

Review Article

Atrial Fibrillation and Thromboembolic Risk in Greece

PANAGIOTIS KORANTZOPOULOS¹, GEORGE ANDRIKOPOULOS², KOSTAS VEMMOS³, JOHN A. GOUDEVENOS¹, PANOS E. VARDAS⁴

¹Department of Cardiology, University of Ioannina Medical School, Ioannina, ²Department of Cardiology, Henry Dunant Hospital, Athens, ³Department of Clinical Therapeutics, Alexandra Hospital, Athens, ⁴Department of Cardiology, Heraklion University Hospital, Heraklion, Crete, Greece

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Address:
Panagiotis Korantzopoulos

Department of Cardiology
University of Ioannina
Medical School
451 10 Ioannina, Greece
e-mail:
p.korantzopoulos@yahoo.gr

Atrial fibrillation (AF) is a rapidly evolving epidemic representing a multifactorial, dynamic disorder with different underlying substrates and serious health consequences.^{1,2} It has been proposed that the aging of the population, along with the increasing prevalence of associated risk factors, accounts for the increase in AF incidence and prevalence during the past few decades.² This is particularly important for the Greek population, which presents both rapid aging and increasing prevalence of the major cardiovascular risk factors.³

It is well-known that AF is independently associated with increased morbidity and mortality, mainly due to an increased incidence of thromboembolic events. In particular, non-valvular AF increases the risk of stroke 5-fold compared to the presence of sinus rhythm. Undoubtedly, antithrombotic therapy is the most significant therapeutic strategy in AF patients who are at increased thromboembolic risk, having an established clinical value for primary and secondary stroke prevention.⁴ In a meta-analysis of published studies it has been shown that aspirin reduces stroke risk by 22%, while warfarin achieves a 68% risk reduction.⁵

The aim of this document is to analyze the current status of antithrombotic treat-

ment in AF and to underline the problems and barriers in the implementation of this therapy with special reference to the particular differences and problems encountered in Greece.

Problems and pitfalls in antithrombotic therapy

Even though AF represents a common clinical entity, problems and pitfalls in the evaluation and management of thromboembolic risk are not rare.⁶ Contributing factors to these problems include the heterogeneity of the disease, the diversity of the underlying clinical conditions, and the uncertainty regarding the therapeutic goals for each individual patient.^{1,6} In everyday clinical practice the treating physician should estimate the risk/benefit ratio for anticoagulation therapy and devise a therapeutic plan tailored to the patient. Thromboembolic risk scores, such as CHADS₂ and the recently released CHA₂DS₂VASc, seem to provide effective tools for the risk stratification of AF patients.⁷ Although the recent European guidelines introduce a bleeding score as well (HAS-BLED score),⁷ the decision concerning anticoagulation, especially in elderly frail patients, is often a difficult task. Despite the solid evidence regard-

ing its protective role there is considerable underutilization of anticoagulation treatment and poor adherence to guidelines. In the Euro Heart Survey only 67% of eligible patients were on anticoagulation, while in another survey from Holland the percentage of high-risk patients who were anticoagulated was 64%.⁸ Along similar lines, a recent systematic review of 54 published studies showed that two thirds of the studies that examined AF patients with prior stroke or transient ischemic attack reported treatment levels of under 60% of eligible patients.⁹ Nevertheless, the utilization of anticoagulation in AF in 'real life' is possibly much lower.⁴ Notably, a multicenter European survey that studied patients who were hospitalized for stroke and had previously known AF showed that only 22% of eligible patients were on anticoagulation before the index event.¹⁰

Several factors have been associated with the low rates of implementation of anticoagulation therapy.^{4,8,11} In particular, these barriers can be classified into 3 main categories, as follows.

Patient characteristics

Recent major bleeding, alcoholism, chronic use of non-steroidal anti-inflammatory drugs, history of falls or perceived risk for falls (epilepsy, instability, neurologic disorders, and others), advanced age, end-stage renal disease/dialysis, severe liver disease, labile INR, paroxysmal AF or infrequent AF episodes.

Physician-related and health service factors

Lack of special outpatient clinics for anticoagulation therapy or well-organized primary care of patients, delays in laboratory results, variability of results between different laboratories, lack of specialized nurses or trained health personnel, inadequate social support, poor adherence to guidelines by the physicians, problematic training and education regarding current guidelines, anticipated responsibility in the case of a severe untoward event. The detection of paroxysmal AF is often challenging.

Patient capabilities and preferences

Difficulties or reluctance in undergoing frequent blood tests or attending appointments, difficult access to laboratory or hospital facilities, cognitive impairment or inability to comprehend medication instructions, inadequate patient support, inability to

limit alcohol consumption, inability to comply with frequent changes in the dose of anticoagulation drug, no comprehension of the risk of thromboembolism or the value of anticoagulation, concerns about bleeding risks and adverse effects, concerns about potential negative effects on the quality of life, low priority for the patient, lack of educational material.

Contemporary assessment of thromboembolic risk

Well-established risk factors for thromboembolism in the setting of AF should be carefully assessed. These include 'major' risk factors, such as previous stroke or transient ischemic attack or thromboembolism, and older age (≥ 75 years), as well as 'non-major' risk factors, such as congestive heart failure or significant left ventricular dysfunction (left ventricular ejection fraction, LVEF $\leq 40\%$), hypertension, and diabetes. According to the current ESC guidelines, 3 additional 'non-major' risk factors should be taken into account.⁷ These include female sex, age 65-74 years, and vascular disease (myocardial infarction, complex aortic plaque, peripheral artery disease). The recently released CHA₂DS₂VASc score assigns 2 points for a history of thromboembolism/stroke or age ≥ 75 years, and 1 point for the rest of the aforementioned risk factors. When the score is 0 the risk for thromboembolism is negligible, while values of 1 or greater indicate an increasing risk. Therefore, the ESC guidelines favour anticoagulation treatment when the CHA₂DS₂VASc score is ≥ 1 .⁷ The calculation of this score should be routine clinical practice in the evaluation of every AF patient. It should be stressed that increased age should not be a reason to withhold anticoagulation therapy. Although exact data for our country are lacking, it is known that many physicians avoid placing their older AF patients (especially the very elderly) on anticoagulation, fearing the hemorrhagic complications. However, current evidence suggests that the benefit outweighs the bleeding risk in patients over 75 years.¹² Despite the clear evidence and the wide dissemination of the ESC guidelines, the aforementioned patient or physician-related problems and barriers are responsible for the underuse of anticoagulation in eligible patients.

Considerations regarding the Greek population

Data regarding specific population characteristics and risk factors for AF in Greek patients are sparse. In addition, the epidemiology of AF in Greece has

not been well studied. The incidence of paroxysmal AF in northwestern Greece has been reported to be 6.2 cases per 100,000 inhabitants per year.¹³ In that study, the prevalence of other comorbidities in paroxysmal AF patients (mean age 62 years, 60% men) was 40.6% for hypertension, 12.7% for coronary artery disease, and 8.6% for diabetes.¹³ Another, more recent Greek study focused on a rural population and investigated only permanent AF.¹⁴ The prevalence of permanent AF in subjects older than 65 years was 5% (6.6% among men, and 3.6% among women). Factors independently associated with the arrhythmia were male sex, ECG evidence of myocardial ischemia, and ventricular premature beats. Although all permanent AF patients without contraindications for anticoagulation (32/36) had a CHADS₂ score >1, 33.3% were taking antiplatelet agents instead of anticoagulation, and 27.7% were not taking any antithrombotic treatment at all.¹⁴

With regard to cardioembolic strokes, it has been demonstrated that Greece has a higher prevalence compared to other countries.^{15,16} Specifically, in the Arcadia Stroke Registry over the 2-year study period 23% of all first-ever strokes were classified as cardioembolic.¹⁵ Remarkably, a high prevalence of AF was noted in this population (34.1%), as well as a high prevalence of other risk factors, such as hypertension (81.1%), and diabetes (29.2%).¹⁵ Vemmos and colleagues have also published data from the Athens Stroke Registry showing similar results.¹⁶ Thirty-two percent of all strokes and 38% of ischemic strokes were categorized as cardioembolic. In this group, AF was evident in 83% of cases, while the prevalence of hypertension and diabetes was 62% and 21%, respectively.¹⁶ Notably, only 12% of the AF patients were receiving anticoagulation.¹⁶ In line with previous reports, patients with cardioembolic stroke had the largest mean infarct volume, while the case fatality at 1 month was considerable (25.7%).

It is therefore evident that the prevalence of AF and hypertension in these Greek registries is higher compared to registries from other countries. More recent data (Vemmos K and colleagues, unpublished data) indicate that the use of oral anticoagulants has increased over time in Greece, but they are still underutilized, especially by primary care/community physicians. The same investigators have recently completed a population survey in the Arcadia province in order to evaluate the prevalence of AF across different ages, to identify independent determinants of AF, and to evaluate the quality of primary stroke preven-

tion (Vemmos K and colleagues, unpublished data). The overall prevalence of AF in the general population was 3.9% (32% had paroxysmal AF), while increasing age, hypertension, heart failure, and prior cardiovascular diseases were independently associated with AF. Interestingly, more than 55% of intermediate-risk and 67% of high-risk patients were not on appropriate antithrombotic therapy. Another recent small Greek study demonstrated that the pharmacological treatment of AF, including anticoagulation, varies considerably between cardiologists and primary care physicians/internists in Greece.¹⁷ In particular, anticoagulation treatment in patients aged >75 years after the first episode of paroxysmal AF was prescribed by nearly 80% of cardiologists, but only by 50% of non-cardiologists.¹⁷ A significant difference with regard to anticoagulation prescription was also evident in patients aged >75 years with permanent AF (94% vs. 84%, respectively).¹⁷ Overall, it is clear that inadequate anticoagulant treatment accounts for the high prevalence of cardioembolic strokes in Greece.

We also have to acknowledge that the rate of aging of the Greek population is alarming and theoretically may lead to a substantial increase of AF cases in the next few decades. Moreover, obesity, diabetes, and metabolic syndrome are highly prevalent in Greece.¹⁸ These factors are clearly associated with an increased risk for cardiovascular disease, including AF.² Another noteworthy issue is that in several rural (including isolated mountain areas or islands) and suburban areas of Greece the access to well-organized health services is problematic.¹⁹ Indeed, despite significant improvements during the past few decades, there is still a marked heterogeneity between urban and rural areas across the country in terms of economic status, health resources, medical services, and ease of transportation to special health facilities. Apparently, the particular geographic morphology and the large number of islands pose significant difficulties in the implementation of anticoagulation therapy. Interestingly, Geitona et al reported a substantial cost benefit with the use of self-monitoring and self-regulation of anticoagulation therapy.²⁰ Although this strategy has many advantages and is highly effective in eligible patients, its widespread use is limited in Greece and the devices used for this purpose are not widely distributed by the national insurance authorities.

Another problem that needs special attention is the absence of organized national health services for

primary care in our country. In fact, many patients seek medical attention from private internists as well as hospital emergency services. In addition, Greek patients do not have a personal medical record relating to their health status, medical history, and medications.

The role of AF type and AF burden

Accumulating evidence suggests that thromboembolic risk does not depend on the type of AF.⁷ Not uncommonly, patients with paroxysmal AF are not treated with anticoagulation, despite the presence of thromboembolic risk factors. Thus, the decision for antithrombotic treatment should be solely based on the CHA₂DS₂VASc score and not on the type of AF.⁷ However, there is still controversy regarding the relation between the burden of AF and thromboembolic risk. Episodes of AF lasting at least 30 seconds are considered worth noting, but it is not known how long the episode should last before it has a clinical impact in terms of thromboembolism. Current implantable pacemakers and defibrillators (ICDs), as well as implantable loop recorders, offer an opportunity to study the burden of AF in association with thromboembolic effects, since they have advanced rhythm monitoring capabilities for extended time periods. In this context, the recently published TRENDS study demonstrated that an AF burden ≥ 5.5 hours on any given day during the antecedent 30 days appears to confer a doubling of thromboembolic risk, while a total time of AF ≥ 10.8 hours in a 30-day window confers an increased risk of thromboembolic events.²¹ Apart from the total burden, the role of the number of AF episodes has not been investigated. Undoubtedly, more data are needed in order to clarify the exact impact of AF burden on thromboembolism. These data are expected to be derived by ongoing studies that use implantable loop recorders (ILRs) to evaluate the underlying burden of AF in patients with stroke.²² Until relevant data become available, it would be prudent to acknowledge that the association of the total AF burden with thromboembolic risk is uncertain; therefore, the management of this risk should not be based on the hypothesized arrhythmia burden.

Asymptomatic AF

The true burden of AF is difficult to estimate, since many episodes of the arrhythmia are asymptomatic, especially in the elderly. Extended electrocardio-

graphic monitoring and device-based diagnostics indicate a high incidence of asymptomatic AF episodes, which in some populations exceeds 80% of the total episodes.²³ It is therefore reasonable to assume that the AF burden is underestimated in many instances. Clinicians dealing with implantable electrophysiological devices should be alert to report in detail the data obtained from the device diagnostics.

The role of gender

As mentioned before, female sex represents a 'non-major' but clinically significant thromboembolic risk factor that has been incorporated in the CHA₂DS₂VASc score.⁷ In fact, epidemiological evidence suggests that women have an increased risk for stroke in the setting of AF.²⁴ The consideration of gender in the new score substantially increases the potential candidates for anticoagulation therapy. However, there is some evidence that women are more likely to have oral anticoagulation withheld, despite their risk, while there seems to be underutilization of anticoagulation therapy in women aged >75 years.²⁵ It has been suggested that the reluctance to use oral anticoagulation may be due to an increased risk of bleeding in women.²⁵

The role of antiplatelet therapy in AF

As stated above, treatment with aspirin has a very limited value for the reduction of thromboembolic events in the setting of AF, when compared to vitamin K antagonists.⁵ It has also been shown that in patients with lone AF, namely younger patients without structural heart disease and risk factors, aspirin is no better than control (without antiplatelet or anticoagulant therapy) for prophylaxis and may increase the risk of major bleeding.²⁶ Consequently, the current ESC guidelines favor the use of anticoagulation even in patients with only 1 non-major risk factor (CHA₂DS₂VASc score=1), but no treatment rather than using aspirin in patients with no risk factors (CHA₂DS₂VASc score=0).⁷ Regarding the combination of aspirin with clopidogrel, the evidence suggests that it is less efficient than anticoagulation, with no difference in bleeding rates (ACTIVE W Study).²⁷ Moreover, the ACTIVE A study showed that, in AF patients unsuitable for vitamin K antagonists, the combination of aspirin plus clopidogrel is superior to aspirin alone in terms of thromboprophylaxis, but at the expense of an increased bleeding risk.²⁸ On the

other hand, there is no evidence for a benefit from clopidogrel monotherapy, and therefore its administration solely for AF is not justified on any occasion. With regard to other antiplatelet agents, such as triflusal, the available data are very limited and do not justify widespread use, apart from selected cases where contraindications of existing therapies are evident.⁷ More specifically, the NASPEAF study²⁹ indicated a superiority of combination antithrombotic therapy with triflusal at 600 mg/d plus oral anticoagulation (INR 1.9-2.5) compared to standard anticoagulation (INR 2-3). However, even this strategy is expected to give way to the use of thrombin inhibitors and Xa antagonists.

Triple antithrombotic therapy

Dual antiplatelet therapy represents a standard treatment after acute coronary syndromes, and especially after percutaneous coronary intervention (PCI). The concomitant use of anticoagulation in such circumstances poses an increased bleeding risk that should be carefully assessed and balanced against thrombotic complications.³⁰ A recent meta-analysis showed that triple therapy (aspirin, clopidogrel and warfarin) after stent implantation in patients who were receiving long-term anticoagulation significantly lowers cardiovascular events and all-cause mortality at the expense of a significant increase in major bleeding.³¹ The ESC recently published guidelines on this specific issue.³² The duration of triple therapy depends on the hemorrhagic risk, on the clinical setting, and on the type of implanted stent. In elective PCI, 4 weeks of triple therapy is recommended for bare-metal stents, and a longer period (3-6 months) for drug-eluting stents, depending on the type of stent (paclitaxel stents need longer therapy). In acute coronary syndromes the implantation of bare-metal stents is favored, followed by triple therapy for 4 weeks in patients with high hemorrhagic risk and for 6 months in those with low or intermediate hemorrhagic risk. These guidelines suggest that after the period of triple therapy the patient should receive anticoagulation plus clopidogrel up to 12 months, and then lifelong anticoagulation alone.³²

It would be prudent to acknowledge that there are considerable gaps in our knowledge regarding the use of combination antithrombotic therapy. Importantly, there are no data on newer antiplatelet drugs, such as prasugrel and ticagrelor, and their combination with conventional or new anticoagulants in the setting of AF.

The role of diet in anticoagulation therapy

It is well known that several clinical and demographic factors have been proposed as factors that influence the stability of oral anticoagulation. Dietary interactions seem to have a significant role in patients taking vitamin-K antagonists. Vitamin-K rich foods counteract the effect of warfarin, leading to sub-therapeutic levels of anticoagulation. These foods include spinach, tea, broccoli, lettuce, soy oil, Brussels sprouts, cabbage, asparagus, and others. It should be noted that patients treated with vitamin-K antagonists should follow a well-balanced diet, avoiding large quantities of foods rich in vitamin-K. More importantly, great variations in the dietary intake of vitamin-K rich foods should be avoided. In other words, the patients should be instructed to consume quite similar quantities of these foods steadily over time. Periods of strict dietary restrictions and fasting should be avoided.

New oral anticoagulants

New oral anticoagulants against AF-related thromboembolic risk will soon become available in our therapeutic armamentarium. The new oral anticoagulants are direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban) and their principal advantage is their administration at a fixed dose, without the need for monitoring the anticoagulant activity and adjusting the dose. In the landmark RE-LY trial, dabigatran 150 mg bid was superior to warfarin in terms of embolic protection, with similar rates of major bleeding, while dabigatran 110 mg bid had comparable efficacy for stroke prevention but fewer major bleedings compared to warfarin.³³ Notably, dabigatran at both doses was associated with significantly fewer intracranial hemorrhages.³³ In addition, a recent comprehensive cost-effectiveness analysis performed in the USA showed that in patients aged 65 years or older with AF and increased risk for stroke, dabigatran may be a cost-effective alternative to warfarin.³⁴

Along similar lines, the recently published ROCKET-AF study showed that rivaroxaban was not inferior to warfarin for stroke prevention or systemic embolism in a high-risk population with a mean CHADS₂ score of 3.5.³⁵ In addition, rivaroxaban administration was associated with fewer intracranial and fatal bleeding complications.³⁵ Importantly, the ARISTOTLE study demonstrated that apixaban was

superior to warfarin in preventing stroke or systemic embolism, causing less major bleeding and lowering all-cause mortality.³⁶

Undoubtedly, the advent of new anticoagulants will open the road for a wide application of anticoagulation therapy in eligible patients, since many of the aforementioned obstacles will be overcome.³⁷ We may hope that many more patients and physicians will benefit from the advantages of this new anticoagulation strategy.³⁷

Concluding remarks

The antithrombotic treatment of AF in the 'real world' is far from ideal, while continuing barriers to the implementation of current guidelines lead to a significant underutilization of anticoagulation therapy. Specifically, several particularities that exist in the Greek population make the optimum treatment strategies even more difficult to achieve. However, we have to acknowledge that detailed data on AF epidemiology and management in our population are sparse. Thus, well-conducted population studies are urgently needed in order to investigate the exact status of AF management in our country and to create future plans for the improvement of therapeutic strategies. In this context, the advent of new oral anticoagulants along with the dissemination of the current knowledge, as well as risk stratification tools adjusted to the Greek population, hold out the hope of improved management and clinical outcomes.

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