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Is anticoagulant therapy always indicated in "medium-risk" patients with first diagnosed atrial fibrillation? Insights from a real world, 10-year observational study

Laura Bonfanti [a,1], Giuseppe Lippi [b,1], Valentina Donelli [c,1], Federica Pigna [a,1], Carlotta Saccenti [a,1], Gianfranco Cervellin [a,*,1]

[a] Emergency Department, University Hospital of Parma, Italy
[b] Section of Clinical Biochemistry, University of Verona, Verona, Italy
[c] Postgraduate Emergency Medicine School, University of Parma, Parma, Italy

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ABSTRACT

Background: The choice of antithrombotic prophylaxis in the so-called "medium-risk" patients (i.e., CHA_2DS_2-VASc score = 1 in males or 2 in females) is one of the major enigmatic issues in clinical management of atrial fibrillation (AF).
Methods: We retrospectively evaluated 30-day and 1-year thromboembolic events in all consecutive medium-risk patients visited for first diagnosed AF in the local Emergency Department during a 10-year period. The main aim was to establish whether anticoagulant or antiplatelet therapy was effective to lower the thromboembolic risk in patients receiving these drugs. Bleeding events, related to anticoagulant or antiplatelet therapy, was defined as secondary end point.
Results: The final study population consisted of 6389 (3640 males and 2749 females) patients for whom a complete dataset regarding targeted follow-up was available. Patients were then subdivided into two subgroups, according to performance of cardioversion and spontaneous sinus rhythm restoring. In both genders, no significant difference in thromboembolic or bleeding events was noted between patients who underwent cardioversion and were discharged with oral anticoagulant therapy or antiplatelet treatment versus those who were not treated with antithrombotic drugs. Moreover, no difference was also observed in thromboembolic or hemorrhagic event rate between low risk and "medium-risk" patients.
Conclusions: The results of this study suggest that anticoagulant or antiplatelet therapy would not produce clinical benefits in "medium-risk" AF patients.

1. Introduction

Although atrial fibrillation (AF) is still considered a growing health care issue, mainly attributable to increasing population aging, uncertainties remain regarding its optimal management. One of the leading problems is the choice of antithrombotic prophylaxis in the so-called "medium-risk" patients [1,2]. Several lines of evidence attest that the yearly risk of stroke in AF patients ranges between 0.4 and 12%, depending on several factors [3]. In order to accurately stratify the thromboembolic risk, and then define the most effective clinical management, several scores have been proposed in the last decades. The CHA_2DS_2-VASc score has been introduced in 2010 as a refinement of the $CHADS_2$ score, is now included in the most recent guidelines for management of AF and is hence accepted and widely used in clinical practice [4,5]. Based on CHA_2DS_2-VASc score, according to the suggestions of the 2016 European Society of Cardiology (ESC) guidelines, patients are classified as follows: i) low risk (CHA_2DS_2-VASc score = 0 in males and 1 in females): antithrombotic therapy of any kind not recommended; ii) "medium-risk" (CHA_2DS_2-VASc score = 1 in males and 2 in females): anticoagulation should be considered; iii) high risk (CHA_2DS_2-VASc score ≥ 2 in males and ≥ 3 in females): anticoagulation for stroke prevention is clearly recommended. Evidence is strong for classes i) and iii), whilst some degrees of uncertainty still surround class ii) [1]. The evidence that patients with a CHA_2DS_2-VASc risk score of ≥2 in men and ≥3 in women would benefit from oral anticoagulant (OAC) therapy is supported by several controlled trials and meta-analyses [6–9]. Unlike these classes of risk, evidence concerning the risk of stroke in patients

* Corresponding author at: Emergency Department, University Hospital of Parma, Via Gramsci 14, 43126 Parma, Italy.
E-mail address: gianfranco.cervellin@gmail.com (G. Cervellin).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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with a single clinical risk factor (i.e. CHA_2DS_2-VASc score of 1 in men and 2 in women, respectively) largely relies on observational studies, performed in patients not receiving OAC [6–9]. The information that has become available so far is somewhat contradictory, since the rate of stroke and thromboembolism varies considerably in this class of patients, and this is mainly attributable to differences in outcomes, populations and anticoagulant status. According to the 2016 ESC guidelines, OAC should hence be considered in these patients, by carefully balancing the predicted reduction of stroke risk, the risk of bleeding and the patient preference. Notably, female sex alone does not appear to increase the risk of stroke in the absence of other risk factors [10,11].

Although the former 2010 ESC guidelines still suggested the use of aspirin in patients refusing anticoagulation, the new 2016 guidelines clearly acknowledge that antiplatelet therapy should be no longer considered for this indication [3]. A peculiar aspect is represented by patients with first diagnosed AF, for whom a cardioversion (both electrical and pharmacological) is scheduled. According to the recent guidelines, patients in whom AF is lasting for >48 h should be invited to assume OAC for at least 3 weeks before cardioversion, and 4 weeks after the procedure [3]. Patients who are eligible for trans-esophageal echocardiography for excluding the presence of atrial thrombi are an exception to this rule. In these patients cardioversion could be considered without previous anticoagulation. The treatment should then be given for the following 4 weeks. At variance with this class of patients, the guidelines only suggest the administration of unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH) just before the procedure in those with AF lasting <48 h and who are not already taking OAC.

Thromboembolic and bleeding risk factors are often overlapping in patients with advanced age and co-morbidities [12,13], so that they shall be accurately identified and managed, when possible. Bleeding risk can be assessed using different scores, but the HAS-BLED [hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (≥65 years), drugs/alcohol concomitantly (1 point each)] is indeed the most widely used [14]. Recently, the ABC (age, biomarkers, clinical history) bleeding score, which also includes some selected biomarkers, has been proposed and validated [13].

Therefore, the aim of this study was to investigate the 30-day and 1-year thromboembolic risk in all consecutive "medium-risk" patients visited for first diagnosed AF in a large urban Emergency Department (ED).

2. Materials and methods

This retrospective and observational study included all patients with episodes of firstly diagnosed AF (both first-diagnosed AF and paroxysmal AF) or first diagnosed atrial flutter (AFl), which is equivalent to AF in terms of thromboembolic risk, included in the electronic hospital database between January 1st, 2007 and December 31st, 2016 (i.e., 3653 days). The University Hospital of Parma, a 900-bed teaching hospital serving a population of nearly 340,000 inhabitants, is the only general hospital in the urban district of Parma, which thus enables an accurate enrolment and follow up of all patients living in that provincial area.

Based on the guidelines on thromboembolic risk stratification, male patients with CHA_2DS_2-VASc = 1 and female patients with CHA_2DS_2-VASc = 2 (i.e., "medium-risk" population) were selected. Our leading purpose was exploring as to whether in these two patient groups the OAC therapy could be effective to lower the thromboembolic risk compared to patients not receiving OAC drugs. The evaluation of bleeding events, related to anticoagulant therapy, was defined as secondary endpoint.

All clinical records were separately examined by two authors (i.e., L.B. and V.D.), to verify and rule out inaccurate recording. The selected exclusion criteria were: age <18 years; pregnancy; no access to personal data; long-standing persistent or permanent AF; death during index hospital episode, or during the follow-up, when due to causes unrelated to arrhythmia; and inaccurate follow-up at 30 days and 1 year.

For each patient, the following items were recorded: age, gender, type of cardioversion (i.e., spontaneous, electrical, or pharmacological) when performed and achieved, rate control strategy when applied, CHA_2DS_2-VASC score, HAS-BLED score, previous home therapy with OAC or antiplatelet drugs (when present), therapy administered whilst in the ED (i.e., heparin, LMWH, or nothing), therapy prescribed at discharge (i.e., OAC or antiplatelet drugs vs. no therapy), new ED visits within 30 days for thromboembolic or bleeding events, new ED visits within 1 year for thromboembolic or bleeding events.

The vast majority of patients undergoing cardioversion received enoxaparin 1 mg/Kg of body weight before the procedure, unless previously treated with OAC, whilst long term OAC or antiplatelet therapy was administered on individual basis, according to CHA_2DS_2-VASc score, HAS-BLED score and clinical judgement. Some discrepancies in treatment protocol were due to the different versions of guidelines available during the study period. The whole population was subdivided by gender, for differential calculation of CHA_2DS_2-VASC score.

Statistical analysis was performed with IBM SPSS Statistics 20.0 software, and was based on Chi-Square testing (with and without Yates' correction). Due to the retrospective design of this study and complete anonymization of patients' data, ethical committee approval was unnecessary, as for local policy. The study was performed in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

3. Results

A total number of 6594 patients with episodes of first diagnosed AF or AFl were initially identified from the hospital database. A complete dataset regarding targeted follow up was available for 6389 patients, who hence represented our final study population (mean age, 69.1 ± 13.6 years). Specifically, 2018 patients (31.6%) were aged <65 years, 1837 (28.7%) between 65 and 74 years, and 2534 (39.7%) were aged ≥75 years. The subdivision of sample size into genders generated a male group (**M group**) encompassing 3640 men and a female group (**F group**) encompassing 2749 women, respectively. The two groups were separately analyzed.

3.1. M group

The mean age in this group was 66.2 ± 14.3 years. Overall, 1433 patients (39.4%) were aged <65 years, 1050 (28.8%) between 65 and 74 years, and 1157 (31.8%) ≥75 years. The following strategies were adopted in this group: electrical cardioversion in 269 patients (7.4%) with UFH or LMWH administered in 223 patients (82.9%); pharmacological cardioversion in 2017 patients (55.4%) with UFH or LMWH administered in 1812 patients (89.8%); spontaneous sinus rhythm restored in 273 patients (7.5%) with UFH or LMWH administered in 200 patients (73.4%); and rate control in 1081 patients (29.7%) with UFH or LMWH administered in 1022 patients (94.5%).

The CHA_2DS_2-VASC score was 0 in 885 patients (24.4%), 1 in 794 patients (21.8%) and ≥2 in 1957 patients (53.9%), whilst the HAS-BLED score was 0 in 972 patients (26.7%), 1 in 1431 patients (39.3%), 2 in 1063 patients (29.2%) and ≥3 in 174 patients (4.8%).

A sub analysis was then performed in the subgroup at "medium-risk" (i.e., CHA_2DS_2-VASC = 1; 794 patients). In this group the following strategies were adopted: electrical cardioversion in 75 patients (9.5%) with UFH or LMWH administered in 68 patients (90.7%); pharmacological cardioversion in 492 patients (61.9%) with UFH or LMWH administered in 444 patients (90.2%); spontaneous sinus rhythm restored in 67 patients (8.4%) with UFH or LMWH administered in 50 patients (57.5%); and rate control in 160 patients (20.2%) with UFH or LMWH administered in 158 patients (98.8%).

The **M group** was then divided into two subgroups, i.e., **MC**, including patients who underwent cardioversion (both electrical or pharmacological) and those who displayed a spontaneous sinus rhythm restoring (634 cases; 79.9%), or **MR**, including patients who did not undergo cardioversion, for whom rate control strategy was adopted (160 cases; 20.1%).

The strategies and events recorded in the **MC** group were:

- No anti-thrombotic therapy at discharge in 405 patients (63.9%): no thromboembolic events within 30 days, 5 thromboembolic events within 1 year; no bleeding events within 30 days and 1 year. All the 5 thromboembolic events occurred in patients who underwent pharmacological cardioversion;
- Prescription of OAC at discharge in 37 patients (5.9%): no thromboembolic events within 30 days, 1 thromboembolic event within 1 year; no bleeding events within 30 days; 2 bleeding events within 1 year;

- Prescription of antiplatelet therapy in 192 patients (30.2%): no thromboembolic events within 30 days, 1 thromboembolic event within 1 year; no bleeding events within 30 days and 1 year.

In the **MR** group the following events were recorded:

- No anti-thrombotic therapy at discharge in 0 cases.
- Prescription of OAC at discharge in 149 patients (93.1%): no thromboembolic events within 30 days, 1 thromboembolic event within 1 year; no bleeding events within 30 days; 2 bleeding events within 1 year;
- Prescription of antiplatelet therapy in 11 patients (6.9%): no thromboembolic events within 30 days and 1 year; no bleeding events within 30 days; 1 bleeding event within 1 year.

As shown in Table 1, the analysis of the **MC** group (i.e., patients with a $CHA_2DS_2VASc = 1$, cardioverted electrically, pharmacologically or spontaneously) showed no significant differences, both in thromboembolic and bleeding event rate. Moreover, no significant difference in the thromboembolic event rate was found when comparing patients with CHA_2DS_2-VASC score of 0 or 1, in both groups discharged without antithrombotic therapy (Table 2).

3.2. F group

The mean age in this group was 73.4 ± 12.9 years. Overall, 585 patients (21.3%) were aged <65 years, 784 (28.5%) between 65 and 74 years, and 1377 (50.2%) ≥75 years. The following strategies were adopted in this group: electrical cardioversion in 87 patients (3.2%) with UFH or LMWH administered in 79 patients (90.1%); pharmacological cardioversion in 1726 patients (62.8%) with UFH or LMWH administered in 1506 patients (87.3%); spontaneous sinus rhythm restored in 221 patients (8%) with UFH or LMWH administered in 119 (53.8%); and rate control in 715 patients (26%) with UFH or LMWH administered in 711 patients (99.4%).

Table 1
Thromboembolic events in the **MC** (**Males Cardioverted**; i.e., male patients who underwent a cardioversion, both electrical and pharmacological, and those who displayed a spontaneous sinus rhythm restoring) group, divided according to the therapy.

	Anticoagulant therapy	No therapy
Thromboembolic events (total events = 6)	1; [2.7%]	5; [1.3%]
No thromboembolic events (total = 436)	36; [97.3%]	400; [98.7%]
Total of patients	37	405
p-Value	0.997 (relative risk[a], 0.5; 95% CI, 0.1–3.8)	
	Antiplatelet therapy	No therapy
Thromboembolic events (total events = 6)	1; [2.7%]	5; [1.3%]
No thromboembolic events (total = 591)	191; [2.7%]	400; [98.7%]
Total of patients	192	405
p-Value	0.818 (relative risk[a], 2.4; 95% CI, 0.6–20.2)	
	Antiplatelet therapy	Anticoagulant therapy
Thromboembolic events (total events = 2)	1; [0.5%]	1; [2.7%]
No thromboembolic events (total = 227)	191; [99.5%]	36; [97.3%]
Total of patients	192	37
p-Value	0.794 (relative risk[b], 5.2; 95% CI, 0.3–81.1)	

In square brackets the percentages of events or no events referred to the total of patients of each group are reported.
[a] Relative risk relative to no therapy versus therapy.
[b] Relative risk anticoagulant versus antiplatelet therapy.

Table 2
Thromboembolic events in the **MC** (**Males Cardioverted**; i.e., male patients who underwent a cardioversion, both electrical and pharmacological, and those who displayed a spontaneous sinus rhythm restoring) group, divided according to the CHA_2DS_2-VASC score.

	CHA_2DS_2-VASC score = 0	CHA_2DS_2-VASC score = 1
Thromboembolic events (total events = 5)	1; [0.1%]	4; [0.5%]
No thromboembolic events (total = 1670)	883; [99.9%]	790; [99.5%]
Total of patients	884	794
p-Value	0.308 (relative risk, 4.5; 95% CI, 0.5–39.8)	

Relative risk of CHA_2DS_2-VASC score 1 versus 0.
In square brackets the percentages of events or no events referred to the total of patients of each group are reported.

The CHA_2DS_2-VASC score was 1 in 233 patients (8.5%), 2 in 321 patients (11.6%) and ≥3 in 2195 patients (79.9%), whilst the HAS-BLED score was 0 in 270 patients (9.8%), 1 in 429 patients (15.6%), 2 in 1591 patients (57.9%) and ≥3 in 459 patients (16.7%).

A sub analysis was then performed in the subgroup at "medium-risk" (i.e., CHA_2DS_2-VASC = 2; 321 patients). In this group the following strategies were adopted: electrical cardioversion in 23 patients (7.1%) with UFH or LMWH administered in 21 patients (91.3%); pharmacological cardioversion in 238 patients (74.1%) with UFH or LMWH administered in 213 patients (89.5%); spontaneous sinus rhythm restored in 21 patients (7%) with UFH or LMWH administered in 13 patients (61.9%); and rate control in 39 patients (11.8%) with UFH or LMWH administered in 33 patients (86.8%).

The **F group** was then divided into two subgroups, i.e., i) **FC**, including patients who underwent a cardioversion (both electrical or pharmacological) and those who displayed a spontaneous sinus rhythm restoring (283 cases; 88.1%), or **FR**, including patients who did not undergo cardioversion, for whom rate control strategy was adopted (38 cases; 11.8%).

The strategies and events recorded in the **FC** group were:

- No anti-thrombotic therapy at discharge in 194 patients (68.6%): no thromboembolic events within 30 days, 4 thromboembolic events within 1 year; no bleeding events within 30 days and 1 year. Three thromboembolic events occurred in patients who underwent pharmacological cardioversion, whereas 1 event in a patient with restoration of spontaneous sinus rhythm; no events in patients electrically cardioverted;
- Prescription of OAC at discharge in 21 patients (7.4%): no thromboembolic events within 30 days, 1 thromboembolic event within 1 year; no bleeding events within 30 days; 1 bleeding event within 1 year;
- Prescription of antiplatelet therapy in 68 patients (24%): no thromboembolic events within 30 days, 1 thromboembolic event within 1 year; no bleeding events within 30 days and 1 year.

In the **FR** group the following events were recorded:

- No anti-thrombotic therapy at discharge in 4 cases (10.5%): no thromboembolic events within 30 days and 1 year; no bleeding events within 30 days and 1 year;
- Prescription of OAC at discharge in 29 patients (76.3%): no thromboembolic events within 30 day and 1 year; no bleeding events within 30 days; 2 bleeding events within 1 year;
- Prescription of antiplatelet therapy in 5 patients (13.2%): no thromboembolic events within 30 days and 1 year; no bleeding events within 30 days and 1 year.

As shown in Table 3, the analysis of the **FC** group (i.e., patients with a CHA_2DS_2-VASC = 2, cardioverted electrically, pharmacologically or spontaneously) showed no significant differences, both in

Table 3
Thromboembolic events in the **FC** (**Females Cardioverted**; i.e., male patients who underwent a cardioversion, both electrical and pharmacological, and those who displayed a spontaneous sinus rhythm restoring) group, further divided according to the therapy.

	Antiplatelet therapy	No therapy
Thromboembolic events (total events = 5)	1; [5%]	4; [2.1%]
No thromboembolic events (total = 210)	20; [95%]	190; [97.9%]
Total of patients	21	194
p-Value	0.633 (relative risk[a], 0.433; 95% CI, 0.1–3.7)	

	Antiplatelet therapy	No therapy
Thromboembolic events (total events = 5)	1; [1.5%]	4; [2.1%]
No thromboembolic events (total = 257)	67; [98.5%]	190; [97.9%]
Total of patients	68	194
p-Value	0.992 (relative risk[a], 1.4; 95% CI, 0.2–12.3)	

	Antiplatelet therapy	Anticoagulant therapy
Thromboembolic events (total events = 2)	1; [1.5%]	1; [5%]
No thromboembolic events (total = 87)	67; [98.5%]	20; [95%]
Total of patients	68	21
p-Value	0.790 (relative risk[b], 6.2; 95% CI, 0.6–64.9)	

In square brackets the percentages of events or no events referred to the total of patients of each group are reported.
[a] Relative risk relative to no therapy versus therapy.
[b] Relative risk anticoagulant versus antiplatelet therapy.

thromboembolic and bleeding event rate. Moreover, no significant difference in the thromboembolic event rate was found when comparing patients with CHA_2DS_2-VASC score of 1 or 2, in both groups discharged without antithrombotic therapy (Table 4).

4. Discussion

The results of this study provides a tentative contribution to the ongoing debate concerning the indication of start OAC in patients with first diagnosed AF and a CHA_2DS_2-VASC score of 1 in men, and 2 in women, respectively [3], which is mostly attributable to the unknown risk-benefit ratio [12,14]. The optimal management is even more controversial in patients at medium risk scheduled for cardioversion. There is widespread perception that cardioversion may be associated with inherent risk of stroke in non-anticoagulated patients, which can be significantly reduced by the administration of anticoagulant drugs [15]. This concept has persuaded some authors to suggest immediate initiation of anticoagulation in all patients scheduled for cardioversion [16,17], despite evidence remains limited and guidelines are still controversial [3,18,19].

In recent times, the ESC guidelines have been updated twice, in 2010 and in 2016, thus influencing the treatment choices of emergency physicians, especially in patients scheduled for pharmacologic or electrical cardioversion. The 2006 ACC/AHA/ESC guidelines on AF currently recommend that cardioversion might be performed, when clinically appropriate, without delay for initiation of anticoagulation in patients with AF of <48-hour duration (Level of Evidence: C), and that the choice of anticoagulant therapy during 48 h after the onset of AF should depend on the individual risk of thromboembolism (Level of Evidence: C) [20].

Despite the availability of updated guidelines, the cardioversion of patients at "medium risk" with acutely onset AF (<48 h) remains an important and almost unresolved issue. The Canadian guidelines recommend anticoagulation with intravenous UFH or LMWH before cardioversion only in selected categories of high-risk patients (e.g., baring mechanical valves, or with rheumatic valve disease, recent stroke or transient ischemic attack) [18]. The ACC/AHA guidelines consider reasonable the administration of heparin (intravenous bolus of UFH followed by infusion, or LMWH) or direct oral anticoagulants (DOACs) [19]. The 2016 ESC guidelines recommend using heparin (intravenous UFH bolus followed by infusion, or weight-adjusted therapeutic dose LMWH) before emergency cardioversion [3]. In patients with low risk of stroke, the ACC/AHA and ESC guidelines both recommend peri-procedural administration of heparin, whilst the Canadian guidelines, in the emergency setting, place high importance on immediate management of haemodynamic instability, and recommend anticoagulation with UFH or LMWH prior to cardioversion only in selected high-risk patients (e.g., those baring mechanical valve, of with rheumatic valve disease, recent stroke or transient ischemic attack), or when the duration of arrhythmia is >48 h or unknown [18]. No randomized clinical trials (RCT) have been published on the efficacy of peri-procedural heparin administration to the best of our knowledge, so that the current recommendations in haemodynamically stable patients with acutely onset AF are only based on observational studies and/or personal opinions.

Due to the lack of definitive indications for anticoagulation in AF episodes lasting for <48 h [21], the general strategy in our local ED has been for long based on cardioversion with no administration of post-procedural OAC. Only after the 2010, when the new ESC guidelines recommended perioperative and long-term anticoagulation in patients with risk factors for stroke [22], the peri-procedural management of cardioversion for acutely onset AF has been modified accordingly. The widespread implementation of this novel approach has been considerably slow, due to a weak recommendation, only supported by small retrospective cardioversion studies.

Bonfanti et al. recently studied 419 consecutive patients electrically cardioverted for first diagnosed AF. The procedure was effective in 403 cases (96.2%), and no strokes or major bleeding or peripheral thromboembolism were recorded during 30-day follow-up. It was hence concluded that it seem reasonable to avert anticoagulation in most of such patients, limiting the strategy to administration of peri-procedural UFH (or LMWH) and then maintenance of OAC based on the risk class [23].

The FinCV study [24], the largest ever published trial on this topic, reported 38 definite thromboembolic events over 7660 cardioversions (0.7%) within a 30-day follow up. In this retrospective study, which included nearly 12% pharmacological cardioversions, no patient received peri-procedural anticoagulant therapy.

Taken together, the results of our study seemingly support the lack of real clinical benefits of administering OAC drugs in "medium-risk" patients. No significant difference in the rate of thromboembolic events was in fact noted between patients discharged on OAC and those who did not receive this treatment. No significant difference was also found in the thromboembolic risk between low risk and "medium-risk" patients. Results were actually similar for both **MC** and **FC** groups, as well as **MR** and **FR**, thus supporting the concept that patient sex does not represent alone a significant risk factor, but is perhaps only a modest risk-modifier [25].

Table 4
Thromboembolic events in the **FC** (**Females Cardioverted**; i.e., male patients who underwent a cardioversion, both electrical and pharmacological, and those who displayed a spontaneous sinus rhythm restoring) group, subdivided according to the CHA_2DS_2-VASC score.

	CHA_2DS_2-VASC score = 1	CHA_2DS_2-VASC score = 2
Thromboembolic events (total events = 5)	1; [0.4%]	4; [1.2%]
No thromboembolic events (total 549)	232; [99.6%]	317; [98.8%]
Total of patients	233	321
p-Value	0.580 (relative risk, 2.9; 95% CI, 0.3–25.8)	

Relative risk of CHA_2DS_2-VASC score 2 versus 1.
In square brackets the percentages of events or no events referred to the total of patients of each group are reported.

Several recent studies seem to suggest that the different variables of the CHA_2DS_2-VASC score do not have the same weight for predicting the thromboembolic risk. Olesen and Torp-Pedersen showed that diabetes mellitus and age have the highest efficiency for predicting thromboembolic events compared to the other items included in the score [26]. Similar data have recently been published by the Taiwanese National Health Insurance Research Database [27]. Since renal failure is an additional determinant of thromboembolic risk, the ROCKET-AF and ATRIA studies have recently introduced and validated a new score (i.e., R_2CHADS_2), which also includes creatinine clearance [28].

Left atrium enlargement [28], along with values of some biomarkers such as B-type Natriuretic Peptide (BNP), cardiac troponins, D-dimer and C-reactive protein among others [29,30], shall now be regarded as additional important factors for risk stratification. In particular, reliable evidence has accumulated that the measurement of some selected biomarkers may help improving the risk assessment in AF patients, and it is hence predictable that an increasing number of new risk scores for stroke will include these parameters. The recent ABC (age, biomarkers, and clinical history) is a paradigmatic example [31,32].

Finally, the AF pattern (i.e., paroxysmal, persistent, or permanent) has never been included in risk stratification. Nevertheless, the experience garnered form the real world suggests that OAC prescription is usually lower in paroxysmal-AF patients than in those with persistent or permanent AF [3,33]. According to these data, the vast majority (93.1% of men, 76.3% of women) of patients for whom a rate-control strategy was planned has received OAC in our study compared to 5.9% of men and 7.4% of women who were pharmacologically or electrically cardioverted. As previously discussed, some therapeutic differences throughout the duration of our study were attributable to the evolution of guidelines and scoring systems, such as the transition from $CHADS_2$ in 2006 to CHA_2DS_2-VASC in 2010 [20,22].

The observational and retrospective nature of this study is indeed a limitation, which may be at least partially offset by the large sample size of our study population. Due to the clinical relevance of prescribing or not OAC in "medium-risk" AF patients, further randomized controlled trials would hence be needed to confirm our findings.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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