Morbility and mortality in 229 elderly patients with nonrheumatic atrial fibrillation. A five-year follow-up

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Anticoagulants; Atrial fibrillation; Embolism; Mortality.

Background. **In the elderly the impact of atrial fibrillation on mortality and morbidity is substantial. Oral anticoagulant therapy reduces the risk of stroke by 70%; nevertheless, it remains largely underused. We evaluated, in a community prospective study, the factors associated with embolic events and death and the feasibility of oral anticoagulant therapy managed by general practitioners.**

Methods. **We enrolled at the Trieste Cardiovascular Center 229 patients aged ≥ 65 years with nonrheumatic atrial fibrillation. At baseline, each patient underwent a transesophageal echocardiography and received instructions about oral anticoagulation. Patients were regularly followed by their general practitioner and finally evaluated at the Center.**

Results. **At baseline, the mean age was 73 years, 14% of patients were free of heart disease, 27% had had a previous embolic event, and 33% had an atrial thrombus. After a 5-year follow-up, 85% of the patients had been admitted to hospital, 17% had suffered an embolic event, and 35% were dead. Diabetes and the presence of a low flow in the left atrial appendage were predictive of embolic events. Heart failure, spontaneous echocontrast and aortic plaques were predictive of death. Anticoagulant therapy increased from 14 to 34% but the incidence of major bleeding did not change. The patients on anticoagulant therapy at follow-up constituted the group with the worst cardiovascular profile and embolic rate, but had a lower death rate (19%) compared with those on antiplatelet therapy (32%) and with those without antithrombotic therapy (67%). The hospitalization rates were respectively 78, 83 and 100%.**

Conclusions. **In a group of elderly patients followed by their general practitioner with the support of a specialized cardiologic unit, oral anticoagulant therapy was well tolerated and associated with a significant decrease in mortality and hospitalization.**

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Introduction

The incidence and prevalence of nonrheumatic atrial fibrillation (NRAF) increase with age, and in the elderly this condition is defined as "an epidemic problem"[1]. The incidence increases from 3.8% among men in their fifties (less in women) to 9% in the general population over 70 years of age[2]. Its prevalence doubles each decade after the fifties: 0.4% in the general population, 1.2-3.8% among sexagenarians, 7.3-13.7% among octogenarians, and 30% among nonagenarians[3,4].

Particularly in the elderly, NRAF reduces the quality of life, functional status and cardiac performance and is also a risk factor for silent multi-infarct dementia, ischemic stroke and death. NRAF is responsible for 15% of strokes and 50% of cardiac emboli. The incidence of stroke is 1% in the population < 50 years and without risk factors, 8% in the population > 75 years and with risk factors, and peaks to 23% for the age groups > 80 years[5].

The impact of NRAF on mortality and morbidity is substantial, as are the socioeconomic consequences of hospital admissions, chronic disease management, and disabilities. Consequently, an epidemiological study of the natural history of NRAF in old people is crucial for an adequate allocation of future resources[6].

Several trials of primary and secondary prevention demonstrated that oral anticoagulant therapy (OAT) reduces the risk of stroke in NRAF by 70% (twice the benefit of aspirin); nevertheless, OAT remains largely underused everywhere, and mostly in elderly patients and females[7-11]. The published studies are mainly retrospective; the prospective ones have a short follow-up and deal with populations lacking aged individuals.

This study deals with a group of elderly patients enrolled in the Trieste Area Study on Nonrheumatic Atrial Fibrillation, a community prospective study[12]. Baseline evaluation also included a transesophageal echocardiography. We evaluated the factors associated with embolic events or death and the efficacy/feasibility of OAT managed by general practitioners (GPs) during a long follow-up.

Methods

We enrolled at the Trieste Cardiovascular Center 229 patients with NRAF living in Trieste and aged ≥ 65 years. All patients with a history of rheumatic fever or valve surgery were excluded. At the time of enrolment, each patient was submitted to clinical evaluation, chest X-ray, electrocardiography, and transthoracic and transesophageal echocardiography. Special attention was paid to a history of arrhythmia, hypertension, coronary heart disease, heart failure, embolic events, carotid plaques or other potential embolic sources and antiplatelet therapy or OAT. Data were completed by review of clinical records if present. A cerebral embolic event was defined as a new neurological deficit not attributable to the dysfunction of either a single cranial nerve or the spinal cord or the peripheral nervous system, with the deficit persisting for less than 24 hours (transient ischemic attack) or more (ischemic stroke) and with no evidence of an intracerebral hemorrhage or tumor on the computed tomographic scan. When appropriate according to the current clinical guidelines, and especially in those cases with a left atrial appendage (LAA) thrombus, we invited the patients and their GPs to start OAT (recommended range for the international normalized ratio 2-3). All these patients were provided with a letter for their GP, an instruction booklet and a diary[13]. Patients were regularly followed by their GP, who also managed the OAT if prescribed. In 2001, all patients were invited to the Cardiovascular Center for the final follow-up. Hemorrhagic events were defined as major if they necessitated hospitalization or blood transfusions, as minor if not. We analyzed the diary of OAT and considered the therapy correct if the desired international normalized ratio range was maintained for more than 60% of the time.

The history and clinical data were completed by analyzing the clinical records and regional health database which reports all the hospital admissions together with the corresponding diagnoses and mortality data. To establish the cause of death, we interviewed the relatives and GPs of those patients who died out of hospital, whereas for in-hospital deaths we checked the database of the Institute of Pathology of the University of Trieste and revised all the *post-mortem* examinations. We reconstructed the clinical history of all the 229 initial patients through a follow-up period of 5 years.

Echocardiography was performed according to the standards of the American Society of Echocardiography, with a biplane or multiplane transducer for transesophageal echocardiography[14]. Having obtained a written informed consent from each patient, transesophageal echocardiography was performed as previously described[15]. Spontaneous echocontrast was defined as dynamic "smoke-like" echoes swirling slowly in the left atrial or LAA cavity. A thrombus was defined as any echo-dense mass attached to the left atrium or LAA. The peak filling flow was defined as normal when the blood velocity in LAA was ≥ 25 cm/s and as low when it was < 25 cm/s.

All images were recorded on VHS videotape and reviewed by a second independent observer; the interobserver variability was tested and found to be < 10%.

Statistical analysis. For statistical analysis, we used the Statistical Package for Social Sciences 10.0 for MS Windows. Continuous variables were expressed as mean ± SD; differences between the means were evaluated using the Student's t-test for unpaired data. Categorical variables were analyzed using the χ^2 test or Fisher's exact test as appropriate. Kaplan-Meier analysis was used to describe the survival curves; the Cox proportional hazards model was used to determine the predictors of mortality and embolic events. The statistical significance was set at the 0.05 level.

Results

A total of 229 patients completed the study; their baseline characteristics are summarized in table I. The mean age was 73 ± 5 years; 126 patients (55%) had

Table I. Baseline characteristics of the study population (n = 229).

Female sex	94 (41%)
Age (years)	73 ± 5
Duration of atrial fibrillation (months)	93 ± 66
Cigarette smoking	16 (7%)
Hypertension	126 (55%)
Diabetes	30 (13%)
Myocardial infarction	19 (8%)
Heart failure	45 (20%)
Pacemaker	8 (3%)
Heart disease	198 (86%)
Previous embolic events	62 (27%)
Central nervous system	55
Peripheral (limbs, abdomen, retina)	7
Left atrial diameter (cm)	4.2 ± 2.4
Left ventricular end-diastolic diameter (cm)	5.2 ± 2.3
Left ventricular dysfunction	47 (21%)
Mitral regurgitation	125 (55%)
Left atrial spontaneous echocontrast	116 (51%)
Low left atrial appendage flow	91 (40%)
Left atrial thrombus	76 (33%)
Aortic plaques	108 (47%)

high blood pressure and 31 (14%) were free of heart disease. Males had less heart disease than females (16 vs 11% free of heart disease, p = NS) but more ischemic disease (19 vs 7%, p = 0.02). Previous embolic events had occurred in 27% of patients of both sexes, concerning the brain in 90% of cases. Echocardiography showed a high prevalence of mitral regurgitation, spontaneous echocontrast, abnormal LAA flow, left atrial thrombus (almost all in the LAA) and aortic plaques (irregular in more than 50% of cases).

The population data after more than 5 years of follow-up are reported in table II. Fifty percent of the patients were admitted to hospital for a cardiac reason, 39 (17%) patients presented with a new embolic event, 21 (9%) had a major hemorrhage and 21 (9%) minor bleeding, and 80 patients died (35%) with 34 autopsies performed. The causes of death were related to cardiovascular disease in 60% of cases, followed by cancer in 14%. Among 12 patients who died of stroke, 9 were on antiplatelet drugs whereas 3 were not on any antithrombotic regimen.

Table II. Events during follow-up (61 ± 24 months) in 229 patients.

Myocardial infarction	14 (6%)
Heart failure	38 (17%)
Total hospital admissions	195 (85%)
Cardiac causes of hospital admissions	120 (52%)
Embolic event	39 (17%)
Central nervous system	35
Peripheral	4
Major hemorrhage	21 (9%)
Minor hemorrhage	21 (9%)
Death	80 (35%)
Cause of death	
Embolism	12 (6%)
Myocardial infarction	11 (5%)
Heart failure	10 (4%)
Sudden death	5 (2%)
Hemorrhage	5 (2%)
Other cardiovascular causes	5 (2%)
Non-cardiovascular deaths	25 (11%)
Undetermined	7 (3%)

Table III compares the group of 39 patients who had an embolic event during follow-up (36 of the central nervous system and 3 peripheral events) with the others. In the first group there was a trend towards more hypertension, diabetes, less use of OAT and a worse LAA function. At Cox regression analysis, diabetes (p = 0.02, hazard ratio-HR 2.9, 95% confidence interval-CI 1.2-6.9) and a low LAA flow (p = 0.009, HR 3.5, 95% CI 1.4-8.9) were predictive of embolic events.

In table IV the data of those patients who died of cardiovascular causes are compared with those of the patients who survived the period of follow-up. The first group was older, had more hypertension, diabetes and heart disease, suffered more embolic events and assumed less OAT. At Cox regression analysis, heart failure (p = 0.002, HR 1.5, 95% CI 1.3-1.8), spontaneous echocontrast (p = 0.02, HR 2.3, 95% CI 1.3-4.2), and aortic plaques (p = 0.04, HR 1.1, 95% CI 1-1.2) were predictive of death, whereas OAT was found to be a protective factor (p = 0.01, HR 0.5, 95% CI 0.2-0.9).

The same trend was noted when the data of the 12 patients who died of embolic events were compared with those of the patients who survived the follow-up period. At Cox regression analysis aortic valve stenosis (p = 0.001, HR 7.2, 95% CI 2.1-24.1), a low LAA flow (p = 0.02, HR 4.6, 95% CI 1.3-16.9), and antiplatelet therapy (p = 0.003, HR 1.7, 95% CI 1.2-2.4) were found to be predictive of embolic death.

During the study period the percentages of the patients on OAT and on antiplatelet therapy increased from 14 to 34% (p = 0.0001) and from 40 to 45% respectively. Table V reports the characteristics of the patients according to the type of antithrombotic therapy at follow-up. OAT was adequately conducted in 77/79 cases (97%); in this group we registered an increased incidence of minor bleeding (19 vs 3% for the group of patients on antiplatelet therapy, p = 0.04) but not of major hemorrhage. The patients assuming OAT during the

Table III. Characteristics associated with embolic events at follow-up.

	Events (n=39)	No events (n=190)	p
Age (years)	73	73	NS
Cigarette smoking	2 (5%)	14 (7%)	NS
Hypertension	23 (59%)	103 (54%)	NS
Diabetes	7 (18%)	23 (12%)	NS
Heart failure	7 (18%)	38 (20%)	NS
Previous embolic event	9 (23%)	53 (28%)	NS
Baseline antiplatelet therapy	18 (46%)	73 (38%)	NS
Baseline anticoagulant therapy	4 (10%)	28 (15%)	NS
Left ventricular dysfunction	6 (15%)	41 (22%)	NS
Mitral annulus calcification	16 (41%)	58 (31%)	NS
Left atrial spontaneous echocontrast	22 (56%)	94 (49%)	NS
Left atrial thrombus	15 (38%)	61 (32%)	NS
Low left atrial appendage flow	20 (51%)	71 (37%)	NS

Table IV. Characteristics associated with cardiovascular death at follow-up.

	Dead (n=48)	Alive (n=149)	p
Basal			
Age (years)	75	72	0.04
Female sex	18 (38%)	65 (44%)	NS
Cigarette smoking	3 (6%)	11 (7%)	NS
Hypertension	30 (63%)	79 (53%)	0.01
Diabetes	10 (21%)	12 (8%)	0.01
Heart failure	16 (33%)	22 (15%)	0.005
Previous embolic event	15 (31%)	34 (23%)	NS
Left ventricular dysfunction	15 (31%)	27 (18%)	0.05
Aortic valve stenosis	10 (21%)	12 (8%)	0.01
Left atrial spontaneous echocontrast	32 (66%)	68 (46%)	0.01
Left atrial thrombus	17 (35%)	44 (30%)	NS
Low left atrial appendage flow	22 (46%)	53 (36%)	NS
Aortic plaque	24 (50%)	67 (45%)	NS
During follow-up			
Antiplatelet therapy	21 (44%)	69 (46%)	NS
Anticoagulant therapy	12 (24%)	64 (43%)	0.03
Embolic event	14 (29%)	19 (13%)	0.008

Table V. Antithrombotic therapy at follow-up: patient characteristics.

	Antiplatelet (n=102)	Anticoagulant (n=79)	None (n=48)	p
Basal				
Age (years)	73 ± 5	72 ± 5	76 ± 6	0.01
Female sex	47 (46%)	30 (38%)	17 (35%)	0.04
Cigarette smoking	8 (8%)	8 (10%)	0	0.04
Hypertension	59 (58%)	45 (57%)	22 (46%)	0.04
Diabetes	12 (12%)	11 (14%)	7 (15%)	NS
Heart failure	3 (3%)	19 (24%)	8 (17%)	0.03
Heart disease	87 (85%)	70 (89%)	41 (85%)	0.04
Embolic event	27 (26%)	26 (33%)	9 (19%)	0.03
Spontaneous echocontrast	42 (41%)	47 (59%)	27 (56%)	NS
Left atrial thrombus	20 (20%)	41 (52%)	15 (31%)	0.04
Aortic plaques	45 (32%)	36 (46%)	27 (56%)	NS
At follow-up				
Embolic event	15 (15%)	18 (23%)	6 (13%)	NS
Major hemorrhage	7 (7%)	6 (8%)	8 (17%)	NS
Minor hemorrhage	3 (3%)	15 (19%)	3 (6%)	0.04
Hospitalization	85 (83%)	62 (78%)	48 (100%)	0.03
Death	33 (32%)	15 (19%)	32 (67%)	0.04

follow-up period had a worse cardiovascular profile and embolic rate; in fact, OAT was started in most cases after an embolic event. Nevertheless, they had significantly lower hospitalization and death rates (19%) than the other groups (32% for those patients on antiplatelet therapy and 67% for those without therapy, p = 0.0001). Kaplan-Meier survival analysis shows that the curve of the group without antithrombotic therapy diverges sharply from those of the antiplatelet therapy and OAT groups. The benefit in terms of survival was significant (log rank 0.000) and increased with time; after adjustment for age (Fig. 1, Cox regression analysis) the three curves started to diverge after a few months of therapy: the HR for antiplatelet therapy was 0.35 (95% CI 0.2-0.6) and that for OAT was 0.2 (95% CI 0.1-0.3).

Discussion

NRAF is the most common and studied cardiac arrhythmia; nevertheless, owing to its clinical relevance and to the lack of consensus regarding its management (e.g., rhythm vs rate control strategy, drugs for antiarrhythmic prophylaxis, very low use of OAT despite the encouraging results of many trials)[11,16,17] it is still object of great interest.

The original contribution of this study is that it combines clinical-epidemiologic data with those obtained at transesophageal echocardiography in a heterogeneous group of elderly patients with NRAF, which is different from the populations selected in big trials and has been observed "in the field" of ambulatory clinical practice

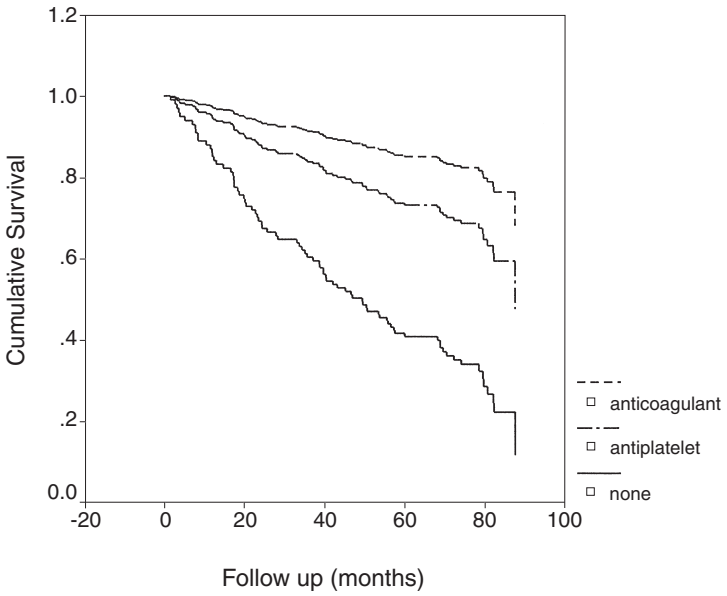

Figure 1. *Antithrombotic therapy and survival (Cox regression analysis adjusted for age).*

during a long follow-up (5 years). All patients were seen at the same center at the time of enrolment and at the end of follow-up; during this time they were regularly visited by their GPs, who were responsible for the final decision about the type of antithrombotic therapy. The patients were aged ≥ 65 years at the time of enrolment and both sexes are well represented in the sample. In contrast, the main trials published in the literature had a follow-up of approximately 2 years and included younger people with a strong prevalence of men[9,18]. Given the special characteristics of our region (homogeneous population, easy access to the hospital, almost all in-patients in the area admitted to hospitals sited in Trieste), the vast majority of subjects who develop a thromboembolic event go to the hospital. We had access to the medical records of almost all patients who had events and could accurately analyze the presence of concomitant diseases and the causes of death. Moreover, our hospital has a high autopsy rate, and among 80 patients who died 34 autopsies were performed.

NRAF is usually associated with underlying heart disease: at autopsy Bharati and Lev[19] found that up to 76% of subjects with atrial fibrillation had pathological features of cardiovascular disease. In the present prospective study only 14% of patients had lone atrial fibrillation. The echocardiographic data reveal a globally preserved left ventricular systolic function (14% with mild dysfunction and 7% with moderate-severe dysfunction), a high rate of mitral regurgitation and a low rate of atrial septal aneurysm (1 vs 8% in the study of Rusznak et al.[20]). Unfortunately, no data regarding the diastolic function are available. We found a very high prevalence of atrial thrombosis (33%) and spontaneous echocontrast (51%); in other studies the prevalence rates of these parameters respectively range between 2.5-10% and between 12-47%; this is probably due to the elevated age of our group, the long duration of the arrhythmia, and the extensive use of the multiplane transducer[21]. On the other hand, our prevalence of aortic plaques is lower than that reported in SPAF III (47 vs 63%)[22].

The high medical costs of NRAF in the elderly are also due to the frequency with which these patients are hospitalized. In this study 85% of the patients were admitted to hospital, most for a cardiovascular reason, and a new episode of heart failure occurred in 17% of cases.

The contribution of NRAF to embolic events has been extensively studied in recent years and has formed the basis of many studies on stroke prevention. Atrial fibrillation is an independent risk factor for stroke and is associated with a 4- to 5-fold increased risk of this event[23]. In the elderly the epidemiologic evidence of an increased risk of stroke is even stronger: old persons are more prone to NRAF and even their risk of stroke is considerably increased compared with younger people with atrial fibrillation, this effect being independent of the concomitance of other cardiovascular diseases[24]. The proportion of stroke associated with NRAF increases from 7% in the sixth decade of life to 36% in octogenarians[25].

The number of thromboembolic events in our study (27 and 17% of the patients at baseline and during follow-up respectively) is noticeably higher than that reported in randomized studies (5-6%), probably due to the older mean age of our population (73 ± 5 vs 63 years in BAATAF[9]) and to the fact that we considered all events and not only stroke. Aronow et al.[26] found a 52% incidence of stroke in a 36-month follow-up, but in a very old and heterogeneous group (312 patients, mean age 84 ± 7 years), with several cases of rheumatic mitral stenosis. The antithrombotic regimen at baseline was not modified following embolic events, but only 40% of

patients were taking antiplatelet therapy and 14% OAT (in most cases not adequately conducted). Despite their high frequency at the time of enrolment, atrial thrombosis, spontaneous echocontrast and aortic plaques were not associated with more embolic events at follow-up, probably because even those patients presenting with these conditions were frequently prescribed OAT.

At multivariate analysis, LAA dysfunction and diabetes were found to be predictive of embolic events. All the indexes of LAA function (LAA ejection fraction, filling and emptying velocity) were significantly lower in the group with events at follow-up. These data are extremely important and support the hypothesis that LAA dysfunction (but not atrial thrombosis nor spontaneous echocontrast) may determine an abnormal atrial hemodynamics and promote the formation of new thrombi. With regard to the impact of the LAA on the genesis of thrombosis and on the long-term prognosis our data are in agreement with those of other studies[27]. Diabetes emerged as a risk factor for stroke in some studies (SPAF). In many studies (SPAF, ELAT, EAFT) stroke was found to be one of the main risk factors for embolism (relative risk 2-3), whereas in our work it reached statistical significance at the medium-term analysis but not at the end of follow-up[18,28]. In fact, the risk of a new stroke is high especially during the first 6 months after the first episode but then progressively decreases[12].

At follow-up, we observed a high mortality (80 deaths, 35%), attributable to an excess in cardiovascular deaths (48 cases, 21% of the total population). The embolic deaths were 12, that is 31% of the embolic events occurring during follow-up were lethal; nobody of these patients was on OAT. The main prognostic factors for death were heart failure, spontaneous echocontrast, LAA dysfunction, aortic plaques, aortic valve stenosis, and OAT.

The relationship between NRAF and mortality is interesting. Several large population studies came to the conclusion that atrial fibrillation of various etiologies increases the risk of death by a factor of 1.3-2.6 in comparison with sinus rhythm[25]. These data have been recently confirmed by Benjamin et al.[29] who observed, in the Framingham study, a risk of death of 2.4 in men and 3.5 in women, thereby greatly reducing women's natural advantage in terms of survival. The mechanism is probably multifactorial. The risk of cardiovascular mortality in aged patients with NRAF is double vs age-matched controls. This is primarily due to thromboembolic stroke and hemodynamic failure; furthermore, the presence of irregular ventricular arrhythmias promotes pump failure in the long term[30].

Probably, the most valuable message of this study concerns OAT. Antithrombotic therapy at baseline (antiplatelet therapy 40%, OAT 14%) involved mainly individuals with previous embolic events or with a pacemaker and was less used than reported in other studies in which OAT was prescribed to 30-40% of candidates[10,11]. In our elderly population, we found that the well-known objections to OAT (low compliance of the patient, the GPs' fear of bleeding, difficult doctor-laboratory-patient communication) are probably exaggerated. We encouraged patients and GPs to start OAT and provided written instructions and the facility for any consultation when requested, but the final responsibility regarding therapy was left to the GPs. During follow-up, the percentages of patients on antiplatelet drugs and OAT rose to 45 and 34% respectively. Besides, even the patients' compliance to OAT definitely improved. Despite our efforts, only one third of patients were on OAT at follow-up, but we must consider that because of age and concomitant diseases another third was excluded from OAT. OAT during follow-up was associated with a 72% decrease in mortality compared to those patients without antithrombotic therapy. A 41% decrease in mortality with respect to patients taking antiplatelet drugs was also observed. The hospitalization rate followed the same trend: during follow-up only 78% of the patients on OAT were hospitalized vs 100 and 83% respectively in the other groups. The apparently high rate of embolic events at follow-up in the OAT group (18/79) is due to the fact that in most cases (13/18) this regimen was started just after the event. Only 5 patients had an embolic event while on OAT. This datum is even more significant if one considers that the OAT group was that with the higher risk and that the therapy did not increase the incidence of major bleeding. There is general agreement in the literature attributing to OAT a 70% reduction in the incidence of stroke, with a conserved cost/benefit ratio even for the older age groups. However, such a strong protective effect in terms of mortality has never been reported[8,11,31]. This positive outcome should encourage the healthcare system to make every effort to render OAT easier to conduct. New strategies in the management of OAT look promising: anticoagulation clinic, computerized decision support software, portable coagulometer, self-monitoring.

In conclusion, NRAF in the elderly population implies a high risk of morbidity, embolic events and cardiovascular mortality. Thrombosis in the LAA is frequent. In our study heart failure, spontaneous echocontrast, LAA dysfunction, aortic plaques and OAT were the variables with a major prognostic impact. Old individuals are less likely to be treated with OAT, although it has been proven to be efficacious for the prevention of stroke. In a group of elderly patients followed by their GPs with the support of a cardiologic unit, OAT was well tolerated and associated with a significant decrease in mortality and hospitalization. Unfortunately, the limitations of warfarin (need for coagulation monitoring, multiple food and drug interactions) will prevent the widespread use of such an approach.

Aspirin should be used when NRAF is not associated with other risk factors or when the management of OAT is too difficult.

The first oral direct thrombin inhibitor ximelagatran is a promising treatment, due to its wide therapeutic window, rapid onset and offset of effect, predictable pharmacokinetics, and few interactions. Besides, it requires no coagulation monitoring. The ongoing SPORTIF III/V study for the prevention of stroke in atrial fibrillation is due to report within 1 year[32].

Given the unsatisfying results in maintaining sinus rhythm with antiarrhythmic drugs, alternative strategies are under investigation. The reports that irbesartan reduces the recurrence of NRAF after electrical cardioversion in amiodarone-treated patients are encouraging[33].

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