

Stroke prevention in atrial fibrillation: findings from Tuscan FADOI Stroke Registry

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ABSTRACT

Despite vitamin K antagonists (VKAs) are considered the first choice treatment for stroke prevention in atrial fibrillation (AF), literature shows their underuse in this context. Since data about VKAs use prior and after acute stroke lack, the aim of this study was to focus on management of anticoagulation with VKAs in this context. Data were retrieved from Tuscan FADOI Stroke Registry, an online data bank aimed to report on characteristics of stroke patients consecutively admitted in Internal Medicine wards in 2010 and 2011. In this period 819 patients with mean age 76.5±12.3 years were enrolled. Data on etiology were available for 715 of them (88.1%), 87% being ischemic and 13% hemorrhagic strokes. AF was present in 238 patients (33%), 165 (69.3%) having a known AF before hospitalization, whereas 73 patients (31.7%) received a new diagnosis of AF. A percentage of 89% of strokes in patients with known AF were ischemic and 11% hemorrhagic. A percentage of 86.7% of patients with known AF had a CHADS₂ ≥2, but only 28.3% were on VKAs before hospitalization. A percentage of 78.8% of patients treated with VKAs before stroke had an international normalized ratio (INR) ≤2.0; 68.7% of patients with VKAs-related hemorrhagic strokes had INR ≤3.0. Combined endpoint mortality or severe disability in patients with ischemic stroke associated with AF was present in 47%, while it was present in 19.30% and 19.20% of atherothrombotic and lacunar strokes, respectively. At hospital discharge, VKAs were prescribed in 25.9% of AF related ischemic stroke patients. AF related strokes are burdened by severe outcome but VKAs are dramatically underused in patients with AF, even in higher risk patients. Efforts to improve anticoagulation in this stroke subtype are warranted.

Introduction

Atrial fibrillation (AF) is the widest cardiac arrhythmia in general and hospital populations and it is

an actual major public health problem and maybe it will be much more in the next future.¹ Prevalence of AF in fact is steadily increasing, especially in the elderly.²⁻⁴ Up to now, around 1% of the American general population suffers from AF, but this prevalence reaches around 10% in the octogenarians,⁵ whereas in Europe the prevalence is esteemed around 5.5% of general population and 17.8% in patients over 85 years.⁶ This prevalence could be underestimated due to unrecognized magnitude of silent AF. The risk of stroke in AF patients is from two to seven fold greater compared with patients without AF, mean stroke rate in AF being around 5% per year.¹

The annual risk of stroke is predictable by using practical scores such as CHADS₂ and the most recent CHA₂DS₂-VASC.¹ A score ≥2 identifies high stroke risk patients, over 4% per year for the CHADS₂ and over 2.2% per year for the CHA₂DS₂-VASC.¹

AF related strokes are burdened by higher early and long term mortality, higher rate of complications such as hemorrhagic transformation and severe residual disability compared to the other ischemic stroke subtypes such as the atherothrombotic and lacunar forms.^{7,8}

Oral anticoagulant therapy (OAT) with vitamin K antagonists (VKAs) has represented, until the publica-

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See online Appendix for Members of Tuscan FADOI Stroke Registry Investigators.

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tion of results of phase III trials on new oral anticoagulants direct inhibitors of thrombin or activated factor X,⁹⁻¹¹ the first choice treatment for the stroke prevention in high and moderate risk non-valvular AF patients.^{1,12,13} A meta-analysis had in fact demonstrated that VKAs reduce the relative risk of stroke by 64% compared to placebo and 39% compared to aspirin (ASA) despite a risk of intracranial and extracranial bleeding increased by 128% and 70% compared to placebo, respectively.¹⁴ In high and moderate stroke risk patients unsuitable for VKAs due to contraindications or refusals, clopidogrel combined with ASA was considered the first alternative to oral anticoagulants as demonstrated from ACTIVE-A study.^{12,15} Before the publication of the ACTIVE-A study, ASA alone was considered a possible alternative to VKAs in patients at high or moderate risk of stroke and was considered the first choice in low risk patients when physicians made decision to treat this group of patients.¹² However the abovementioned meta-analysis demonstrated that ASA alone gives a non-significant prevention compared to placebo with a relative risk reduction of 19% [confidence interval (CI) 95%: from -1 to 35%].¹⁴

Despite VKAs are available for the clinical use since fifty years, these drugs have many limitation leading to their underuse in clinical practice. VKAs have a slow onset of action, an unpredictable response due to wide genetic variability and multiple food and drugs interactions and a narrow therapeutic window.¹⁶ Treatment with VKAs needs of routine laboratory monitoring of the international normalized ratio (INR) with patients discomfort and frequent dose adjustment.¹⁶ VKAs limitations have lead that only around one half of patients are effectively treated by OAT, low percentage of patients (less than 60%) who spent their time in therapeutic range [time in therapeutic range (TTR)] and frequent withdrawals.¹⁷

Major, especially intracranial, and non major bleedings, which occur respectively around in 3% and 6% per year in patients taking VKAs, represent the most feared complication of VKAs treatment.¹⁸ Intracranial bleedings occur in 0.2-1% per year, but are often devastating.¹⁸ Mortality rate in VKAs related intracranial bleedings is 10-40% higher than non VKAs related intracranial bleedings and it reaches 50-80%.¹⁹ The majority of patients who develops a VKAs-related intracranial bleeding takes VKAs for cardioembolism prevention in AF.²⁰ Despite increased INR values are a major determinant of risk for VKAs-related intracranial bleeding, from 50% to 90% of patients with VKAs-related intracranial bleedings present values of the INR in the therapeutic range (2.0-3.0).²⁰

Since literature evidence referred to cardioembolism prevention in AF before, during and after the acute phase of stroke other than its clinical and prognostic characteristics and management lacks, the aim

of the present study was to focus on this topic in patients admitted in the Internal Medicine wards of Tuscany (Italy).

Materials and Methods

We analyzed data of patients enrolled in the Tuscan FADOI Stroke Registry, an online database where we included demographic, clinical, pharmacological, instrumental, functional and prognostic characteristics of patients consecutively admitted for acute ischemic and hemorrhagic stroke in the Internal Medicine wards of Tuscany. Some Stroke Units of Tuscany were also enclosed. The enrollment period ranged from July 1, 2010 to December 31, 2011. Within the entire cohort enrolled, we focused on patients with AF both known before hospital admission or diagnosed during hospitalization. We analyzed demographic data, cardiovascular risk factors and co-morbidities, the annual cardioembolic risk by using the CHADS₂ score, the antithrombotic prophylaxis used before the stroke, the clinical severity of stroke as measured by the National Institute of Health Stroke Scale (NIHSS), the occurrence of hemorrhagic transformation, the rate of in-hospital mortality, the functional dependence at discharge as measured by the modified Rankin scale (mRS), the secondary cardioembolic prophylaxis at hospital discharge. The data of patients with ischemic stroke associated with AF were compared with those of patients with atherothrombotic, lacunar or uncertain etiology ischemic stroke subtypes according to TOAST criteria on prognostic outcomes, whereas the data of patients with hemorrhagic stroke and AF were compared with those of patients with hemorrhagic stroke without AF.

Results

In the analyzed period 819 patients, 50.2% females and 40.8% males, with mean age 76.5±12.3 year, were enrolled in the Tuscan FADOI Stroke Registry. The majority of patients (more than 90%) were enrolled from July to December 2010. Data on etiology were available for 715 of them (88.1%), 87% being ischemic and 13% hemorrhagic strokes (Table 1). AF was present in 238 patients (33%). A number of 201 of 238 patients with AF (84.4%) suffered from ischemic strokes, 37 (15.6%) for hemorrhagic strokes. A number of 165 patients (69.3%) had a known AF before hospitalization, whereas 73 patients (31.7%) received a new diagnosis of AF. 89% of strokes in patients with known AF were ischemic and 11% hemorrhagic.

A percentage of 86.7% of patients with known AF had a CHADS₂ score ≥2 (Figure 1), but only 28.3% were on VKAs before hospitalization (Figure 2).

Forty-nine percent of patients with known AF was treated with antiplatelet drugs, while 22.7% of patients did not receive any antithrombotic prophylaxis. Table 2 shows the prevalence of CHADS₂ score variables in patients with known AF and Figure 3 shows the antithrombotic drugs distribution according to CHADS₂ score in this population. Any patient with CHADS₂ score 0 was under antithrombotic prophylaxis. VKAs use fell from 40% in patients with CHADS₂ score 1 to 16.6% in patients with CHADS₂ score 5, whereas an-

tiplatelet drugs increased from 38.6% in patients with CHADS₂ score 1 to 58.4% in patients with CHADS₂ score 5. A percentage of patients between 15.2% to 38.6% with known AF and CHADS₂ score 1-5 received any cardioembolic prophylaxis. 78.8% of patients treated with VKAs before ischemic stroke had INR values ≤ 2.0 , whereas 68.7% of patients with VKAs-related hemorrhagic strokes had INR values ≤ 3.0 (Figure 4).

The burden of ischemic strokes was more severe in patients with AF. More than one half of patients with

Table 1. General characteristics and stroke subtypes.

	No. (%)
Patients	819 (100%)
Mean age \pm SD (years)	76.49 \pm 12.35
Gender (F/M)	50.2%/49.8%
Number of patients with available data on etiology	715 (88.1%)
Stroke subtypes	
Ischemic	622 (87%)
Atherothrombotic	169 (27.1%)
AF associated	201 (32.3%)
Lacunar	112 (18%)
Uncertain etiology	135 (21.7%)
Venous thrombosis	5 (0.8%)
Hemorrhagic	93 (13%)
Intraparenchymal	87 (93.5%)
Sub-arachnoideal	6 (6.5%)
Patients with known AF	165
Patients with available data on antithrombotic prevention before hospitalization	155
Total ischemic stroke	(89%)
Total hemorrhagic stroke	17 (11%)
Patients taking VKAs before hospitalization	44 (28.3%)
Ischemic stroke in patients taking VKAs	33 (75%)
Hemorrhagic stroke in patients taking VKAs	11 (25%)
Patients with newly diagnosed AF	73
Total ischemic stroke	63 (86.3%)
Total hemorrhagic stroke	10 (13.7%)

SD, standard deviation; AF, atrial fibrillation; VKAs, vitamin K antagonists.

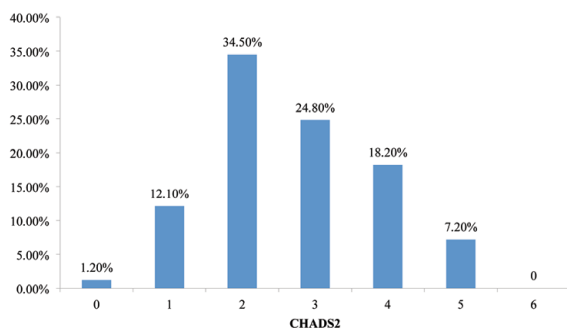


Figure 1. CHADS₂ distribution in patients with known atrial fibrillation.

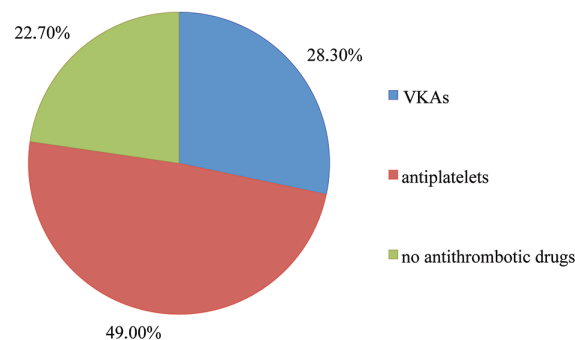


Figure 2. Cardioembolic prophylaxis before hospital admission in patients with known atrial fibrillation. VKAs, vitamin K antagonists.

AF-related stroke presented NIHSS score ≥ 10 points at hospital admission, whereas patients with atherothrombotic or lacunar strokes presented a NIHSS score ≥ 10 in around 20% of cases. Hemorrhagic transformation occurred in 12.7% of patients with AF, while this occurrence was detected in 10.9% and 2.2% of atherothrombotic and lacunar strokes, respectively. Mortality in patients with AF-related stroke was near double compared with the other stroke subtypes (8.8%

in AF patients vs 4.7% and 4.3% in atherothrombotic and lacunar strokes, respectively). Combined endpoint mortality or severe disability in patients with ischemic stroke associated with AF was present in 47%. Figure 5 summarizes the prognostic endpoints.

In patients with known AF taking VKAs before hospitalization the burden of ischemic stroke was less severe compared with patients with known AF not undergone to this pharmacological treatment. NIHSS score at hospital admission >10 points and mRS ≥ 4 at hospital discharge were 40% and 29.6% respectively in patients treated with VKAs before hospitalization compared to 54% and 53.1% in patients untreated. Instead, hemorrhagic transformation was 11.1% in patients taking VKAs before hospitalization versus 8.1% in non-taking patients.

At hospital discharge, VKAs were prescribed in 25.9% of AF-related ischemic stroke patients. The main prescribed antithrombotic treatment was represented by antiplatelet drugs (61.6%). None of the patients with VKAs-related hemorrhagic stroke was discharged with VKAs (Figure 6).

Table 2. Prevalence of CHADS₂ score variables in patients with known atrial fibrillation.

Congestive heart failure	21.6%
Hypertension	80%
Age >75 year	85.6%
Diabetes	24.8%
Previous TIA/stroke	31.2%

TIA, transient ischemic attack.

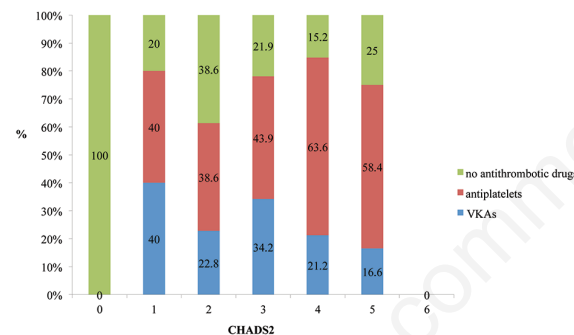


Figure 3. CHADS₂ distribution in patients with known atrial fibrillation and cardioembolic prophylaxis according to risk score. VKAs, vitamin K antagonists.

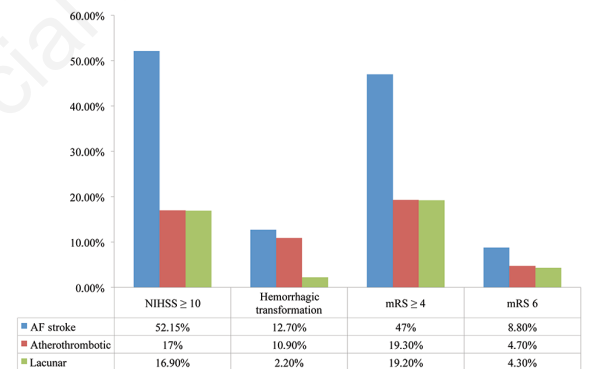


Figure 5. Stroke subtype and outcomes. AF, atrial fibrillation.



Figure 4. International normalized ratio (INR) values in patients on vitamin K antagonists at hospital admission.

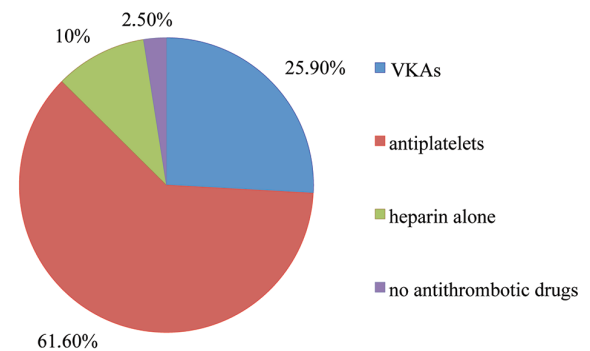


Figure 6. Cardioembolic prophylaxis at hospital discharge. VKAs, vitamin K antagonists.

Discussion

Registries or data banks are of utmost importance for understanding and improving the knowledge of many aspects of diseases. The Tuscan Stroke Registry was mainly performed in the second half of 2010 year with the aim of giving, if possible, answers to unresolved questions in the field of stroke patients admitted to internal medicine wards of this Italian region.

In the present study we have focused on AF-related stroke with particular attention to anticoagulation management before and after the acute phase of stroke. The scenario we have found demonstrates the dramatic underuse of VKAs in Tuscany before and after acute stroke even if in high and very high risk patients. Despite population studies show that the VKAs prescription is increased over the years reducing the stroke risk in patients with AF, literature demonstrates that patients with known AF are worldwide yet undertreated, especially when studies focus on preadmission treatment of patients with acute stroke.²¹⁻²⁶ In this context less than 40% of patients with known AF are on VKAs treatment.²²⁻²⁶ A population based study performed in Denmark has demonstrated that the underuse of VKAs is a major determinant of cardioembolic stroke in patient with AF and could burden for 4-5% of strokes.²⁷

In our study less than one third of patients with known AF admitted to internal medicine wards of Tuscany for acute stroke took VKAs for stroke prevention (28.3%) with a gap between patients needing VKAs (CHADS₂ ≥ 2, 86.7%) and patients really treated of around 60% (58.4%) and the underuse of VKAs increased in patients with major risk of stroke reaching percentage less than 25% in patients with CHADS₂ score ≥ 4. Moreover the majority of patients who took VKAs were not protected for stroke risk due to sub-optimal anticoagulation control. On the other hand, around one half of patients was treated with antiplatelet drugs, confirming their non-protective effect for stroke prevention in AF, such as found from the abovementioned meta-analyses.¹⁴ Our findings are not completely surprising, since than an Italian survey in the setting of primary care demonstrated that only around 30% of patients with AF are treated with VKAs alone (26.6%) or in combination with antiplatelet drugs (5.5%).²⁸ Moreover this survey showed that advanced age was a major determinant for not prescribing VKAs and prescribing antiplatelet drugs and only 42% and 24% persisted on treatment with VKAs after one and two years from prescription, respectively.²⁸

Our study confirms literature reports that burden of ischemic stroke in AF patients is more severe compared to non-AF patients.⁷ In fact, severity at presentation, severe discharge disability and in-hospital

mortality were from two to three fold greater in AF patients compared with non AF patients in our cohort. Of much interest, we found that these outcomes were less severe in patients with known AF taking oral anticoagulants compared to non-taking patients. Our findings confirm those of a much recent study which demonstrated that the use of VKAs before a cardioembolic stroke significantly reduces disability measured by mRS and mortality compared with no antithrombotic treatment (odds ratio 0.64; CI 95%: 0.45-0.91).²⁹

Another major point of our study is that only around one out of four patients with acute AF-related stroke is discharged from hospital on treatment with VKAs. The much recently published ATA-AF study encompassing more than 7000 patients with AF and performed in the internal medicine and cardiology wards of Italy, demonstrates that VKAs were prescribed in around one half of patients (49.6%) discharged from internal medicine wards and internal medicine ward recovery was associated with significantly lower probability to be treated with VKAs.³⁰ Only a small proportion of patients (7.1%) enrolled in internal medicine wards in this study were in the context of acute stroke.³⁰ Concerns exist on the optimal timing to start with anticoagulation in the acute phase of stroke. To now, due to literature evidence, available guidelines suggest to avoid anticoagulation in the first 48 h from cardioembolic stroke onset and to use antiplatelet drugs which have demonstrated the best efficacy/safety profile.³¹ After this time, the choice to anticoagulate or not a patient suffering from acute cardioembolic stroke depends from neurological severity, size of ischemic lesion and cardiac comorbidity.³¹ Briefly, anticoagulation could be started within the first two weeks and preferably within the first week if neurological deficit is mild or moderate, if the size of ischemic lesion is quite small and if there is cardiac comorbidity such as an atrial thrombus or a prosthetic valve. On the other hand anticoagulation should be delayed to the next two weeks from stroke onset if neurological deficit is severe, the size of infarct is wide and there are no cardiac comorbidities.³¹ What are the reasons for the low percentage of patients discharged from hospitals on VKAs treatment in our study are impossible to detect. We could speculate that physicians were reluctant to use VKAs for the fear of bleeding complications in frailty patients or because they found absolute or relative contraindications or poor compliance. Moreover, due to lack of follow-up, we could speculate that in a lot of patients VKAs were started in the next months.

Finally, our study confirms findings of previous studies, highlighting that the majority of patients suffering from spontaneous VKAs-related hemorrhagic stroke are in therapeutic range.²⁰ This is a cumbersome problem, since it is widely and wrongly believed that

the optimal VKAs control could avoid bleeding complications.

Conclusions

AF-related stroke is a major public health and the lack of adequate and appropriate prevention continue to be disarming as confirmed in our study performed in the Italian medicine wards of Tuscany. Despite VKAs have been considered the first line antithrombotic approach for cardioembolism prevention, these are dramatically underused in clinical practice even in high-risk subjects. Many patients pay the consequence of this under-treatment in terms of ischemic strokes. When VKAs are used, a lot of patients have a sub-optimal treatment control, demonstrated by low TTR and low INR values at hospital admission, consequence of it being the under-protection against cardioembolism. Finally, nevertheless an optimal control of treatment as showed from the good profile of INR values, a not negligible percentage of patients are burdened by spontaneous VKAs-related hemorrhagic strokes.

Therefore efforts to reduce the gap between patients needing cardioembolism prevention and patients really treated or to improve the quality of anticoagulation to avoid often devastating consequences such as ischemic or hemorrhagic stroke are strongly warranted. Much recently new oral anticoagulants have been marketed for stroke prevention in atrial fibrillation due to positive results of phase III randomized clinical trials.^{9,10} Overall, new oral anticoagulants have demonstrated to be effective and safety at least as warfarin, but for many considered endpoints new oral anticoagulants resulted significantly superior to warfarin, especially in safety profile.³² Whether new oral anticoagulants could help physicians in improving the gap between patients needing for OAT and patients effectively treated and their outcomes, to date is impossible to predict. However the road is opened.

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