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Original research paper

Real-practice thromboprophylaxis in atrial fibrillation

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This retrospective observational study was based on databases of the Local Health Authority of Treviso, Italy. It evaluated the prevalence and the effectiveness of oral anticoagulation treatment (OAT) for the management of non-valvular atrial fibrillation (NVAF) in everyday clinical practice. Out of 6,138 NVAF patients, only 3,024 received vitamin K antagonist (VKA). Potential barriers decreasing the probability of being treated with VKA were female sex, older age, antiplatelet treatment and history of bleeding. In addition, VKA-treatment was not in line with current ESC and AIAC guidelines, since the patients at high or low risk of stroke were under- or over-treated, resp. Among VKA-treated patients, 73 % of subjects were not at target with anticoagulation. OAT resulted to be effective in reducing stroke risk. However, stroke events were significantly influenced also by previous stroke or transient ischemic attack (hazard ratio, HR = 2.99, $p < 0.001$) and by previous bleeding events (HR = 1.60, $p < 0.001$).

Keywords: atrial fibrillation, thromboprophylaxis, real-practice, vitamin K antagonists, stroke risk

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major preventable cause of stroke and hospitalization (1, 2). Its prevalence has increased over years (3); in Italy it was found to be 1.9 % (4, 5).

This arrhythmia confers, on average, a five-fold risk of stroke, doubles the risk of mortality, increases the risk of heart failure and is responsible for one-fifth of all strokes. In addition, strokes caused by AF tend to be more frequently fatal, disabling and recurring when compared to other causes of stroke (6–9).

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Current ESC and AIAC guidelines (10, 11) recommend oral anticoagulation therapy (OAT) for AF patients at high risk of stroke, according to CHADS2 or CHA2DS2-VASC scores of individual risk. In particular, anticoagulant treatment is highly recommended for patients with CHADS2 or CHA2DS2-VASC scores ≥ 2. However, even if oral anticoagulation is effective in preventing strokes due to AF (12), there is extensive evidence suggesting that this therapy remains underused (4, 10, 13–15). Despite, the data from the literature is clearly showing that the efficacy of antiplatelet agents in thromboembolic prevention is significantly lower than that of oral anticoagulant therapy (14). Antiplatelet agents are often used in substitution of the oral anticoagulant agents. Also, among patients treated with vitamin K antagonist (VKA) the quality of anticoagulation control is often poor (14) and many discontinue treatment permanently (16). In Italy, strokes connected to the absence of treatment or related to an inadequate control of INR are estimated to be around 11,000 per year (17). Given the recognized limitations of VKA, the availability of novel oral anticoagulants could represent a valid alternative therapy to minimize stroke risk and to guarantee an appropriate management of AF.

The aims of this study were to evaluate if the anticoagulant treatment of non-valvular AF (NVAF) in real clinical practice is in line with current guideline recommendations, and to assess the role of the oral anticoagulant treatment in the prevention of stroke in everyday clinical practice.

EXPERIMENTAL

A retrospective observational cohort study was conducted in the Local Health Authority (LHA) of Treviso, Italy, from January 1, 2007 to December 31, 2013 using several databases containing an annual mean of 409,000 subjects. All information was collected from national databases of the Health Care Authority, which contain information related to age, sex, prescriptions and pathologies. Additionally, local databases with information on international normalized ratio (INR) monitoring and hospital admissions were used and linked with previously detected data. This article does not contain any studies with human participants or animals performed by any of the authors.

The eligible population included all participants hospitalized with a diagnosis of atrial fibrillation (ICD-9 CM 427.3) during a hospital admission (considered as the index date, ID), resident in the LHA of Treviso. Exclusion criteria were: valvular AF defined according to the current guidelines (18), patients who died within 7 days from the diagnosis and patients who received the anticoagulant therapy occasionally (= number of prescriptions which covered less than 6 months in continuation) (Fig. 1). The follow-up period was defined as the time between the ID and 31 December 2013 or death date.

Two different populations with non valvular atrial fibrillation were defined to answer the study objectives: N-VKA group – participants who did not receive any VKA treatment and VKA group – participants who received at least 6 months of VKA treatment.

The individual stroke risk for each patient was defined according to CHADS2 and CHA2DS2-VASC scores (19–21). The CHADS2 score was the sum of points obtained after addition of one point each for heart failure, hypertension, age ≥ 75 and diabetes, and two points for previous stroke/transient ischemic attack (TIA). The CHA2DS2-VASC score was the sum of points after addition of one point each for heart failure, hypertension, diabetes,

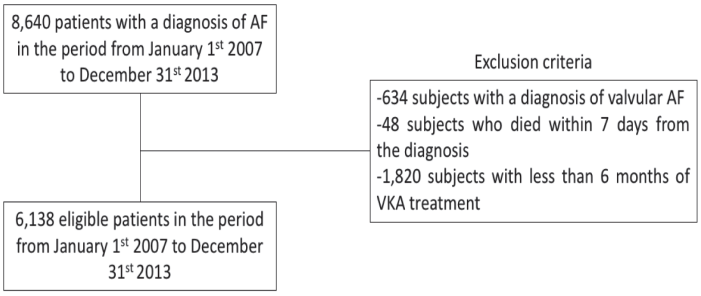

Fig. 1. Flow chart of patients with non-valvular atrial fibrillation. AF – atrial fibrillation, VKA – vitamin K antagonist.

vascular disease, age 60–74 and female sex, and two points each for previous stroke or transient ischemic attack, previous systemic embolism and age ≥ 75. Given the 7-years follow up study, both scores have been considered.

Use of antiplatelet agents, non-steroidal anti-inflammatory drugs and corticosteroids before the ID were considered. Similarly, hospitalizations with a diagnosis of bleeding occurring before the ID were considered, as well.

Subgroups defined according to therapeutic categories and risk of stroke

All drugs were identified through the international anatomical therapeutic chemical classification system (ATC code).

Vitamin K antagonist users were identified through the prescription of warfarin or acenocumarol (ATC B01AA). In addition, INR controls were collected and reported as the time in therapeutic range (TTR) (22). To calculate TTR, each patient should have a sufficient number of INR controls, *i.e.*, one INR control per month according to the guidelines (18). Antiplatelet agent prescriptions where identified through the ATC B01AC. To determine the influence of risk factors and treatments on occurrence of stroke, a multivariate regression analysis (Cox analysis) was performed, with regard to age, sex, previous heart failure, hypertension, diabetes mellitus, stroke/TIA, myocardial infarction, previous bleeding, previous or concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs and corticosteroids. The contribution of CHADS2-VASC or CHADS2 scores was evaluated as well. However, since they also include information on age, sex and previous stroke or TIA, they were not included in this analysis. According to the treatment, four subcategories were therefore identified (Fig. 2) and also included in the regression analysis: group VKA, TTR ≥ 65 % – participants who received VKA treatment for at least 6 months and reached the target (14); group VKA, TTR < 65 % – participants who received at least 6 months of VKA treatment and did not reach the target (14); N-VKA, N-antiplatelet group – participants who did not receive either VKA or antiplatelet treatment; N-VKA, antiplatelet+ group – participants who received only antiplatelet drugs for at least of 6 months.

The first stroke recorded after the ID, defined as the first hospital admission with diagnosis of stroke, was considered.

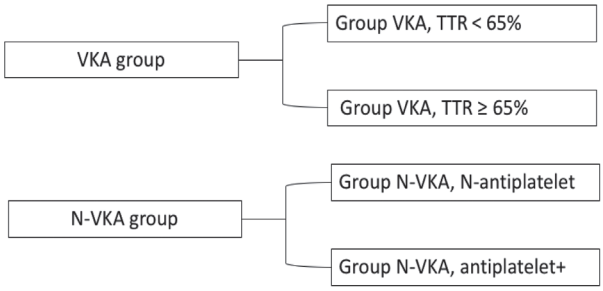

Fig. 2. Flow chart of subcategories identified by treatment. N-antiplatelet – patients not treated with antiplatelet agent, N-VKA – patients not treated with vitamin K antagonist, TTR – time in therapeutic range, VKA – vitamin K antagonist.

Data analysis

The baseline characteristics of the populations were reported by means or medians and standard deviations (SDs) for quantitative information and with frequencies and percentages for qualitative characteristics. Statistical differences were identified with a *t*-test or chi-square analysis.

To define possible associations between risk factors and occurrence of stroke, a preliminary univariate analysis was made. Statistical analysis was performed using STATA software version 14. Two-sided statistical significance was considered with significance level < 0.05, < 0.01 and < 0.001.

RESULTS AND DISCUSSION

This 7-year follow up study was aimed to describe the anticoagulation therapy in patients with atrial fibrillation. Applying the inclusion and exclusion criteria, 6138 participants were considered as eligible for the study (Fig. 1). The baseline characteristics of the NVAF population are reported in Table I.

Among patients with NVAF, about 60 % received a first prescription of VKA after the ID. The underuse of oral anticoagulant treatment is well-documented in the literature: a recent meta-analysis of quantitative studies revealed that less than 70 % of high-risk patients receive adequate oral anticoagulation therapy (13).

In our study, statistical differences were found between VKA-treated and non-treated patients for the most part of the considered baseline characteristics, except for the following: prior stroke/TIA, peripheral artery disease and NSAID/corticosteroids use (Table I). These differences reflected the clinical judgement on deciding whether patient should be treated or not, *i.e.*, if the risk/benefit profile of the treatment was positive. In particular, female sex, increasing age (≥ 75), antiplatelet drugs and history of major bleeding, resulted negatively to the possibility of receiving VKA therapy. Also, different studies have identified inadequate risk stratification; the advanced age of the patient, bleeding and falling risk, and the difficulties of warfarin management, including adverse events and patient compliance, as potential barriers to an appropriate treatment prescription (13, 15, 23).

Table I. Baseline characteristics, VKA group vs. *N-VKA group*

	Total population (n = 6,138)	VKA group (n = 3,024)	N-VKA group (n = 3,114)	p-value
Age (y)	75.59 ± 11.51	75.09 ± 8.90[a]	76.08 ± 13.67[b]	< 0.001
Sex				
Male (%)	3053 (49.7)	1594 (52.7)	1459 (46.9)	< 0.001
Female (%)	3085 (50.3)	1430 (47.3)	1655 (53.1)	< 0.001
Follow up (death or study end date, *i.e.*, 31.12.2013) (median month ± min-max)	37.70 (0–85.17)	48.73 (6.70–85.17)	23.47 (0–85.13)	
Thromboembolic risk factors				
Prior heart failure	1726 (28.12)	951 (31.45)	775 (24.89)	< 0.001
Prior hypertension	4045 (65.90)	2177 (72.00)	1868 (60.00)	< 0.001
Age ≥ 75 y	3651 (59.48)	1810 (59.85)	2058 (66.09)	< 0.001
Prior diabetes	1272 (20.72)	676 (22.35)	596 (19.14)	< 0.001
Prior stroke/TIA	1089 (17.74)	519 (17.16)	570 (18.30)	ns
Prior peripheral artery disease (including myocardial infarction)	868 (14.14)	413 (13.66)	455 (14.61)	ns
CHA_2DS_2-VASC				
0	297 (4.84)	67 (2.31)	230 (7.39)	< 0.001
1	504 (8.21)	197 (6.51)	307 (9.86)	< 0.001
≥ 2	5337 (86.95)	2760 (91.27)	2577 (82.75)	< 0.001
CHADS2				
0	815 (13.28)	252 (8.34)	563 (18.08)	< 0.001
1	1435 (23.38)	762 (25.20)	673 (21.61)	< 0.001
≥ 2	3888(63.34)	2010 (66.47)	1878 (60.31)	< 0.001
Antiplatelet agents at baseline	2504 (40.79)	1146 (37.90)	1358 (43.61)	< 0.001
Antiplatelet agents after AF diagnosis	1742 (28.38)	340 (11.24)	1402 (45.02)	< 0.001
NSAID	2111 (34.39)	1064 (35.18)	1047 (33.62)	ns
History of major bleeding	279 (4.55)	80 (2.62)	199 (6.39)	< 0.001

95 % confidence interval: [a] 74.77–75.40, [b] 75.61–76.56.

ns – not significant difference, NSAID – nonsteroidal anti-inflammatory drugs, N-VKA group – patients not treated with vitamin K antagonist, TIA – transient ischemic attack, VKA group – patients on vitamin K antagonist therapy

Values are mean ± SD, median or %.

Of total of VKA-treated patients, 1,820, ca 37 % patients discontinued the anticoagulant treatment within 6 months. This rate of discontinuation is similar to what has been reported in the literature, where discontinuation rate ranges from 20 to more than 50 % (15, 24).

Although European clinical guidelines would have influenced practice strongly recommending thromboprophylaxis in high risk patients and no treatment in low risk patients (CHA2DS2-VASC or CHADS2 score) (10, 18), we still found a suboptimal use of antithrombotic therapy. According to CHA2DS2-VASC and CHADS2 respectively, 82.8 and 60.3 % in the N-VKA group, resp., did not receive the therapy despite the score ≥2 indicating a major stroke risk. Our findings highlight therefore underuse of anticoagulants among high thromboembolic risk patients. This remains a persistent problem together with an elevated rate of discontinuation.

On the other hand, 2.3 % of patients in the VKA group received a thromboprophylaxis although their score was zero. Zimetbaum *et al*. (25) found similar proportions of patients in the low, moderate and high stroke-risk groups receiving warfarin. Thus, patients who would benefit the most from anticoagulants due to high risk of stroke do not receive treatment, while those considered at low risk may perhaps be unnecessarily exposed to the inconvenience and risks associated with anticoagulant therapy (23, 26).

Comparing the antiplatelet treatment before and after the ID, we observed a discontinuation rate of around 70 % in the VKA-group. Otherwise, the antiplatelet treatment in N-VKA group increased up to 45.0 %. Despite the data from the literature clearly showing that the efficacy of antiplatelet agents in thromboembolic prevention is significantly lower than that of oral anticoagulant therapy (14), the present study revealed that general practitioners preferred to use antiplatelet agents in about 45 % of N-VKA-treated patients. This behavior could be partially explained by specific contraindications to VKA, difficulties in performing the INR control, concerns over bleeding risk and the elevated age of treated patients. However, further analysis should be performed in order to investigate the reason of a large use of antiplatelet therapy instead of a VKA treatment in order to identify which patients will benefit the most by switching from an antiplatelet drug to an oral anticoagulant treatment. Clearly, concerns over bleeding risk lead physicians to not prescribing a VKA treatment, since history of major bleeding events was more frequent among the group of no treated patients (6.4 and 2.6 % of N-VKA and VKA patients, resp.).

Of note, the median follow-up period was very different between groups: 48.73 and 23.47 months for the VKA and N-VKA groups, resp. ($p < 0.001$). No specific reason was detected to justify this difference.

The TTR was calculated for the 3,024 patients in the VKA group: overall, the mean TTR was 55.76 (± 14.83) months and only 27.2 % of patients reached the target (TTR ≥ 65 %), with an increase over years from 24.6 % in 2007 to 37.2 % in 2013. Such a result is particularly dramatic, since a recent study by Connolly *et al*. (14) highlighted that TTR < 65 % abolishes the protective effect of oral anticoagulant therapy and reaches that comparable to antiplatelet agents. Comparable results were found only in the study of Sarawate *et al*. (27) where the average TTR was 28.6 months. Differently from the present study, most prior observational studies reporting higher TTR were conducted in patients in hospital setting, under supervision of hospital-based physicians or by anticoagulation clinics (28). What is evident in this real world study performed in a community setting covering a long period of time, is a persisting difficulty for general practitioners of managing especially elderly patients (aged 75 or older) affected by several comorbidities.

Stroke risk

In Table II, the clinical outcome, *i.e.*, stroke events, was subject to a multivariate regression analysis.

Increasing age was a major risk factor for stroke (HR =1.82, 2.97 and 4.48 for patients aged 65–74, 75–84 and ≥ 85, respectively, $p < 0.001$). With regard to comorbidities, previous stroke/TIA (HR = 2.99, $p < 0.001$) and previous bleeding events (HR = 1.60, $p < 0.001$) were

Table II. Hazard ratio (HR) for stroke risk evaluation (Cox regression model)

Anamnestic information	Multivariate analysis				
	No. patients	Hazard ratio	SE	*p*-value[a]	95 % CI
Sex					
Male	3,053				
Female	3,085	0.913	0.076	0.273	0.814–1.119
Age class (y)					
< 65	922				
65–74	1,565	1.824	0.362	0.002	1.237–2.690
75–84	2,304	2.971	0.558	< 0.001	2.056–4.294
≥ 85	1,347	4.475	0.886	< 0.001	3.036–6.595
Previous stroke/TIA					
No	5,049				
Yes	1,089	2.986	0.249	< 0.001	2.535–3.517
Previous bleeding events					
No	5,859				
Yes	279	1.598	0.203	< 0.001	1.246–2.049
Antiplatelet agents at baseline					
No	3,634				
Yes	2,504	1.460	0.123	< 0.001	1.238–1.721
Therapeutic management					
N-VKA, N-antiplatelet	1,712				
N-VKA, antiplatelet+	1,402	0.916	0.114	0.483	0.717–1.170
VKA, TTR < 65%	2,201	0.786	0.089	0.034	0.629–0.982
VKA, TTR ≥ 65%	823	0.594	0.094	0.001	0.435–0.810

[a] *p*-value beyond |z|.

CI – confidence interval, N-antiplatelet – patients not treated with antiplatelet agent, NSAID – nonsteroidal anti-inflammatory drug, N-VKA group – patients not treated with vitamin K antagonist, SE – standard error, TIA – transient ischemic attack, TTR – time in therapeutic range, VKA – group of patients on vitamin K antagonist therapy

significantly associated with the risk of stroke, thus confirming the well-documented role of these factors in risk determination (20).

Similarly, the use of antiplatelet agents at baseline significantly increased stroke risk (HR = 1.46, $p < 0.001$), probably because patients treated with these drugs were more complex in term of cardiovascular complications. On the other hand, sex was no significantly associated with stroke risk (HR = 0.91).

According to the treatments, the N-VKA, N-antiplatelet group was considered the group with the highest stroke risk. The addition of antiplatelet drug (N-VKA, antiplatelet + group) did not allow a significant decrease in such a risk (HR = 0.92). VKA treatment significantly reduced the stroke risk, as extensively described in the literature (14). In fact, the VKA group with TTR < 65 % had an HR = 0.79 ($p < 0.05$). Such a risk further decreased to 0.59 ($p < 0.01$) for patients with TTR ≥ 65 % (VKA group, TTR ≥ 65 %).

CONCLUSIONS

In conclusion, better quality of care of AF patients should be provided by increasing adherence to anticoagulation guidelines and improving patients compliance with anticoagulation therapy through education and established protocols. A systematic approach should be implemented in order to assess the presence of stroke risk factors, to determine the presence of specific contraindications, and to schedule and ensure an appropriate follow-up and INR control. The introduction of novel oral anticoagulant may facilitate better adherence due to ease of administration and reduced monitoring burden. Further analysis comparing VKA *vs.* non oral anticoagulant therapy should be performed.

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