Original Research

Clinical Profile and Therapeutic Management of Patients with Atrial Fibrillation in Greece: Results from the Registry of Atrial Fibrillation to Investigate New Guidelines (RAFTING)

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Background: Atrial fibrillation (AF) is the most common arrhythmia with significant morbidity, including a 5-fold increase in stroke risk. The management of AF, including antithrombotic therapy (AT), varies considerably among countries. Representative data concerning AF features and management in Greece are generally lacking.

Methods: The Registry of Atrial Fibrillation To Investigate New Guidelines (RAFTING) is a country-wide prospective observational study of AF in Greece that enrolled consecutive patients with a diagnosis of AF in emergency departments of 31 hospitals of different types according to the population's geographical distribution.

Results: RAFTING enrolled 1127 patients, 51% females, aged 71 ± 12 years. Paroxysmal AF was present in 54% of patients and newly diagnosed AF in 28%; 68% of patients with a previous AF history had undergone a median of 4 cardioversions. A high rate of comorbidities was present, including arterial hypertension in 75% and heart failure in 40%. The median CHADS$_2$ and CHA$_2$DS$_2$VASc scores were 2 and 3, respectively; AT had been prescribed in 87% of non-newly diagnosed patients, with warfarin being prescribed in 56% of them. Among all patients on warfarin, INR values were within therapeutic range in 34% of cases during in-hospital measurement. Hospital admission occurred in 82% of cases, with in-hospital mortality 0.8%.

Conclusions: RAFTING provides updated insights into the current features and management of AF in Greece. The majority of patients have a sufficiently high risk to warrant oral anticoagulation and further attempts to comply with the existing guidelines are warranted.

Atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia in clinical practice and is characterized by a constantly increasing prevalence and significant associated morbidity and mortality.[1-3] Besides other clinical consequences, including heart failure and need for hospitalization, AF patients have a 5-fold increase in the risk of stroke compared to individuals of the same age who are in sinus rhythm.[1,2] Antithrombotic therapy (AT) is the most im-

portant therapeutic strategy in AF, with a proven efficacy in the primary and secondary prevention of stroke.[2,4] However, the use of AT in AF patients remains generally low and rarely exceeds 60% in eligible patients.[4-10] At the same time, the setting of AT is currently changing, as a number of novel agents are being introduced into clinical practice, such as the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban, all approved for stroke prevention in patients with non-valvular AF by the European authorities.

The management of AF and the application of AT in particular seem to vary considerably among different countries.[9] Data on AF epidemiology and management in Greece are quite limited.[11-14] Previous studies included patients confined to a specific geographical region.[11-13] Similarly, the study by Vasilikos et al[14] was not representative of the whole country, while Greece's participation in the EuroHeart survey in 2005 included mainly cardiology ward patients.[15]

In view of the above, the Hellenic Society of Cardiology undertook the Registry of Atrial Fibrillation To Investigate New Guidelines (RAFTING), a country-wide prospective epidemiological survey of AF, in order to depict the current clinical and management profile of AF in Greece, with particular emphasis on AT, including the applied AT strategies, patients' perception of and compliance with AT, and the adherence to clinical practice guidelines. The derived data may be valuable for the design of national strategies to enhance physicians' and patients' awareness, and to reinforce the adherence to guidelines.

Methods

Study population

The RAFTING registry is a countrywide multicenter prospective observational study designed to depict the current clinical and management profile of AF patients in Greece. Patients were enrolled if they were 18 years or older and had a diagnosis of AF (paroxysmal, persistent or permanent) during their admission to the emergency department (ED), regardless of the reason for admission. The diagnosis and classification of AF was made according to the recommendations of the European Society of Cardiology.[2] Before enrolment, all patients were asked to provide written informed consent. Exclusion criteria were the patient's participation in any clinical trial

concerning AF therapy, or refusal to provide written informed consent. The study was performed according to the ethical principles for medical research involving human subjects specified in the Declaration of Helsinki. The study protocol was designed by the Hellenic Society of Cardiology and approved by the ethics committees of all participating institutions as well as the Hellenic drug authorities (National Organization of Medicines).

The RAFTING network consisted of 31 hospitals that were selected to provide a representative picture of current medical practice regarding AF throughout Greece. For this reason, recruiting hospitals were selected on the basis of their geographical distribution and type (regional/secondary, tertiary/university). To avoid over- or under-representation of certain geographical regions or institutions, each center was asked to contribute with a pre-specified number of consecutive patients, according to the distribution of the country's population in the major regions of Greece. The sampling was based on data from the last general population census in 2001, derived from the database of the Hellenic Statistical Authority (http://www.statistics.gr). The full list of centers and investigators participating in the RAFTING network is provided in the Appendix.

Data collection

The parameters of the RAFTING data set included demographics, reason for admission, diagnosis on admission, vital signs, medical history, the type (paroxysmal, persistent or permanent) and duration of AF, AF risk factors, prior AF therapies and related complications, with a particular focus on AT. All definitions were clearly printed on the case report forms in order to achieve consistency among all participating centers. Duration of AF less than 7 days (with spontaneous return to sinus rhythm) or duration more than 7 days distinguished paroxysmal from persistent AF.[2] Major bleeding was defined as a hemorrhage that was fatal, intracranial, required transfusion or surgical intervention, or resulted in a hemoglobin drop of more than 3 g/dL. A recent stroke was defined as one occurring within the previous 6 months. Ex-smokers were those who had quit for more than 12 months. Hypertension was defined as blood pressure above 140/90 mmHg, hyperlipidemia as total cholesterol above 200 mg/dL and diabetes as fasting blood glucose above 125 mg/dL, or the use of antihypertensive, hypolipidemic or antidiabetic drug thera-

Table 1. Geographical distribution of patients in 6 major regions of Greece. Representation of each region was predefined according to the distribution of the Greek population based on the 2001 census (shown in last column).

Region	No. of centers	No. of patients	% of cases	% of population
Attica	11	413	36.6	35.3
Macedonia & Thrace	7	274	24.3	25.6
Epirus, Ionian islands & Western Greece (incl. Patras)	5	141	12.5	11.3
Central Greece & Thessaly	3	130	11.5	11.9
Peloponnese	2	66	5.9	5.4
Aegean & Crete	3	103	9.1	10.5
Total	31	1127	100	100

py, respectively. The indication for AT was based on the $CHADS_2$ score, computed by the recorded data, which was in use during most of the enrolment period.[16] Parameters to assess the patients' perception of AF and of the need and risks of AT were also included, as well as the specialty of the treating physician. In the case of hospitalization, discharge date and diagnosis were also recorded. Follow up was performed by the attending physicians with phone contacts at 6 months post-enrolment to assess the occurrence of major events, including death, major hemorrhage, or thromboembolic events, as well as patients' compliance with AT.

Statistical analysis

The statistical analysis was basically descriptive. Categorical variables are summarized as relative frequencies, whereas means of central tendency are employed for all continuous variables. The analysis was performed using SPSS v.18 software (SPSS Inc., Chicago, Illinois, USA).

Results

During the study period (January 2010 to January 2011), 1127 consecutive patients with AF, 51% females, aged 71 ± 12 years, were enrolled in 31 centers throughout Greece. The distribution of patients according to geographical region is outlined in Table 1. Patients' demographics and main clinical features at baseline are shown in Table 2, while gender and age distributions are presented in Figure 1.

The main presenting complaint of patients in the ED included palpitations (483 patients, 43%), dyspnea (22%), chest pain (8%), dizziness (4%), and faintness or syncope (3%). Other less frequent complaints included epigastric pain, fever, vomiting, lower limb edema, hypertension, falls, paresis, while 3%

of cases concerned scheduled appointments or admissions.

The features of AF are summarized in Table 3. Paroxysmal AF was present in 54% of patients, persistent in 11% and permanent in 35%. Atrial flutter

Table 2. Patients' demographic and clinical characteristics at baseline (n=1127).

Demographics:	
Age, years	70.9 ± 11.8
Gender, female, %	51.3
Nationality, %:	
Greek	97.3
Albanian	1.0
Turkish	1.0
Other	0.7
Medical history, comorbid states, %:	
Heart failure	39.9
Coronary artery disease	25.6
Valvular/rheumatic heart disease	4.8
Cardiomyopathy	6.4
Recent stroke:	
Ischemic	4.7
Hemorrhagic	0.2
Transient ischemic attack	0.6
Thromboembolic events other than stroke	2.5
Carotid artery disease	4.6
Peripheral artery disease	6.3
Hyperthyroidism	8.1
Chronic obstructive pulmonary disease	13.2
Chronic renal failure	10.0
Hepatic disease	1.9
Peptic ulcer	7.3
Syncope	12.4
Mental/kinetic disease	6.5
Cardiovascular risk factors, %:	
Arterial hypertension	74.4
Diabetes mellitus	24.1
Hyperlipidemia	44.8
Current smoker	13.5
Previous smoker	31.6
Previous interventions,%:	
Mechanical valve implantation	3.9
Pacemaker implantation	5.5

Table 3. Characteristics of atrial fibrillation (AF).

	n=1127
Newly diagnosed, %	28.3
Paroxysmal, %	53.5
Persistent, %	11.2
Permanent, %	35.3
Atrial flutter, %	9.9
Median AF duration, months	48.7
Mean age at AF diagnosis, years	65.1 ± 12.6
Prior cardioversion, %	68.4
Median number of cardioversions/patient	4
Medical cardioversion, %	85.1
Electrical cardioversion, %	6.9
Electrical and medical cardioversion, %	7.9

was encountered in 10% of patients and was significantly more frequent in patients with permanent arrhythmia compared to those with persistent or paroxysmal (p<0.001, Figure 2). Newly diagnosed AF was present in 28% of cases. The mean age at AF di-
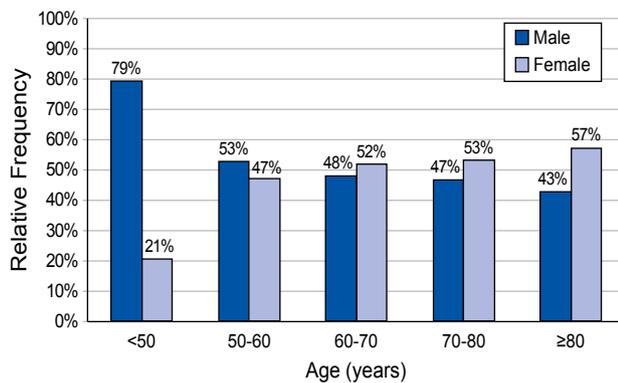
agnosis was 65 ± 13 years (median 66 years); 68% of cases had undergone a median number of 4 prior cardioversions, mostly pharmacological ones (85%). The median CHADS$_2$ and CHA$_2$DS$_2$VASc scores were 2 and 3, respectively; the distribution of patients according to these scores is shown in Figure 3. The median HAS-BLED score was 5.

Drug therapy at baseline is presented in Table 4. Overall, 86.6% of non-newly diagnosed patients were receiving AT and warfarin was the most frequently prescribed antithrombotic medication, being received by 55.9% of cases. In patients on warfarin therapy, the INR values fell within the therapeutic range (2-3) in 60% of cases based on the latest ambulatory measurement reported by patients, but only in 34% of cases based on in-hospital measurement when such a measurement was performed (Figure 4). The majority of patients were having their INR value measured in a private lab (71.0%), 19.6% of them in hospital

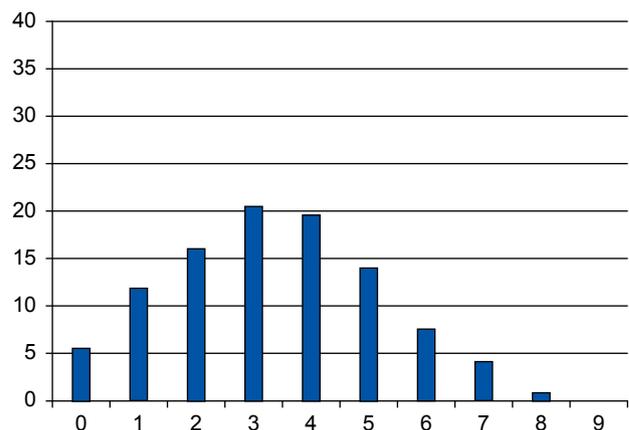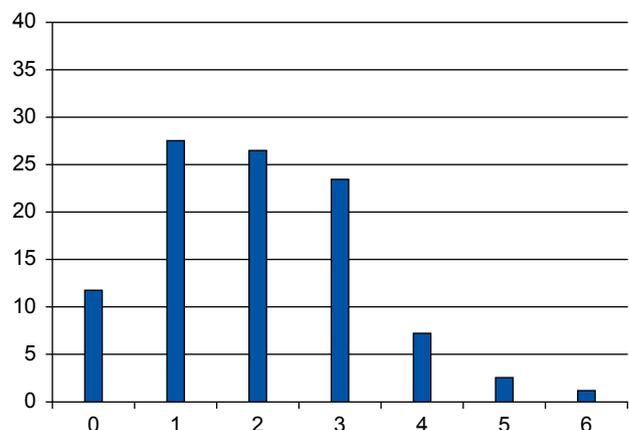**Figure 1.** Distribution of atrial fibrillation patients according to gender and age (decades).
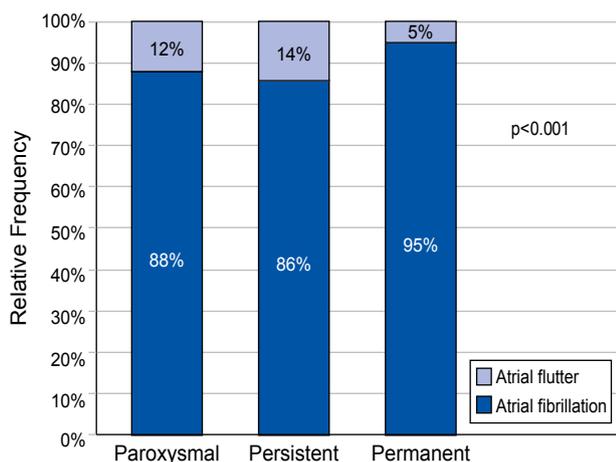
Figure 2. Relative percentage of atrial flutter in the different types of atrial fibrillation.

Figure 3. The distribution of patients according to the CHADS$_2$ (upper panel) and CHA$_2$DS$_2$VASc (lower panel) scores.

Table 4. Drug therapy at baseline.

Medication	All patients (n=1127)	Non-newly diagnosed patients (n=807)
Anti-thrombotic, %:		
Warfarin	44.1	55.9
Aspirin	26.2	26.3
Clopidogrel	14.6	15.1
Low-molecular-weight heparin	1.0	0.7
Other	0.9	1.1
None	25.2	13.4
Antiarrhythmic, %:		
Propafenone	9.7	12.5
Beta-blocker	44.3	47.9
Amiodarone	9.3	10.6
Sotalol	5.2	6.9
Diltiazem	8.5	10.3
Verapamil	1.6	2.0
Digitalis	17.2	22.0
Other cardioactive, %:		
Angiotensin-converting enzyme inhibitor	28.0	28.1
Angiotensin II antagonist	35.9	38.4
Other calcium channel blocker	17.5	18.0
Statin	36.0	37.5
Diuretic	51.7	56.8
Nitrate	11.1	12.0
Other, %:		
Bronchodilator	12.1	13.8
Thyroid hormone therapy	13.1	13.5
Insulin	5.3	6.1
Oral antidiabetic	18.1	19.0
Non-steroidal anti-inflammatory drug	2.4	2.2
Steroid	3.3	3.7

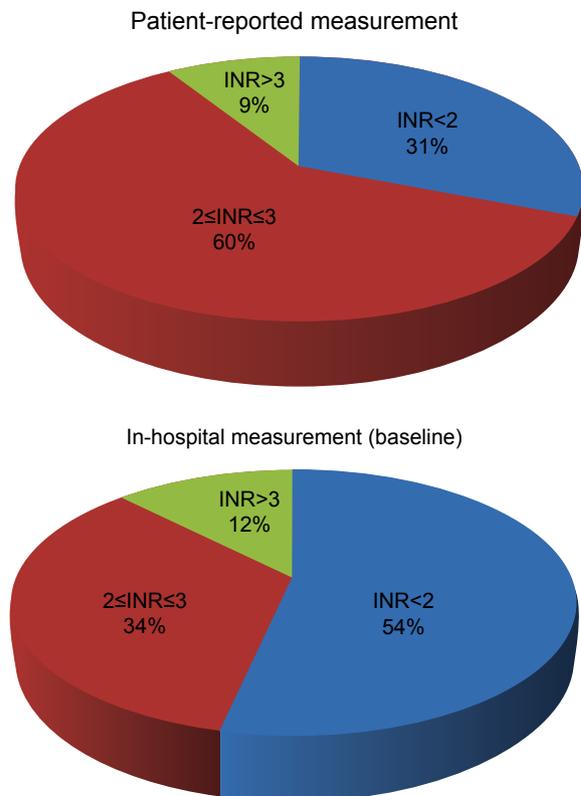**Figure 4.** Values of INR in patients on warfarin therapy.

and the remainder in other facilities, including local public medical centers and social security organization labs. The interval between sequential INR measurements was 4.0 ± 2.4 weeks (median, 4 weeks).

The treating physician was a cardiologist (82%), an internist (12%), or a general practitioner (2%), while 2% of patients were not being followed by any physician.

Of 1127 patients who visited the ED, 924 (82%) were finally admitted. The median hospitalization time was 2 days (range, 0-198 days). During hospitalization, 9 patients (0.8%) died because of cardiopulmonary arrest (3 patients), acute pulmonary edema (2 patients), acute abdomen (2 patients), acute myocardial infarction (1 patient) and stroke (1 patient).

Discussion

Atrial fibrillation is a very common clinical entity, being present in almost 10% of the population above 80 years of age.[2] Since AF carries a certain morbidity, with ischemic stroke and other embolism as the most feared consequences, during the last decade special attention has been paid to the proper management of patients with AF. Several guidelines have been issued and proper anticoagulation treatment is recommended. However, a large portion of AF patients receive suboptimal care.

Registries are very important as a means of identifying a possible gap between recommended therapies and actual everyday practice. National registries are always needed, since each country has specific features and data from other countries may not apply everywhere. In this report we present data from a representative cohort of 1127 consecutive patients with AF from the RAFTING registry. This registry aimed to represent the whole country, and to achieve this goal it included patients from all types of hospital and from all geographic regions, with each center contributing a pre-specified number of cases in order to avoid over- or under-representation of any particular area or type of hospital.

Previous epidemiological studies and registries

of AF in Greece have given important, yet limited results. A study from Epirus showed that the prevalence of new cases of AF was approximately 6 per 10,000 population per year.[11] In Arcadia, 3.9% of the population had AF, with 55% not receiving appropriate anticoagulation.[12] In another study from rural Greece only 40% of patients received anticoagulation.[13] Vasilikos et al demonstrated a disturbingly high rate of prescription of antiplatelet clopidogrel by internists.[14] The participation of Greece in the EuroHeart survey in 2005 included only 323 patients, most of whom were from cardiology wards and were therefore more likely to comply with guidelines.[15] In the present registry, we enrolled patients who came to the ED for any reason and therefore represent the way AF is managed outside the hospital.

The most common AF type was paroxysmal AF (54%). In contrast, in the EuroHeart Survey for AF and the Registry of the German Competence NETwork on Atrial Fibrillation (AFNET), which included 5333 patients from 35 European countries and 9582 patients from Germany, respectively, the most frequent type was permanent AF, followed closely by paroxysmal AF.[15,17] One potential explanation for this discrepancy may be that RAFTING enrolled patients only from the ED, where a higher representation of symptomatic paroxysmal AF cases is normally expected. On the other hand, the classification of AF suffers from significant inconsistency, as on several occasions there is a need for reclassification, due either to the emergence of new clinical evidence or to the application of novel therapeutic approaches that may modify the natural course of the disease.[17] Thus, catheter ablation may cure an AF case that has previously been classified as persistent.[17] Moreover, according to the current guidelines, the type of AF should not play a role in the decision-making regarding AT, and the latter should be entirely based on the thrombotic and hemorrhagic risk profile.[2]

In the present survey, 28% of cases had newly diagnosed AF, while in the remaining cases with a previous history of AF the majority (68%) had undergone a median number of 4 cardioversions, mostly pharmacological (85%). Cardioversion, mainly pharmacological, had also been performed in about half the cases in the EuroHeart and AFNET surveys.[15,17]

As pointed out by the aforementioned AF registries,[15,17] the vast majority of AF patients have several other comorbid conditions. Thus, in line with previously published data, almost 40% of cases aged 70 years or older and the majority of patients, almost 75%, had arterial hypertension. Other comorbid states included heart failure in 40%, coronary artery disease and diabetes mellitus in nearly 25%, chronic obstructive pulmonary disease in 13%, and chronic renal failure in 10%, while 45% of patients were previous or active smokers. Moreover, 5% had a recent ischemic stroke or transient ischemic attack. It should be pointed out that comorbidities such as heart failure or coronary artery disease might render the therapeutic decisions more complex in AF patients.

Concomitant drug therapies reflect the patients' clinical profile. In accordance with the EuroHeart and AFNET registries,[15,17] the most frequently prescribed anti-arrhythmic agents were beta-blockers in 44% of patients, followed by digoxin in 17% of patients, while the use of other rate- or rhythm-control medications was much lower (propafenone, amiodarone, sotalol, diltiazem and verapamil each in less than 10% of patients). In fact, propafenone was used as frequently as amiodarone. Antihypertensive medications were also commonly prescribed.

The heart rate at presentation seemed high. This is not necessarily proof of inadequate rate control, since in some patients the AF is newly diagnosed and therefore a fast heart rate is expected. In addition, since many patients with established AF were enrolled in the study as a result of another medical condition presented in the ED, it is reasonable to record a faster than usual heart rate.

Our study reconfirms that a certain population of high-risk patients with AF do not receive oral anticoagulation.[18] Sole use of clopidogrel, a treatment not supported by any study, was recorded in several patients. Of course, many patients will have reasons not to receive anticoagulants; nevertheless, the proportion of patients on antiplatelets is rather high.

Nor was the INR control ideal. In large randomized clinical trials in most countries, the time within therapeutic ratio (TTR) is around 50%. For example, in the ACTIVE study, the Greek participating hospitals had a TTR of 45%.[19] In RAFTING, there were no detailed measurements for TTR calculation, but when patients were asked to report their last INR value, it seemed that 60% were within optimal range. This percentage was much lower when the INR measurement was carried out in hospital and verified by the investigators. This shows that good control of antivitamin K is difficult in real life, and this is an argument in favor of the newer anticoagulants, such as dabigatran, rivaroxaban or apixaban, that require no monitoring.[20-22]

Our study has some strengths but also some limitations. First, it is a representative study of all types of hospitals and all geographical regions. Since patients were entered in the ED setting, the recorded medication reflects the treatment chosen by their own doctor and not the treatment of the admitting institute. One limitation of our registry is the inclusion of only 31 centers. Certainly a larger study would be desirable. Moreover, some of the data were self-reported and therefore might not have been accurate; however, they are still relevant as representative of everyday clinical practice.

In conclusion, the majority of patients with AF have a sufficiently high risk to warrant oral anticoagulation. Antiplatelet therapy is still widely used, especially in paroxysmal cases. Further attempts to comply fully with the existing guidelines are necessary.

Acknowledgements

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Appendix

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