



## REGULAR ARTICLE

# Risk of bleeding in very old atrial fibrillation patients on warfarin: Relationship with ageing and CHADS<sub>2</sub> score

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**Abstract**

**Aims:** In atrial fibrillation (AF) patients, age  $\geq 75$  years is one of the major risk factors for stroke. However, it is not clear if an upper limit for the indication to OAT exists.

**Methods and results:** For this reason, we performed a prospective study on 290 AF patients on OAT aged  $\geq 75$  years (median age 82 years, total follow-up period 814 pt/years) followed by our Anticoagulation Clinic. Seventeen major bleeding events were recorded (rate  $2.1 \times 100$  pt/years), 11 of which cerebral ( $1.35 \times 100$  pt/years). The occurrence of major bleedings was associated with history of previous TIA or stroke [OR 3.4 (1.1–12.5),  $p=0.01$ ] and with diabetes [OR 4.4 (1.3–14.7)  $p=0.01$ ]. We found a trend to a progressive increase in the rate of bleeding risk with the increase of the CHADS<sub>2</sub> score: patients with score 4–6 showed a rate of  $3.4 \times 100$  pt/years with respect to  $1.5 \times 100$  pt/years of patients with lower score. Number Needed to Harm (NNH) was calculated in relation to different classes of age (75–89, 80–84,  $\geq 85$  years) and to CHADS<sub>2</sub> score. For patients in CHADS<sub>2</sub> score 1–3 NNH remained stable across the different age classes. Instead for patients in CHADS<sub>2</sub> score 4–6, NNH varied among the 3 groups of ages, reaching a value of 10 in patients  $\geq 85$  years.

**Conclusion:** Our data suggest that: 1) in AF patients older than 75 years with CHADS<sub>2</sub> score 1–3 the risk of bleeding is low, 2) in AF patients  $>85$  years with CHADS<sub>2</sub> 4–6 the risk of bleeding is high so that the use of OAT should be highly individualised.

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## Introduction

Atrial fibrillation (AF) is a strong, independent risk factor for stroke because it leads to formation and embolism of thrombi in left atrial appendage. The prevention of embolism is particularly important because strokes associated with AF are severely large and disabling. The antithrombotic therapy is the mainstay for prevention especially after the finding that rhythm control is not able to prevent embolism [1]. The rate of stroke in AF patients widely ranges in relation to the presence of associated risk factors. The narrow therapeutic window of warfarin and the difficulties related to its management raise concerns on a widespread prescription of this drug [2]. Several international and national scientific societies [3,4] have produced guidelines to help physicians to stratify the risk of stroke according to the presence of different risk factors. In particular, a score has been recently proposed and validated to obtain an easy and practical stratification (CHADS<sub>2</sub>) [5]. Age is one of the main risk factors for the occurrence of stroke and has consistently been considered a critical point in the different studies. The American College of Chest Physicians recommends the use of warfarin in all patients aged more than 75 years and age over 75 years is one of the 6 points associated to a high risk in the CHADS<sub>2</sub> score. The number of elderly patients is progressively increasing and the risk of complications in AF patients may significantly differ according to how old they are. There are several studies dealing with the issue of the bleeding risk in elderly patients on OAT [6,7] and an increased risk of intracranial, frequently fatal, bleeding has been reported in these patients [8]. Instead data on the risk of bleeding of very old AF patients on OAT are limited and we do not know if we should establish an upper limit for the prescription of OAT. To answer this question, we performed a prospective study on AF patients on OAT aged from 75 to 96 years, followed by our Anticoagulation Clinic. During follow-up all bleeding events were recorded and the risk of different age groups was assessed.

## Methods

### Patients

We prospectively investigated 290 AF patients referred for the control of OAT to the Anticoagulation Clinic of the Azienda Ospedaliero Universitaria Careggi of Florence. Patients' demographic and clinical data were collected. A computerized program (P.A.R.M.A System; Instrumentation Laboratory, Milan, Italy) [9] was used for the routine management of OAT. At each follow-up visit OAT was monitored by PT expressed as International Normalized Ratio (INR),

determined by capillary blood test (Thrombotest®, Nycomed Pharma AS, Oslo Norway, commercialised in Italy by Sentinel Diagnostic, Milan). During each follow-up visit INR, dose prescription, hospital admissions, intercurrent illnesses, bleeding and thrombotic events were recorded. Patients who missed check-ups for more than 2 months were contacted (personally or through their family or general practitioner) and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. When this information was lacking, national register of causes of death and autopsy results (if available) were consulted.

Data were censored after the first major complication, after the cessation of OAT or when the patient stopped being monitored by our Anticoagulation Clinic. The INRs were maintained at the intended therapeutic range of 2–3.

A software programme was used for the assessment of the quality of anticoagulation by determining the percentage time spent at different INR levels [10]. All overanticoagulation episodes (defined as INR  $\geq$  6.5) in asymptomatic patients were recorded and treated with 2 mg vitamin K1 *per os* administration.

### Outcome measures

The occurrence of all types of bleeding and ischemic complications was recorded. INR was defined as temporally related to the adverse event when it was obtained at the time of the event or during the preceding 8 days. Bleeding was classified as major when: fatal, intracranial (documented by imaging),

**Table 1** Characteristic of patients

	n(%)
Number	290
Male	173
Female	117
Median age (range) years	82 (75–96)
Patients/years	814
Hypertension	177 (61%)
Diabetes	57 (20%)
Dyslipidemia	57 (20%)
Coronary artery disease	64 (22%)
Left ventricular dysfunction	71 (24.5%)
History of TIA/stroke	111 (38%)
Peripheral artery disease	36 (12.4%)
CHADS <sub>2</sub> score	
1	42 (14.5%)
2	83 (28.6%)
3	79 (27.2%)
4	64 (22.1%)
5	18 (6.2%)
6	4 (1.4%)

**Table 2** Rate of major bleeding events in relation to age

Age	Pt/years	Total			Cerebral			Fatal	
		Rate(n)	RR (95%CI)	p	Rate(n)	RR (95%CI)	p	Rate(n)	RR (95%CI)
75–79	433	1.4 (6)	1	0.4	0.7 (3)	1	0.3	0	
80–84	271	2.6 (7)	1.8 (0.3–6.7)	0.3	2.2 (6)	3.1 (0.6–20)	0.6	1.8 (5)	NA
85–96	110	3.6 (4)	2.6 (0.5–11)	0.3	1.8 (2)	2.6 (0.2–23)	0.4	0.9 (1)	NA

Pt/years = patient/years.

NA = not applicable.

ocular causing blindness, articular, or retroperitoneal, when surgery or transfusion of more than two blood units were required or when haemoglobin was reduced by at least 2 g/dL.

Stroke was defined as a syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, lasting >24 h, and with no apparent cause other than vascular. Ischemic stroke was defined as a stroke with either a normal brain CT or evidence of a recent infarction in the clinically relevant area of the brain on a CT or MR scan within three weeks of the event, while Transient Ischemic Attack (TIA) was diagnosed when neurological defects lasted <24 h. Peripheral embolism was diagnosed when proved with angiography or thrombectomy.

The presence of traditional cardiovascular risk factors and characteristics associated with ischemic complications in AF was assessed on the basis of patients' interview, echocardiography and hospital records. Hypertension was defined in the presence of blood pressure above 160 mm Hg and/or an antihypertensive treatment and diabetes was defined according to American Diabetes Association criteria [11]. Coronary artery disease was defined on the basis of a history of myocardial infarction or stable and unstable angina. Impaired left ventricular function was defined as a recent diagnosis of congestive heart failure or a fractional shortening <25% by transthoracic echocardiography.

All patients underwent an electrocardiogram and transthoracic echocardiography. CHADS<sub>2</sub> score [12] was taken to stratify the risk of stroke. The CHADS<sub>2</sub> score ranges from 0 to 6 and is calculated by adding 1 point for each of the following risk factors: recent congestive heart failure, hypertension, age >75 years, or diabetes mellitus, and adding 2 points for having had a previous stroke or TIA. For the sake of simplicity the scale was collapsed into high (4,5,6), medium (2,3), and low risk of stroke (1).

### Statistical analysis

The SPSS statistical software package (Statistical Package for Social Sciences, Chicago USA, software

for Windows; version 10.0) was used for data processing. Data are expressed as median and range due to their skewed distribution. Preliminary statistical analysis was performed using Wilcoxon's signed rank test, or Fisher's exact test (categorical data). The non parametric Mann–Whitney test was used for comparison between individual groups. The independent effect of various possible risk factors, sex and age were investigated by performing the incidence rate ratio (RR) [13].

Univariate and multivariate Cox regression models was used to ascertain which factors (hypertension, diabetes mellitus, history of TIA or stroke, heart failure and coronary artery disease) were significantly associated with risk of bleeding and ischemic events during follow-up. All odds ratios (OR) are given with their 95% confidence intervals (CI) and a value of  $p < 0.05$  was chosen for statistical significance.

The relative risk for major bleeds were converted in annual Number Needed to Harm (NNH) to provide additional clarity in the risk related with OAT. NNHs were calculated in the different age group in relation to CHADS<sub>2</sub> score.

### Results

From June 1995 to October 2005, among the 736 AF patients referred to our Anticoagulation Clinic for the management of OAT, we prospectively followed up 290 patients over 75 years. Two hundred fifty one patients were over 75 years at the beginning of OAT whereas 39 were already on treatment at their 75th

**Table 3** Rate of major bleeding events in patients on OAT in relation to CHADS<sub>2</sub> score and related annual NNHs

CHADS <sub>2</sub> score	Bleeding risk on OAT		
	n/pt/years	Rate × 100 pt/years	NNH
1	2/103	1.9	51
2–3	7/478	1.5	68
4–6	8/233	3.4	29
All	17/814	2.1	60

**Table 4** Rate of major bleeding events in relation to CHADS<sub>2</sub> score

CHADS <sub>2</sub>	75–79 years			80–84 years			85–96 years		
	n/pt/years	Rate × 100 pt/years	NNH	n/pt/years	Rate × 100 pt/years	NNH	n/pt/years	Rate × 100 pt/years	NNH
1–3	5/308	1.6	62	3/195	1.5	65	1/80	1.2	80
4–6	1/126	0.8	126	4/177	2.2	44	3/30	10.0	10
All	6/433	1.4	72	7/271	2.6	39	4/110	3.6	27

birthday when they were included in the follow-up which is the object of this study. Median age at the end of follow-up was 82 years (76–96) and the total time of observation was 814 patient years (pt/years). Characteristics, comorbidity and CHADS<sub>2</sub> score of these patients are listed in Table 1.

Patients were assessed for the quality of anticoagulant treatment: time spent within, above and below the intended therapeutic range was 69%, 16% and 15%, respectively. Total mortality rate during follow-up was 3.2 × 100 pt/years. Five patients died of cerebral bleeding (0.6 × 100 pt/years), 1 patient (0.1 × 100 pt/years) had a fatal gastrointestinal bleeding, 13 patients (1.6 × 100 pt/years) died of heart failure, 3 patients (0.4 × 100 pt/years) died of cancer, 3 patients (0.4 × 100 pt/years) had sudden death, and 1 patient (0.1 × 100 pt/years) died of ischemic stroke.

During follow-up 17 major bleeding events were recorded (rate 2.1 × 100 pt/years). In particular, 6 patients had gastrointestinal bleeding and 11 patients had cerebral bleeding (rate 1.35 × 100 pt/years). Among cerebral bleedings, 9 were spontaneous and 2 occurred after trauma. We analysed the events in relation to the increasing age, and in particular according to three age classes (75–79, 80–84 and ≥ 85 years). In Table 2 we have reported total, cerebral and fatal bleedings in the 3 groups of age. The rates of total major bleeding events were 1.4, 2.6 and 3.6 × 100 pt/years in the 3 groups respectively, but these differences were not statistically significant. No difference was found in relation to the quality of OAT between patients with (time spent in, above and below the therapeutic range was 69%, 13% and 18% respectively) and those free from bleeding complications (time spent in, above and below the therapeutic range was 69%, 16% and 15%,  $p=0.7$ ,  $p=0.2$ ,  $p=0.5$  respectively). The rate of major bleeding events was similar between patients who started OAT after the age of 75 years and patients who were already on treatment at their 75th birthday. The median INR related to major bleeding events was 2.5 (1.2–8); 10/17 patients had INR < 3, 4/17 had INR 3–4 and 3 had INR > 5 at the occurrence of bleeding. Bleeding events occurred a median time of 31 months after starting OAT (range 3–108 months). No difference

was found in relation to sex. At univariate Cox analysis the occurrence of major bleeding events was associated with history of previous TIA or stroke [OR 3.4 (1.1–12.5),  $p=0.01$ ]. A trend to a higher risk of major bleeding was found also in the presence of diabetes [OR 2.4 (0.7–7.1),  $p=0.09$ ], whereas no relation was found with arterial hypertension, heart failure and coronary artery disease. Cox regression analysis adjusted for the above reported variables confirmed that history of previous TIA or stroke [OR 3.6 (1.1–11.6)  $p=0.03$ ] and the presence of diabetes [OR 4.4 (1.3–14.7)  $p=0.01$ ] were independently associated with the risk of major bleeding.

When we examined patients in relation to the CHADS<sub>2</sub> score, we found a trend to a progressive increase in the rate of bleeding with the increase of the score. In particular, patients classified as at high risk (score 4–6) showed a rate of 3.4 × 100 pt/years with respect to 1.9 and 1.5 × 100 pt/years of patients at low and moderate risk respectively (Table 3). In Table 3 we have reported the corresponding annual NNHs. Rates of bleeding and corresponding NNHs were also calculated in the 3 age groups in relation to CHADS<sub>2</sub> score (Table 4). A trend to an increased rate of bleeding was observed in patients aged 80–84 and 85–96 years with CHADS<sub>2</sub> score 4–6.

## Discussion

To better understand if the risk of complications varies in the different age groups of elderly AF patients on OAT, we performed this prospective study in AF patients over 75 years. The present study showed that the risk of bleeds is growing in relation to ageing, as expected. However, our data demonstrated that the risk is growing also in relation to CHADS<sub>2</sub> score.

Fihn et al. [6] found an increase of fatal and life-threatening bleeds. The higher risk of fatal bleeding in elderly patients was especially related to cerebral haemorrhages [6,8]. In keeping with published data, in our series there was a high prevalence of cerebral bleeding in elderly patients, with a high case-fatality rate. Palareti et al. [7], among patients over 75 years, reported a rate of cerebral bleedings of 1.1 per 100 pt/years, a finding similar to ours. As



previously observed by several Authors [6–8,14–19], most bleeding events occurred with INR within the therapeutic range. Fang et al. [16] found an increase in intracranial haemorrhages in AF patients over the age of 85 years; the rate was increased in particular in those with INR > 3.5, but intracranial haemorrhage did occur also in patients with subtherapeutic INRs (< 2). In agreement with these data, in our cohort only 3/17 patients with haemorrhagic complications had INR values > 5. In addition, the quality of anticoagulation control was not different between patients who did and those who did not experience bleeding events. Gage et al. observed that the history of previous stroke was an independent risk factor for both recurrent cerebral ischemia and cerebral bleeding (RR 2.2) and they concluded that prescribing warfarin in AF patients with high risk for stroke (CHADS<sub>2</sub> ≥ 2) [20] is cost-effective. The association between prior stroke and intracranial haemorrhage was reported by other Authors [21–23] and loss of microvascular integrity or disruption was the mechanism proposed to explain this association.

Analysing our data according to age groups and CHADS<sub>2</sub> score, we observed an increased risk of bleeding not only in relation to ageing, but also to the increase of the thrombotic risk expressed by the CHADS<sub>2</sub> score. CHADS<sub>2</sub> score is an easy-to-use classification scheme that has been validated [13] as an useful tool to assess the risk of stroke in elderly AF patients. The application of this score to our population allowed us to compare the risk of stroke with that of bleeding. Although subdivision of patients in relation to both age groups and CHADS<sub>2</sub> score leads to a very low number of bleeding events in each group, this led us to identify patients ≥ 80 years with CHADS<sub>2</sub> score 4–6 as a group at high risk both for bleeding and ischemic stroke. In addition, patients older than 85 years with high CHADS<sub>2</sub> score showed an even higher risk (NNH = 10). Therefore, this group of patients is exposed at same time both to an elevated risk of bleeding and of stroke. A recent meta-analysis by Lip and Edwards [24] reports a Number Needed to Treat (NNT) of 16 to prevent stroke with OAT in AF patients with CHADS<sub>2</sub> score 4–6. The comparison of our data with those available in the literature, with the limitation due to the absence of a specific analysis on very old patients, seems to suggest that older AF patients with CHADS<sub>2</sub> 1–3 have a relatively low rate of bleeding. In particular, low-risk patients with CHADS<sub>2</sub> 1 (no other risk factor than age) show a NNH of 51. Interestingly, the NNT of CHADS<sub>2</sub> = 1 patients in the quoted meta-analysis [24] is similar (58) to NNH calculated in our patients. This could indirectly suggest that older AF patients with

CHADS<sub>2</sub> = 1 have relatively low rates of stroke and may not benefit from OAT. On the other hand, in very old patients with CHADS<sub>2</sub> 4–6 the high risk of both bleeding and thrombotic events, suggests that the use of OAT should be highly individualised.

A limitation of this study is the fact that it was performed in a single centre, with a low statistical power. In addition, patients were followed up in a specialised Anticoagulation Clinic which likely contributed to achieve a good anticoagulation control and to have a low number of bleeding events. However, our study reflects directly the clinical practice and patients were unselected differently from those of clinical trials.

In conclusion, our study performed in very old AF patients on OAT suggests that the risk of bleeding is quite low in those with CHADS<sub>2</sub> scores 1–3 but it becomes very high in patients ≥ 85 years with CHADS<sub>2</sub> score 4–6. A multicentre study on a larger population of elderly AF patients would be very useful to establish if the benefit of OAT persists in very old patients with high CHADS<sub>2</sub> score.

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