antithrombotic options for AFF, a 4-level nominal variable was also used as dependent variable, coded as 0 for no therapy, 1 for antiplatelet therapy, 2 for VKAs, and 3 for VKAs plus antiplatelet agents. The variable levels were chosen in order to simulate an ordinal variable where each further level corresponded to an increasing antithrombotic burden. The association between this variable and the scores was explored using an ordered logistic regression when the proportional odds assumption was met, i.e. when the effect of the score on each therapeutic step was constant (the *omodel* user's command for STATA was used to verify the assumption). If this assumption was not met, a multinomial logistic regression was used, where the no-therapy choice was taken as reference and the association of the score with any other therapeutic choice was compared to the reference.

Then the analyses exploring the association between the risk scores and antithrombotic therapy were repeated adjusting for patient age, in order to look at the effect of the scores after holding the patient age constant; this is equivalent to remove the effect of age (a component of the scores) from the effect of the scores.

In order to take into account the multi-center origin of the REPOSI data, we adopted robust variance estimates that were obtained in all regression models by means of the Huber/White/sandwich estimator which considers observations as independent across groups (the REPOSI centers in this case).

STATA was used to perform all the analyses (version 12, Statacorp, College Station, Tx, US).

3. Results

3.1. Study population

The 2008–2010 installments of REPOSI included 2712 patients, 1332 enrolled in 2008 and 1380 in 2010. Five hundred and forty-three patients (20.0%) were admitted to hospital with a known diagnosis of AFF, 247 in 2008 (18.5%) and 296 in 2010 (21.4%). Patients with AFF at admission (Table 1) were significantly older than those without (median age = 81.1, range 65.4–100.6 years, versus median age = 78.6, range 65.0–101.4 years, $p < 0.001$); approximately 80% of patients were older than 75 years. Two hundred sixty-five were males (48.8%), with no difference in gender composition compared to patients without AFF. Twenty-eight patients with AFF at admission (5%) died during the hospitalization. Table 1 shows also the proportion of patients presenting a stroke or a bleeding event as reason for admission or during the hospital stay.

3.2. Cardio-embolic and bleeding risk stratification

Table 1 reports the mean and median score values at admission. Table 2 shows how the study population was stratified into cardio-embolic and bleeding risk categories based upon the different scores.

Table 1
Demographic and clinical characteristics of the study population.[a]

Characteristic	
Male, n (%)	265 (48.8)
Mean age ± SD (median, range)	81.0 ± 7.3 (81.1, 65.4–100.6)
Median number of drugs per patient (range)	6 (1–15)
Mean $CHADS_2$ ± SD (median, range)	2.2 ± 1.1 (2, 0–6)
Mean CHA_2DS_2–VASc ± SD (median, range)	3.8 ± 1.2 (4, 1–9)
Mean $HEMORR_2HAGES$ ± SD (median, range)	2.6 ± 1.2 (3, 0–7)
Mean HAS-BLED ± SD (median, range)	2.6 ± 1.1 (2, 1–6)
Oral antithrombotic therapy at admission, n (%)[b]	
Vitamin K antagonist	210 (38.7)
Antiplatelet agent	174 (32.0)
VKA + antiplatelet	16 (3.0)
None	143 (26.3)
Stroke as reason for admission, n (%)	22 (4.0)
Stroke as adverse event during the hospital stay, n (%)	2 (0.4)
Bleeding as reason for admission, n (%)	16 (2.9)[c]
Bleeding as adverse event during the hospital stay, n (%)	8 (1.5)[c]

[a] The risk scores were calculated counting the risk factors at admission.
[b] 15% of patients not receiving VKAs at admission were on low molecular weight heparin (LMWH) or fondaparinux at therapeutic or prophylactic doses.
[c] Two patients presented a bleeding event both as reason for admission and during the hospital stay.

A high correlation was found between the two cardio-embolic risk scores (Spearman correlation coefficient 0.86, p value < 0.001), but with a discordance of 25% between the two risk classifications. In detail, all patients classified at intermediate or high risk using $CHADS_2$ were classified at high risk according to CHA_2DS_2–VASc; patients with a low cardio-embolic risk according to $CHADS_2$ were reclassified by CHA_2DS_2–VASc as having an intermediate (9 of 16, 56%) or a high (7 of 16, 43%) risk. There was a high correlation between the two bleeding risk scores (Spearman correlation coefficient 0.82, p value < 0.001), but with a discordance of 43% between the two risk classifications. In detail, nearly all (117 of 119, 98%) patients classified at high risk according to $HEMORR_2HAGES$ were classified at high risk also according to HAS-BLED; 57% (193/340) of patients classified at intermediate risk according to $HEMORR_2HAGES$ were also classified at intermediate risk according to HAS-BLED, whereas the remaining 43% patients (147/340) were classified at high HAS-BLED risk. Patients with a low bleeding risk according to $HEMORR_2HAGES$ were classified at intermediate (83 among 84, 99%) or, in one case only, at high HAS-BLED risk. Fig. 1 (plots a and b) in the online Appendix B exemplifies the average relationship between risk categories defined by each couple of scores.

Table 2
Risk stratification according to cardio-embolic and bleeding scores.

a. Cardio-embolic risk scores

Cardio-embolic risk category	$CHADS_2$			CHA_2DS_2–VASc		
	Score	Number of patients	%	Score	Number of patients	%
Low	0	16	3.0	0	0	0
Intermediate	1	118	21.7	1	9	1.7
High	≥2	409	75.3	≥2	534	98.3

b. Bleeding risk scores

Bleeding risk category	$HEMORR_2HAGES$			HAS-BLED		
	Score	Number of patients	%	Score	Number of patients	%
Low	0–1	84	15.5	0	0	0
Intermediate	2–3	340	62.6	1–2[a]	278	51.2
High	≥4	119	21.9	≥3	265	48.8

[a] 60 patients (11.0%) had a HAS-BLED score 1.

Table 3
Patient distribution according to cardio-embolic and bleeding risk categories: number of patients (% of the whole population).

$CHADS_2$ \ $HEMORR_2HAGES$	Low risk	Intermediate risk	High risk	Total
Low risk	11 (2.0)	5 (0.9)	–	
Intermediate risk	47 (8.7)	62 (11.4)	9 (1.7)	
High risk	26 (4.8)	273 (50.3)	110 (20.2)	
				543 (100)

CHA_2DS_2–VASc \ HAS-BLED	Low risk	Intermediate risk	High risk	Total
Low risk	–	–	–	
Intermediate risk	–	8 (1.5)	1 (0.2)	
High risk	–	270 (49.7)	264 (48.6)	
				543 (100)

According to the predicted risk associated with the scores reported in the original papers (see the online Appendix A for details): White cells: the predicted annualized cardio-embolic risk tends to be larger than the predicted annualized bleeding risk (and the predicted absolute risk reduction of cardio-embolic events with warfarin tends to be larger than the predicted absolute risk increase of bleeding events with warfarin). Dark gray cells: the predicted annualized bleeding risk tends to be larger than the predicted annualized cardio-embolic risk (and the predicted absolute risk increase of bleeding events with warfarin tends to be larger than the predicted absolute risk reduction of cardio-embolic events with warfarin). Light gray cells: the predicted annualized bleeding risk tends to be equal or larger than the predicted annualized cardio-embolic risk (and the predicted absolute risk increase of bleeding events with warfarin tends to be equal or larger than the predicted absolute risk reduction of cardio-embolic events with warfarin). Predicted denotes as reported in score validation studies.

Table 3 shows how the study population was co-classified according to both the cardio-embolic and bleeding risks using two different score combinations. The Spearman correlation between $CHADS_2$ and $HEMORR_2HAGES$ scores and between CHA_2DS_2–VASc and HAS-BLED scores was, respectively, 0.424 and 0.316. Most of the patients were at high cardio-embolic/high-intermediate bleeding risk (70.5% when $CHADS_2$ plus $HEMORR_2HAGES$ were used, 98.3% when CHA_2DS_2–VASc plus HAS-BLED were used). Plots c, d, e and f in Fig. 1 (online Appendix A) show the average relationship between cardio-embolic and bleeding risk categories using the 4 possible score combinations.

3.3. Antithrombotic therapy and risk scores

The antithrombotic therapy that REPOSI patients were receiving at admission is shown in Table 1.

3.3.1. Risk scores as predictors of VKA prescription

Table 4 reports the number and percentage of patients on VKAs in each cell co-defined by the cardio-embolic and bleeding risk. The highest rate of VKA prescription was found among patients at intermediate cardio-embolic and low bleeding risk when the $CHADS_2$/$HEMORR_2HAGES$ co-classification was used, and among patients at high cardio-embolic and intermediate bleeding risk when the CHA_2DS_2–VASc/HAS-BLED combination was used (ignoring the 100% cell including only 1 patient). In simple logistic regressions, a higher bleeding score, using either $HEMORR_2HAGES$ or HAS-BLED, was associated with a lower probability to receive VKA ($p < 0.001$). Neither cardio-embolic risk score was significantly associated with VKAs prescription in unadjusted analysis. Only after adjusting for the bleeding risk score (either $HEMORR_2HAGES$ or HAS-BLED) was a higher cardio-embolic risk score (either $CHADS_2$ or CHA_2DS_2–VASc) associated with a higher probability to receive VKAs ($p < 0.001$ for any combination). When all the 4 scores were included as covariates, the $HEMORR_2HAGES$

Table 4
Frequency of VKA prescription according to cardio-embolic and bleeding risk categories: number of patients (% of the total number of patients in each cell).

$CHADS_2$ \ $HEMORR_2HAGES$	Low risk	Intermediate risk	High risk	
Low risk	4 (36.4)	1 (20.0)	–	5 (31.2)
Intermediate risk	31 (66.0)	19 (30.6)	0 (0.0)	40 (33.9)
High risk	16 (61.5)	130 (47.6)	25 (22.7)	171 (41.8)

CHA_2DS_2–VASc \ HAS-BLED	Low risk	Intermediate risk	High risk	
Low risk	–	–	–	–
Intermediate risk	–	2 (25.0)	1 (100.0)	3 (33.3)
High risk	–	150 (55.6)	73 (27.6)	223 (41.8)

According to the predicted risk associated with the scores reported in the original papers (see the online Appendix A for details): White cells: the predicted annualized cardio-embolic risk tends to be larger than the predicted annualized bleeding risk (and the predicted absolute risk reduction of cardio-embolic events with warfarin tends to be larger than the predicted absolute risk increase of bleeding events with warfarin). Dark gray cells: the predicted annualized bleeding risk tends to be larger than the predicted annualized cardio-embolic risk (and the predicted absolute risk increase of bleeding events with warfarin tends to be larger than the predicted absolute risk reduction of cardio-embolic events with warfarin). Light gray cells: the predicted annualized bleeding risk tends to be equal or larger than the predicted annualized cardio-embolic risk (and the predicted absolute risk increase of bleeding events with warfarin tends to be equal or larger than the predicted absolute risk reduction of cardio-embolic events with warfarin). Predicted denotes as reported in score validation studies.

and $CHADS_2$ scores remained significant predictors. The CART analysis confirmed these results, and pointed out that a low bleeding risk score seemed to affect positively the probability of VKA prescription, whereas cardio-embolic risk scores were associated with the probability of VKA prescription only among higher bleeding risk scores (Fig. 2 in the online Appendix A).

3.3.2. Risk scores as predictors of the type of antithrombotic therapy

When an ordered 4-level variable was used for antithrombotic therapy, the proportional odds assumption was met for both cardio-embolic risk scores, i.e. higher scores were associated to therapeutic choices with a higher antithrombotic potency, but in a quasi statistically significant way only for $CHADS_2$ ($p = 0.054$). The proportional odds assumption was not met for the bleeding risk scores. In simple multinomial analysis, and also after adjusting for any cardio-embolic risk score, the $HEMORR_2HAGES$ score was associated with the therapeutic choice, but in different ways: a higher $HEMORR_2HAGES$ score was negatively associated with the prescription of VKA compared to no therapy, but it was positively associated with the prescription of antiplatelet agents compared to no therapy. A direct association between a higher score and antiplatelet prescription was also found for the HAS-BLED score in simple multinomial logistic regression, and after adjusting for any cardio-embolic risk score. Conversely HAS-BLED was not associated with the prescription of VKA. None of the reported findings changed when patients on LMWH or fondaparinux were excluded from the analyses. After adjusting for patient age, both the cardio-embolic risk scores became significantly associated with the antithrombotic therapy in all types of analysis even without adjusting for the bleeding risk scores. All the remaining results did not change.

4. Discussion

The REPOSI registry was designed in order to collect data on a representative sample of patients admitted to internal medicine wards, increasingly characterized in Italy and elsewhere in Europe by advanced age and multimorbidity. The first aim of these post-hoc analyses was to describe how the available scores for cardio-embolic and bleeding risks would classify patients with AFF in this complex population. We then evaluated whether or not risk assessment according to the scores was related the choice of antithrombotic therapy.

The main novelty of this study was to look, albeit retrospectively, at the co-classification of this elderly population using a combination of scores for both cardio-embolic and bleeding risk, that might theoretically provide the physician with a higher potential for tailoring each individual treatment than using a strategy based only on the cardio-embolic. As expected, the REPOSI population was on average both at high cardio-embolic and bleeding risk (see Table 2a), even though the patients' cardio-embolic risk category tended to be higher than the bleeding risk category. In particular, the percentage of patients belonging to a cardio-embolic risk category higher than the bleeding risk category was more than 60% when $CHADS_2$ plus $HEMORR_2HAGES$ were jointly used, and approximately 50% when CHA_2DS_2–VASc plus HAS-BLED were used. This co-classification would apparently lead to recommend anticoagulation for approximately 50% of REPOSI patients. However, the same definitions for risk category (i.e. low, intermediate or high) for different scores do not correspond to the same annual risk of stroke or bleeding (and so to the same absolute effect of the treatment), as reported in the online Appendix A. In addition, a more appropriate way of using the score-based predictions of risk to individualize treatment recommendations should take into account also the different weight that a patient might assign to such clinical events, as stroke and bleeding [20–22].

Our data confirm the well-known reclassification effect of CHA_2DS_2–VASc [6,7,19], which moved almost all patients at low and intermediate $CHADS_2$ score to the high risk category. As expected by definition for a ≥ 65 year population, none of the REPOSI patients was classified as having a low CHA_2DS_2–VASc risk [7,19], with the implication that according to this score all REPOSI patients with AFF would be treated with anticoagulants.

The cardio-embolic risk stratification of REPOSI patients resembled that recently described in an elderly cohort from the UK General Practice Research Database (GPRD) [5]. However, the REPOSI population had a higher representation of patients at intermediate-high $CHADS_2$ score, presumably because of a higher mean age and different selection criteria (patients at the time of hospital admission, with a likely higher rate of morbidity than those referred to general practitioners).

There was also a high representation of the high risk category for bleeding among REPOSI patients, higher than in the UK cohort [5]. As for the cardio-embolic scores, a reclassification effect with HAS-BLED was observed compared to $HEMORR_2HAGES$. Indeed, none of the REPOSI patients was at low HAS-BLED risk (because of age, none had a 0 score), and in 40% of them HAS-BLED classified patients into a higher risk category than $HEMORR_2HAGES$. This effect was attenuated provided that a HAS-BLED score of 1 was included in the low risk category together with score 0 (as done in other studies [5,18]), yet only 11% of patients had a HAS-BLED score of 1. In fact, HAS-BLED was developed in order to provide a therapeutic guideline easier to memorize and includes more practicable risk factors than $HEMORR_2HAGES$ [14].

We observed a low overall rate of prescription of VKAs, confirming a previous analysis based on REPOSI [16]. More interesting, the distribution of the percentages of patients treated with VKAs across the cells defined by the scores (Table 3) and the results of the logistic analyses showed that the patient's bleeding risk, but not the cardio-embolic risk alone, predicted the therapeutic choice. These findings on the relationship between the bleeding score and VKA prescription are consistent with those of the UK cohort [5]. In the literature, evidence on the relationship between cardio-embolic scores and VKA prescription in real settings is not uniform [5,23,24]. In the present study, the cardio-embolic risk was a predictor of VKA prescription, only after adjusting for the bleeding score or patient age. In addition, the association found between a higher bleeding score and antiplatelet therapy clearly

confirms the tendency to prescribe aspirin in clinical practice when evidence or perception of a higher risk of bleeding prevents VKA prescription. Irrespective of the cardio-embolic risk, this situation materializes especially in the elderly, even though this behavior is not justified by a safer profile of aspirin compared to VKAs [25,26], and either by a clear efficacy of aspirin [27].

This study has several limitations. First, a certain degree of underreporting is expected because of the post-hoc nature of our research question. Thus, it is possible that the actual risk scores were underestimated. Second, this was only an indirect and theoretical investigation of the association between patients' risks and physician's decisions, because it is not known whether or not REPOSI physicians applied these scores to take decisions. Another limitation is the assumption that the risk scores proposed in the literature for patients with AFF have a good predictive ability in a REPOSI-like elderly population. A further fundamental step should be the evaluation of the impact on patient outcomes of a decision strategy based on combined cardio-embolic and bleeding risk assessment compared to a strategy of cardio-embolic risk assessment alone.

Learning points

- Scores for cardio-embolic and bleeding risk in patients with atrial fibrillation are described in the literature to aid at tailoring the long term antithrombotic therapy; all of them include age as risk factor.
- We observed how the available scores ($CHADS_2$ and CHA_2DS_2–VASc, for cardio-embolic risk, and $HEMORR_2HAGES$ and HAS-BLED, for bleeding risk) co-classified complex elderly patients with multimorbidity admitted to Italian internal medicine and geriatric wards, and we confirmed that they configured a population both at high cardio-embolic and at high bleeding risk.
- 50–60% of patients (depending on the score couples used) were classified in a cardio-embolic risk category higher than the bleeding risk category.
- In those patients, the prescription and the type of antithrombotic therapy appeared to be primarily influenced by the bleeding risk; both the cardio-embolic scores were associated with the therapeutic choice only after adjusting for the patient bleeding score or age.

Conflict of interest

The authors declare that they do not have any conflict of interests.

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Appendix A. Supplementary data

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