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ORIGINAL RESEARCH ARTICLE

Diagnosis and Management of Atrial Fibrillation by Primary Care Physicians in Italy

A Retrospective, Observational Analysis

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Abstract
Background Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a heavy burden of morbidity and mortality, mainly due to an increased risk of cerebrovascular events and cardiac failure. Oral anticoagulant (OAC) treatment prevents stroke and systemic thromboembolism in patients with AF and its use is strongly recommended in guidelines. However, its use in this patient group remains limited. Primary care physicians (PCPs) have an important role to play in this context.
Objective The primary objective was to estimate prevalence and epidemiological features of AF in the primary care setting, focusing on ischaemic and bleeding risk assessment. A secondary objective was to examine the PCPs' level of adherence to the guidelines for the prevention of thromboembolic risk in these patients.
Methods This retrospective, observational study was based on data entered by 128 PCPs into the Health Search (HS) Thales database, identifying patients with a diagnosis of AF at the time of the analysis.
Results Out of 167,056 patients analysed, 2,173 (1.3 %) were diagnosed with AF, with 86 % at high risk for ischaemic stroke, according to CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65–74 years, sex category [female]) stratification. After the diagnosis of AF, 84 % of patients were prescribed OAC treatment. However, at 2 years' follow-up, only 29.6 % were still being treated with OACs.
Conclusion The prevalence of AF in this analysis was consistent with previously reported Italian national epidemiological data. Adherence to the European Society of Cardiology AF guidelines by PCPs was low, despite the high levels of stroke risk. At the end of the observation period less than one-third of patients were still on OAC therapy. Awareness of the benefits of OACs in stroke prevention in AF patients needs to be improved.

1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia observed in clinical practice. It is associated with a heavy burden of morbidity and mortality, mainly due to an increased risk of cerebrovascular events and cardiac failure. The prevalence of AF in the general population increases exponentially with age (approximately 0.4 % in the general population, 3–5 % in subjects aged >65 years and 10 % in subjects aged >80 years) [1, 2]. AF is associated with a high risk of systemic thromboembolism, of which stroke is the most frequent manifestation [1–5]. Recently, it has been hypothesized that AF can be a threat to the brain not only because of the risk of stroke, but also because it leads to cognitive deterioration resulting in dementia, even without first having developed a stroke [6, 7].

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The efficacy of oral anticoagulant (OAC) treatment in the prevention of stroke and systemic thromboembolism has been demonstrated in randomized controlled trials [8] and is strongly recommended in the guidelines from the European Society of Cardiology (ESC) [3]. Despite strong evidence of the efficacy of OAC treatment, its use in clinical practice for prevention of thromboembolism in patients with AF is still limited [9, 10]. Although diagnostic and therapeutic strategies in AF patients are usually initiated by cardiologists or other in-hospital specialists, management of co-morbidities and drug adherence also involves primary care physicians (PCPs). In this context, prevention of thromboembolism associated with AF is an essential component of the global cardiovascular prevention strategy in primary care.

A Canadian registry showed limited use of the $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke [doubled]) score by family physicians for assessing the need for anticoagulant therapy for stroke prevention in AF patients [4, 11]. A number of other observational studies in the primary care setting have also found that adherence to guidelines for stroke prevention in patients with AF is low and that anticoagulation is underused [9, 12]. Moreover, even when warfarin is prescribed, achievement of target International Normalized Ratio (INR) 2.0–3.0 is inadequate [13]. The primary objective of this study was to estimate the prevalence and epidemiological features of AF in this population with a focus on ischaemic and bleeding risk assessment. A secondary objective was to examine the PCPs' level of adherence to the guidelines for the prevention of thromboembolic risk in these patients.

2 Methods

Data were obtained from 128 PCPs in Naples who provided information to the Health Search (HS)/Thales database. We performed an observational, retrospective analysis of patients with a diagnosis of AF over a 2-year period (April 2009–April 2011). Institutional Review Board/Ethics Committee approval is not required for retrospective, observational studies based on database analysis in Italy.

2.1 Health Search (HS)/Thales Database

The HS/Thales database is an Italian general practice registry that collects data from the electronic patient records of a selected group of Italian PCPs who voluntarily agreed to collect patient information and to attend specific training courses on data entry. In the HS/Thales database patient demographic details are linked with a range of clinical parameters (e.g., diagnosis, diagnostic procedures, drug prescription information, hospital admissions) by the use of an encrypted patient code. The research validity of the HS/Thales database has been confirmed by a number of published comparative studies [14–16].

2.2 Study Population

All subjects ≥18 years of age recorded in the database in April 2009 were included in the analysis if they persisted with the same PCP for at least 1 year after the index diagnosis. We identified patients with a diagnosis of AF according to the *International Classification of Diseases*, 9th revision, Clinical Modification (ICD-9-CM) [items 427.3 and 427.32] [17]. However, diagnoses derived from electronic medical records did not distinguish between paroxysmal, persistent or permanent AF, or patients whose AF subsequently resolved.

In order to reduce potential bias due to the missing diagnoses of AF, use of amiodarone, dronedarone, flecainide, sotalol and warfarin was considered as potential markers of AF and matched with diagnostic and electrocardiography (ECG) findings. Demographic and clinical data (risk factors, co-morbidities) were collected for all the enrolled subjects, and diagnostic procedures and therapeutic management were also analysed for patients with a diagnosis of AF. Co-morbidities and risk factors for cardiovascular events were identified according to the ICD-9-CM. Risk stratification of patients was performed with the $CHADS_2$ and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65–74 years, sex category [female]) scores for ischaemic risk [18] and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [>65 years], drugs/alcohol concomitantly) score [19] for bleeding risk in accordance with ESC guidelines [3]. In addition, we compared the patients' HAS-BLED and ATRIA (anticoagulation and risk factors in atrial fibrillation) [20] scores. Predefined algorithms for the automatic calculation of these scores were applied. Biochemical analysis and instrumental diagnostic procedures (ECG, echocardiography) were carried out at specialist centres and recorded in the database. Since this was an observational study, no additional diagnostic or therapeutic interventions were performed.

2.3 Statistical Analyses

Due to the observational nature of the study a formal calculation of the study sample size was not applicable and only descriptive analyses were performed. Standardized definitions of all patient-related variables were used and clinical diagnoses were assessed according to the ICD-9-CM system. Categorical variables are presented as

percentage and comparisons were performed using a Chi-squared (χ^2) test.

3 Results

A total of 2,173 patients (out of 167,056 eligible subjects enrolled in the HS/Thales database) had a diagnosis of AF (1.3 %) and details of their demographic and clinical characteristics at baseline are shown in Table 1. The prevalence of AF was highest in women (women 1.4 % vs men 1.2 %), and in the age group ≥75 years (6.9 % vs 3.5 % in patients aged <75 years). The majority of patients with AF were regular smokers (85.3 %) and had a history of hypertension (75.5 %). Diabetes mellitus and thyroid dysfunction were observed in 24.3 % and 29.5 % of patients, respectively. Other risk factors commonly associated with AF (valvular heart disease and chronic obstructive pulmonary disease [COPD]) were more frequent among patients with AF compared with patients without AF (COPD 10.9 % vs 2.6 %, respectively; valvular heart disease 9.5 % vs 2.4 %, respectively). Notably, 9.9 % of patients with AF had an anamnestic diagnosis of heart failure, compared with 0.6 % in the overall population. AF patients were also more likely to have a history of previous transient ischaemic attack (TIA) or stroke than patients without AF ($p < 0.001$). Echocardiographic evaluations were carried out on 490 patients with AF (22.5 %), and findings suggestive of some structural anomaly were reported in 240 cases (49 %).

Assessment of the AF patients' $CHADS_2$ scores indicated that 20 % of patients were at high risk for ischaemic stroke, compared with 68.6 % at moderate risk (Fig. 1). In accordance with the current ESC AF guidelines [3], the ischaemic risk was also calculated using CHA_2DS_2-VASc scores, which indicated that 4.3 % of patients with AF were at low risk of ischaemic stroke, 9.7 % were at moderate risk, and 86 % were at high risk (Fig. 1). According to the HAS-BLED score [19], 35.2 % of patients were at high risk of bleeding (Fig. 2), while the recently validated ATRIA score [20] indicated that 82.2 % were at low risk of bleeding (0–3), 3.5 % were at intermediate risk (5), and 14.3 % were at high risk (≥5) (Fig. 3).

Of the 2,173 patients with AF, 84 % ($n = 1,827$) took OAC treatment at the time of diagnosis. Among patients on OAC treatment, 91 % had a CHA_2DS_2-VASc score ≥2, 7.3 % were at moderate risk and 1.7 % were at low risk; similar rates were observed for antiplatelet drugs. However, at the 2-year follow-up, 64.8 % of patients ($n = 1184$) had discontinued OACs in favour of antiplatelet treatment and only 29.6 % ($n = 643$) were still being treated with OACs. INR values were available in the database for only 620 patients but the majority of them (63.2 %; $n = 392$) were not within the target therapeutic range for AF (INR 2.0–3.0) at the last recorded examination.

4 Discussion

AF is the most common cardiac arrhythmia, conferring substantial mortality and morbidity from stroke, thromboembolism and heart failure, and significant impairment of quality of life [21, 22]. However, as it is often asymptomatic, its prevalence is underestimated. It has been suggested that a regular pulse measurement followed by ECG can detect a number of additional cases in comparison with the current clinical practice [23].

The prevalence of AF has been strongly associated with increasing age, affecting about 5 % of people over 65 years of age and 9 % of people aged more than 80 years [1, 24]. The results of an observational cohort study of 1,599 Italian patients aged ≥65 years showed a 7.4 % prevalence for AF [25]. In our study we have reported a 6.9 % prevalence in patients ≥75 years. In contrast to epidemiological data from the literature, which has indicated a higher rate of AF in men [1], we observed a higher prevalence in women, which can probably be attributed to a higher number of visits to PCPs by female patients.

According to the ESC guidelines, the $CHADS_2$ score should be used as an initial, rapid and easy-to-remember means of assessing stroke risk [3]. A limitation to the use of the $CHADS_2$ score is that it only includes a few stroke risk factors; as a result more 'moderate-risk patients' (with a $CHADS_2$ score of 1) could potentially derive greater benefit with OAC therapy compared with aspirin (acetylsalicylic acid). In order to improve the choice of antithrombotic strategy in non-valvular AF, some 'stroke risk modifier' risk factors have been added to the $CHADS_2$ score, thus deriving a more refined stroke risk stratification, named CHA_2DS_2-VASc. This scheme identifies 'truly low risk' atrial fibrillation patients as those with a CHA_2DS_2-VASc score of 0, who can probably be treated with no antithrombotic therapy. All others (i.e., CHA_2DS_2-VASc score of 1), can be considered for oral anticoagulation [18]. The ESC guidelines suggest that the CHA_2DS_2-VASc score should be assessed in all patients presenting with at least one stroke risk factor (resulting in 'moderate risk') according to the $CHADS_2$ score [3].

In our analysis, stroke risk stratification according to $CHADS_2$ showed that 20 % of AF patients were at high risk but, when stratified by the more refined CHA_2DS_2-VASc scores, the proportion at high risk of stroke increased up to 86 %.

The patient's risk of bleeding should also be evaluated prior to the initiation of OAC treatment, and the

Table 1 Baseline demographics and clinical characteristics of the study population

	Patients examined ($N = 167,056$)		Patients with AF ($n = 2,173$)		Patients without AF ($n = 164,883$)		p value
	No. of patients	%	No. of patients	%	No. of patients	%	
All subjects			2,173/167,056	1.3	164,883/167,056	98.7	
Male	78,767/167,056	47.2	964/78,767	1.2	77,803/78,767	98. 8	
Female	88,289/167,056	52.8	1,209/88,289	1.4	87,080/88,289	98.6	
<65 years	131,535/167,056	78.7	372/131,535	0.3	131,163/131,535	99.7	
≥65 to <74 years	17,761/167,056	10.6	572/17,761	3.2	17,189/17,761	96.8	
≥75 years	17,760/167,056	10.6	1,229/17,760	6.9	16,531/17,760	93.1	
BMI >30 kg/m^2	10,768/57,691	18.7	403/1,533	26.3	10,365/56,158	18.5	
BMI 25–30 kg/m^2	20,973/57,691	36.3	631/1,533	41.2	20,342/56,158	36.2	
BMI <25 kg/m^2	25,950/57,691	45.0	499/1,533	32.5	25,451/56,158	45.3	
Smoker	14,812/167,056	8.9	1,854/2,173	85.3	12,958/164,883	7.9	<0.001
Alcoholism	53/167,056	0.03	2/2,173	0.19	51/164,883	0.03	0.11
eGFR ≥60 mL/min/1.73 m^2	12,406/20,696	59.9	305/872	35.0	12,102/19,825	61.0	<0.001
eGFR <60 mL/min/1.73 m^2	8,290/20,696	40.1	567/872	65.0	7,723/19,825	39.0	<0.001
History of hypertension	45,438/167,056	27.2	1,641/2,173	75.5	43,797/164,883	26.5	<0.001
Heart failure	1,270/167,056	0.8	216/2,173	9.9	1,054/164,883	0.6	<0.001
Valvular defect	1,755/167,056	1.0	207/2,173	9.5	1,548/164,883	0.93	<0.001
Congenital heart defect	115/167,056	0.1	4/2,173	0.2	111/164,883	0.1	<0.001
Acquired cardiomyopathies	93/167,056	0.1	14/2,173	0.6	79/164,883	0.05	<0.001
Coronary heart disease	179/167,056	0.1	10/2,173	0.5	169/164,883	0.1	<0.001
Diabetes mellitus	12,956/167,056	7.7	528/2,173	24.3	12,428/164,883	7.5	<0.001
Dyslipidaemias	22,837/167,056	13.7	668/2,173	30.7	22,169/164,883	13.4	<0.001
Thyroid dysfunction	23,596/167,056	14.1	641/2,173	29.5	22,955/164,883	13.9	<0.001
COPD	4,529/167,056	2.7	237/2,173	10.9	4,292/164,883	2.6	<0.001
Sleep apnoea	1,197/167,056	0.7	47/2,173	2.2	1,150/164,883	0.7	<0.001
Previous stroke/TIA	23/167,056	0.0	4/2,173	0.2	19/164,883	0.01	<0.001
Anaemia (Hb <13 g/dL males, Hb <12 g/dL females)	28,046/167,056	16.8	818/2,173	37.6	27,228/164,883	16.5	<0.001
History of bleeding	4,876/167,056	2.9	133/2,173	6.1	4,743/164,883	2.9	<0.001

AF atrial fibrillation, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *Hb* haemoglobin, *TIA* transient ischaemic attack

HAS-BLED score should be used for this purpose. A HAS-BLED score of ≥3 indicates 'high bleeding risk' and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with oral anticoagulation or aspirin [3]. The HAS-BLED score was derived and validated in an AF population and its predictability has been recently compared to the HE-MORR$_2$HAGES (hepatic or renal disease, ethanol use, malignancy, older age [>75 years], reduced platelet count, re-bleeding [doubled], hypertension uncontrolled, anaemia, genetic factors, elevated risk of fall, stroke) score [26]. Both of these schemes performed similarly in predicting major bleeding, but a substantial advantage of HAS-BLED is its relative simplicity, allowing ease of use in everyday clinical practice [19, 26].

It has been suggested that the ATRIA score (including five weighted risk factors: anaemia, severe renal disease, age 75 years and older, previous haemorrhage, and diagnosed hypertension) may be used to support the choice of antithrombotic strategy in patients at moderate ischaemic risk, especially in view of the introduction of the novel OACs. We compared the results from HAS-BLED to ATRIA and found that the latter identified a lower number of high risk patients. A debate has recently followed the ATRIA score publication, as some concerns have been raised with regard to the derivation of the new schema and its applicability. In particular, inclusion criteria and risk factors from which the model was derived have been criticized. Because of the selection of a 'warfarin-experienced' cohort in the study, ATRIA might not be applicable

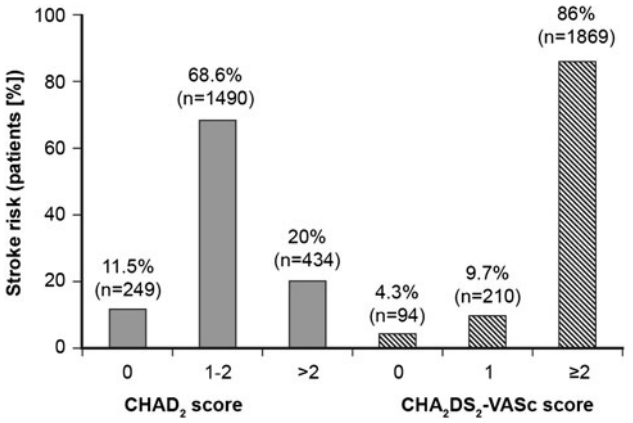

Fig. 1 Stratification of ischaemic stroke risk in patients with atrial fibrillation based on $CHADS_2$ and CHA_2DS_2-VASc scores ($n = 2{,}173$). *$CHADS_2$* cardiac failure, hypertension, age, diabetes, stroke (doubled); *CHA_2DS_2-VASc* congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, sex category (female)

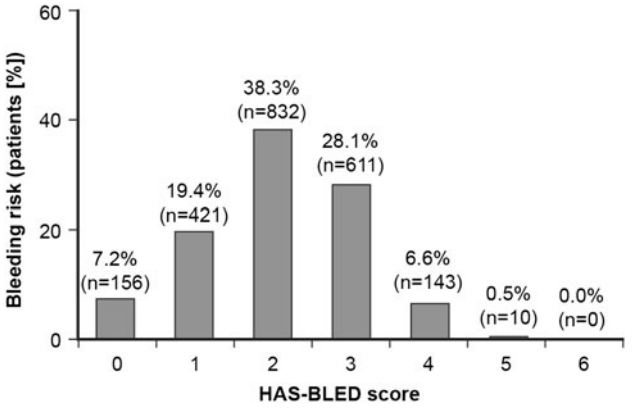

Fig. 2 Risk of bleeding in patients with atrial fibrillation based on HAS-BLED score ($n = 2{,}173$). *HAS-BLED* hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio, elderly (>65 years), drugs/alcohol concomitantly

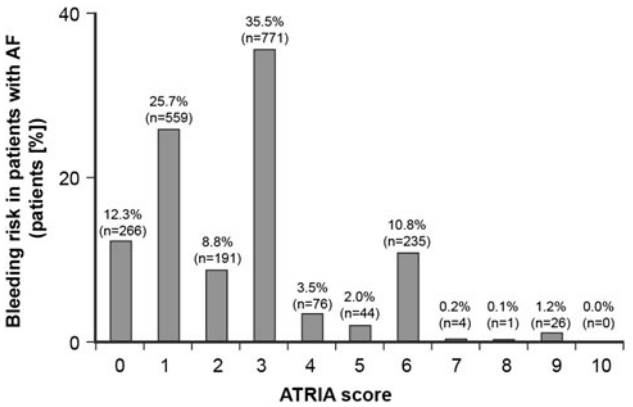

Fig. 3 Risk of bleeding in patients with AF based on ATRIA score ($n = 2{,}173$). *AF* atrial fibrillation; *ATRIA* anticoagulation and risk factors in atrial fibrillation

in warfarin-naïve patients, notoriously at higher risk of bleeding [27]. Thus, to date, the use of the ATRIA score does not seem to be considered as an alternative to the HAS-BLED score for stratification of bleeding risk.

Many observational studies have shown that in clinical practice OACs are frequently underutilized, with reported percentages of prescriptions between 30 and 60 % despite the recognized clinical benefits of prevention of AF-related strokes [28–30]. A previous Italian primary care registry [31] has shown a significantly lower proportion of AF patients treated with OACs (persistence with OAC was <50 % at 1 year and reduced to approximately 25 % by 2 years), when compared with the Euro Heart Survey of AF patients [28] or other European Countries [32]. In our analysis, despite a higher percentage of OAC prescriptions following the diagnosis of AF, levels of adherence among the PCPs' patients were very low with less than one-third of patients maintained on warfarin at the end of the 2-year follow-up. Notably, INR values were recorded in a minority of cases and were not within the target therapeutic range in most of them.

The underutilization of OAC therapy may also be explained by a lack of awareness of patient risk stratification criteria or poor appreciation of the risk–benefit ratio of OACs, with an overestimation of their bleeding risks [9, 13]. Moreover, this may reflect the difficulty of managing patients on conventional OAC treatment regimens. INR monitoring is important for management of OACs currently used in clinical practice but is not easy to arrange for all patients due to the need for regular blood tests and frequent dose adjustments. Furthermore, the established OACs have a narrow therapeutic range and exhibit a wide variability of patient response, which leads many patients to spend significant amounts of time outside the therapeutic INR range and may favour drug discontinuation. Response variability itself may represent a barrier to prescribing, particularly in the elderly [33]. Thus, thromboembolic risk stratification only partially influences the choice of the OAC therapy for stroke prophylaxis and is underutilized, even in high-risk patients. An Italian survey of antithrombotic therapy in patients with AF showed that treatment was discontinued in one-third of patients due to fear of bleeding and difficulty in performing adequate monitoring [31].

The lack of use of OAC therapy is particularly evident in elderly patients who were also at highest risk of stroke. Even when there is evidence that age and AF independently increase stroke risk, elderly people with AF are less likely to receive OAC therapy. Recently, Olesen et al. demonstrated in a nationwide cohort analysis in Denmark that the net clinical benefit was more positive in patients at high bleeding risk, and the absolute benefit in reducing stroke with warfarin would outweigh the small increase in

intracranial haemorrhage with warfarin [34]. BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study) showed that warfarin significantly reduces stroke risk in the elderly [35]. In the ATRIA cohort, Singer et al. also showed a reduction in absolute stroke risk with warfarin: the benefit was greater in very elderly patients (age ≥85 years) and among those at high stroke risk [36]. The bleeding risk with antiplatelet therapy is similar to that with warfarin, especially in the elderly who can benefit most, in terms of risk of bleeding, from the accurate use of OAC treatment, as compared with the use of antiplatelet treatments [9, 35, 37]. The recent European position document on bleeding risk assessment and management in AF states that "bleeding risk is almost inevitably lower than stroke in patients with AF" but can be minimized by refining antithrombotic therapy in patients identified to be at high risk [33].

This study was subject to a number of limitations. Firstly, data were collected retrospectively and the analysis was based on the diagnoses recorded by the PCPs in their database, which may affect the accuracy in reporting anamnestic data. Nevertheless, since it was our intent to describe the epidemiology and management of AF patients referred to PCPs, these data represent a picture of 'real world' clinical practice in this setting. A second issue is that in Italy there are some local directives and restrictions affecting the prescription of drugs and diagnostic procedures that could potentially influence physicians' behaviour, which may limit the generalizability of these results to a non-Italian population. This survey does not provide information on outcomes and the potential relationship with management strategies, and cannot be considered a study on the appropriateness of diagnostic or therapeutic approaches in patients with AF as the aim was to provide epidemiological data in the PCP setting.

5 Conclusion

This study provides confirmation of previous epidemiological data on AF prevalence in Italy [31]. Despite the high stroke risk in this population, anticoagulant therapy is underutilized, although, in comparison with other observational studies, we found a higher rate of OAC prescription at the time of the diagnosis. In contrast, we detected a very high rate of drug discontinuation and poor attention to monitoring of the effectiveness of OAC therapy by measurement of patients' INR values.

In 'real world practice', evaluation of ischaemic and bleeding risks, which should direct therapeutic decisions concerning the prevention of thromboembolism in AF patients, are not balanced and often the choice to avoid OAC therapy is led by an overestimation of the haemorrhagic risk. In addition, the management of chronic OAC therapy using INR monitoring appears to represent a real challenge in the PCP setting. The utilization of simple risk scores could provide more sensitive instruments for a real risk profile definition in these patients, and support physicians' therapeutic decisions in the primary care setting. Our results strengthen the importance of promoting educational programmes amongst PCPs, focusing on risk stratification and adequate monitoring of patients on OAC therapy. How much the availability of novel OACs will change prevention strategies in this setting is still unknown. However, even in this new landscape, net clinical benefit in stroke prophylaxis will remain bound to balancing ischaemic and bleeding risk.

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