Low incidence of hemorrhagic complications of oral anticoagulant therapy in patients with atrial fibrillation in the daily practice of an Anticoagulation Clinic

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Anticoagulants; Atrial fibrillation; Bleeding complications.

Background. **Over the last years, the use of oral anticoagulant treatment (OAT) has increased dramatically, principally for the prevention of embolic stroke in patients with atrial fibrillation. This study was aimed at evaluating the efficacy and safety of the management of OAT in a real-practice situation.**

Methods. **Nine hundred and three consecutive unselected patients, 250 of whom with atrial fibrillation, referred for the control of OAT to the Anticoagulation Clinic of the University of Florence were studied. The total follow-up period was 1679 patient-years.**

Results. **The rate of major bleeding events was 0.8 per 100 patient-years in atrial fibrillation patients. In patients with a target INR ≥ 3 a significantly higher rate of bleeding (p = 0.02) with respect to patients with a target INR < 3 was observed.**

Conclusions. **A low incidence of complications may be obtained even in elderly atrial fibrillation patients on OAT followed in an Anticoagulation Clinic specifically devoted to this management.**

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Introduction

Oral anticoagulation is being prescribed to a steadily increasing number of patients. However, the narrow therapeutic range of the oral anticoagulant drugs and the potentially life-threatening effects of both underdosing and overdosing necessitate a close monitoring of the actual degree of anticoagulation[1].

With advancing age, atrial fibrillation (AF) becomes an important cause of stroke. In the Framingham Heart Study it has been reported that the attributable risk of stroke increases significantly with age, rising from 1.5% for patients aged 50-59 years to 23.5% for those aged 80-89 years[2]. It is known that dose-adjusted warfarin anticoagulation is very effective in decreasing the risk of stroke in AF patients and that it is more effective than aspirin[3]. However, the risk of bleeding, which represents the main complication of oral anticoagulant treatment (OAT), is a major concern to be borne in mind when taking the decision about the best antithrombotic therapy. Bleeding is correlated with the INR levels and with the quality of the anticoagulation monitoring. In several countries specialized centers are addressed to the management of OAT. In order to evaluate the efficacy and safety of OAT in a routine real-practice situation, we performed a follow-up study among the consecutive unselected patients referred to the Anticoagulation Clinic of the University of Florence.

Methods

Patients. We prospectively observed 903 unselected, consecutive patients referred for the monitoring of OAT to the Anticoagulation Clinic of the University of Florence from June 1st, 1995 to January 31st, 2001. Among the patients, 624 (69%) started OAT during the period of enrollment, whereas 279 (31%) were already on treatment.

The indications for OAT are listed in table I. Two hundred and fifty patients had a history of AF. Among the AF patients, 197 (79%) started OAT during the period of enrollment.

At the first visit patients were clinically evaluated and the therapeutic INR range was defined on the basis of the recommendations of the Italian Federation of Anticoagulation Clinics (FCSA)[4]. The patients' demographic and clinical data were com-

Table I. Characteristics of the patients.

	Whole population (n=903)	AF patients (n=250)
Patient-years	1679	370
Age (years)	63.5 ± 14.1	72.1 ± 12
Time in therapeutic range (%)		
Below	18	16
Within	66	71
Above	16	13

AF = atrial fibrillation.

puterized using the P.A.R.M.A. System (Instrumentation Laboratory, Milan, Italy)[5]. This system allows the registration of follow-up visits and the daily dose prescription which is automatically suggested in about two thirds of controls[5]; in any case the final decision about dose prescription and the date of the following scheduled visit was taken by the physician of the Clinic who gave a printed prescription to the patient.

At each follow-up visit, the OAT was monitored by determining the prothrombin time expressed as the INR. The capillary blood test (Thrombotest, Nycomed Pharma AS, Oslo, Norway) was used for this purpose. The INR results obtained with this method have been reported to be significantly correlated with the standard plasma prothrombin time-INR[6]. During the visit a short history including the patient's compliance, treatment complications, comedications, intercurrent illnesses and surgical procedures was taken.

Most patients were treated with warfarin (95%), whereas the remaining patients were on acenocoumarol.

Data collection and analysis. During each follow-up visit, the INR, the dose prescription, hospital admissions, intercurrent illnesses and bleeding and thrombotic events were recorded. Patients who did not turn up for the visit for more than 2 months were contacted (personally of through their general practitioner), and the reason for stopping treatment monitoring was recorded. In case of death further information about its cause was requested. When information was lacking, the national register of the causes of death and autoptic results (if available) were consulted.

Data were censored after the first major complication, after the cessation of oral anticoagulation or when a patient stopped being monitored.

A software program, kindly provided by Dr. F.R. Rosendaal, University Hospital Leiden, The Netherlands, was used for the assessment of the quality of anticoagulation by determining the percentage time spent at different INR levels[7].

The occurrence of bleeding complications was recorded. Bleeding was classified as major when it was fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal and when surgery or transfusion of more than two blood units were required or when the hemoglobin levels fell by 2 g/dl or more. All cases of bleeding not classified as major were considered minor; clinically irrelevant episodes of bleeding were not recorded[8].

Statistical analysis. The STATA statistical software package (STATA Corporation, College Station, TX, USA) (version 7.0) was used for data processing.

The independent effects of various possible risk factors (sex, age, intended degree of anticoagulation) were investigated by performing the incidence rate ratio.

Data were censored after the first serious complication, following cessation of the anticoagulant therapy and when the patient chose not to be monitored any further at the Anticoagulation Clinic.

Results

We investigated 903 patients (533 males, 370 females, mean age 63.5 ± 14.1 years) (Table I), with a total follow-up period of 1679 patient-years (mean 1.86 years). The interval between controls, which is dependent on the stability of the anticoagulant level, was on average 18 days (range 1-35 days). Two hundred and fifty patients received OAT for AF (168 males, 82 females, mean age 72.1 ± 12 years).

The percentage time spent within, above and below the intended therapeutic range was 71, 13 and 16% in patients with AF and 66, 16 and 18% respectively in all the other patients (Table I).

Bleeding events are reported in table II. Twenty patients presented with a major bleeding. In one case, bleeding was fatal. Out of these 20 patients, 2 females had a recurrence of gastrointestinal bleeding after restarting OAT; recurrent events were not included in the statistical analysis. Among AF patients the rates of total and major bleeding events were 3.8 and 0.8 per 100 patient-years respectively and no fatal events occurred. The rates of total and major bleeding events in all the other patients with a target INR < 3, were 4.1 and 1.0 per 100 patient-years respectively. These differences were not statistically significant (Table II). In both groups the rate of bleeding events was independent of sex and age.

The rate of bleeding events varied significantly in relation to the intended therapeutic range. Actually, patients with a target INR ≥ 3 had a relative risk of developing a hemorrhage of 1.6 (95% confidence interval 1-2.5, p = 0.02) with respect to patients with a target INR < 3.

The frequency of bleeding events was investigated according to the different achieved degrees of anticoagulation. When the time spent at an INR ≥ 4.5 was considered, a significantly higher rate of bleeding events was observed with respect to lower INRs (p = 0.003) (Table III).

Table II. Bleeding events.

	Patient-years of follow-up	Major (× 100 patient-years)	RR (95% CI)	Total (× 100 patient-years)	RR (95% CI)
AF patients	370	3 (0.8)		14 (3.8)	
All other patients	1309	17 (1.2)*		71 (5.4)	
Target INR < 3	943	9 (0.9)		38 (4.0)	
AF patients	370	3 (0.8)	0.7 (0.1-3.6)	14 (3.8)	0.9 (0.4-1.8)
All other patients	573	6 (1.0)	p = 0.7	24 (4.1)	p = 0.8
Target INR ≥ 3	736	11 (1.5)		47 (6.4)**	

AF = atrial fibrillation; CI = confidence interval; RR = relative risk. * one fatal (0.07 per patient-years) (gastrointestinal hemorrhage); ** INR ≥ 3 vs < 3: RR 1.6 (95% CI 1-2.5), p = 0.02.

Table III. Hemorrhagic complications of the oral anticoagulant treatment in relation to the achieved INR.

Achieved INR	Patient-years of follow-up	Major (× 100 patient-years)	Total (× 100 patient-years)
< 2	112	1 (0.9)	12 (10.7)
2-2.9	842	12 (1.4)	42 (5.7)
3-4.4	428	4 (0.9)	26 (6)
4.5-6.9	25	2 (8)	3 (12)
≥ 7	0.6	1 (166)	2 (333)
< 4.5	1382	17 (1.2)*	80 (5.8)**
≥ 4.5	26	3 (11.5)	5 (19.2)

* INR ≥ 4.5 vs < 4.5: relative risk 9.4 (95% confidence interval 1.7-32.4), p = 0.003; ** INR ≥ 4.5 vs < 4.5: relative risk 3.3 (95% confidence interval 1.0-8.0), p = 0.02.

Discussion

The results of this observational study show the low incidence of bleeding complications in the normal daily practice of the Anticoagulation Clinic of the University of Florence. The data collected from each control visit were included in the clinical follow-up; so, all relevant complications have undoubtedly been recorded. With regard to clinically irrelevant events, it is possible that these have been underestimated.

The major complication of OAT is bleeding[1]. The rates of major and minor bleeding events in AF patients were respectively 0.8 and 3.8 per 100 patient-years of treatment. The rate calculated with the same intended INR therapeutic range for the other patients was similar, whereas a higher rate of bleeding was observed in patients with an INR therapeutic range ≥ 3. In contrast to other studies[9,10], in our patients the rate of bleeding events was not influenced by age. In particular, patients with AF, although about 10 years older than the remaining population, had a tendency to a lower (though not statistically significant) rate of bleeding events. As a matter of fact, this group of patients spent more time in the therapeutic range (71%) in comparison to the other patients (60%).

As mentioned above, patients with AF are treated in such a way as to maintain a moderate-intensity regimen of anticoagulation. This level of anticoagulation is associated with a low frequency of fluctuations in the dose response and seems to be the safest and most effective[8].

As the use of OAT in patients > 75 years is becoming ever more widespread, our finding of an unmodified risk of bleeding is of clinical relevance for the evaluation of the risk/benefit ratio in these patients.

Actually, despite strong evidence that OAT is effective in reducing stroke in patients with AF, a substantial proportion of patients who are eligible for this treatment, do not receive it[11-13]. The fear of bleeding and of difficulties related to the management of OAT are the reasons for the less than optimal use of OAT in AF patients. Previous studies suggested a better outcome for patients on OAT when monitored by specialized agencies[13-15]. Our study adds further weight to the role of a clinical unit setting specifically devoted to the management of patients on OAT if the risk of complications in such patients is to be decreased.

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