Original Research

Management of Atrial Fibrillation in Greece: the MANAGE-AF Study

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Key words: **Atrial fibrillation, anticoagulant therapy, stroke.**

Background: Although atrial fibrillation (AF) is a highly prevalent health problem with high morbidity and mortality, data regarding the clinical characteristics and management of AF in the Greek population are scarce. The "Current Clinical Practice in the MANAGEment of Atrial Fibrillation in Greece'' study (MANAGE-AF) aimed to assess the epidemiological features as well as the daily clinical practice in the management of Greek patients with AF.

Methods: Taking into consideration the distribution of the Greek population, 603 consecutive patients over 18 years of age, with any type of AF, presenting at the emergency departments or outpatient clinics of 27 different centers, were included in our study.

Results: The mean age of the patients was 68.5 ± 12.1 years, with male patients representing 52.5% of the study population. The most common AF type in our cohort was non-paroxysmal AF (60%), including the patients with permanent (24.1%), persistent (17.4%), long-standing (4.8%) and first diagnosed AF (13.8%). Hypertension was the most common comorbidity (70.3%). A history of stroke or transient ischemic attack was detected in 9.2% of the patients, while 6.2% had a history of gastrointestinal bleeding. About half of the patients (49.3%) were treated with anticoagulant drugs, mainly vitamin K antagonists (46.9%), while 34.2% were on antiplatelet drugs, aspirin and/or clopidogrel. The mean INR level (1.7 ± 0.8) was sub-therapeutic, although the mean values for $CHADS_2$ and CHA_2DS_2-VASc scores were 1.6 ± 1.2 and 3.0 ± 1.7, respectively.

Conclusion: The MANAGE-AF baseline results indicate unsatisfactory levels of compliance with the current guidelines for the management of AF in Greece. Considering the undisputed effectiveness of anticoagulant treatment for preventing AF-related strokes, MANAGE-AF demonstrates the need for optimization of our therapeutic strategies for the management of cardioembolic stroke risk.

Manuscript received:
February 24, 2014;
Accepted:
May 27, 2014.

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Atrial fibrillation (AF) is the most common sustained arrhythmic disorder in daily clinical practice.[1] Its prevalence in the general population has been estimated at around 1-2%, with a progressively increasing prevalence in people older than 70 years.[2] Current data suggest that the prevalence of AF will

double in the next 50 years.[3] Atrial fibrillation is associated with increased hospitalization rates, mainly due to stroke episodes and decompensated chronic heart failure. Ischemic strokes related to AF often lead patients to severe disability or even to death.[4] Anticoagulant treatment is the cornerstone in the management of AF, either with vitamin K antagonists (VKAs) or with the new oral anticoagulants (NOACs). The latter include the direct thrombin inhibitor dabigatran etexilate and the anti Xa inhibitors rivaroxaban and apixaban, which have gained approval for stroke prevention in non-valvular AF patients. The recent European Society of Cardiology (ESC) guidelines for the management of patients with AF have introduced new algorithms for the assessment of thromboembolic as well as bleeding risks. Thus, the CHA_2DS_2-VASc score extends the previous $CHADS_2$ score for the assessment of thromboembolic risk and the HAS-BLED score is used to assess the potential bleeding risk.[5]

Only limited data are available regarding the clinical characteristics of Greek patients suffering from AF and its management in Greece. Few studies have been published representing the epidemiological trends in specific geographic regions. Recently, data were published from the Greek RAFTING registry for patients with AF.[6] Our study, named ''Current Clinical Practice in the MANAGEment of Atrial Fibrillation in Greece'' (MANAGE-AF), was an observational prospective multicenter study. It was designed by the Hellenic Cardiovascular Research Society to record the "real world conditions" in both urban and rural Greek regions, regarding the management of AF and the adherence of physicians to the recently published guidelines.

Methods

The MANAGE-AF study was a 1-year prospective, observational study that enrolled consecutive patients from the emergency department or outpatient clinics in 27 Greek hospitals, in a manner reflecting the populations from different geographic regions and social strata of the country. Their selection was made mainly on the basis of their geographical distribution, aiming to encompass the full spectrum of hospitals admitting patients with AF in each geographical area. The names of the study investigators and of the participating centers are given in the Appendix. For the purposes of the study, the country was divided into five major regions: Attica, Thessaloniki, Northern Greece, Central Greece and Southern Greece. In order to avoid the overrepresentation of older individuals in some of the country's regions due to demographic reasons, we used the population over 18 years of age as the target population for AF. Aiming to recruit a representative sample of patients treated for AF in the country, we followed the methodology of the HELIOS study.[7] We enrolled patients over 18 years of age with any type of AF (first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent) as defined in the ESC guidelines, who were eligible to participate after giving written informed consent. Patients with an anticipated life expectancy less than 1 year or patients who were involved in another interventional clinical trial for AF at the time of enrolment were excluded from the study. The study was organized according to ethical considerations, as described in the Declaration of Helsinki for human medical studies, and the protocol of the study was approved by the ethics committees of all participating hospitals. A detailed medical history was taken from each patient and a detailed physical examination was performed at the time of enrollment. Data from the electrocardiogram and echocardiogram as well as the biochemical profile of each patient were also recorded if they were available. Two follow-up visits at 6 and 12 months were programmed for all enrolled patients.

Types of AF were defined according to ESC guidelines.[5] Patients who present with AF for the first time are considered as first diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms. Paroxysmal AF is defined as self-terminating, usually within 48 hours or 7 days. Persistent AF is considered as an AF episode that either lasts longer than 7 days or requires termination by cardioversion. Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient and the physician. Stroke risk was assessed by the CHA_2DS_2-VASc score: Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female). The EHRA score was used to classify AF symptoms according to their severity and the HAS-BLED score—Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years old), Drugs/alcohol concomitantly—was used to define the potential bleeding risk.[5]

Statistical analysis

Data analysis was performed using SPSS statistical software (version 15.0, SPSS, Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation, and categorical variables as number of observed patients (percentage).

Results

In the MANAGE-AF study a total of 603 consecutive patients were enrolled in the emergency departments and outpatients' clinics from 27 Greek hospitals. Table 1 shows the baseline demographic and clinical characteristics of the study population. The mean age was 68.5 ± 12.1 years and the majority were male (52.5%, n=317) and married (76.17%, n=457).

Most of the patients (58.9%) were non-smokers and 28.9% were ex-smokers. The most common AF type in our cohort was non-paroxysmal AF (60%), including the patients with permanent (24.1%), persistent (17.4%), long-standing (4.8%) and first diagnosed AF (13.8%). The mean heart rate was 88.9 ± 31.7 /min and the mean values for systolic and diastolic blood pressure were 127.6 ± 18.1 and 77.2 ± 10.3 mmHg, respectively. Hypertension was the most common comorbidity in patients with AF (70.3%). Regarding the other stroke risk factors, 23.3% of the patients suffered from heart failure, 21.8% of them had diabetes mellitus, and 20.5% had coronary artery disease. A history of stroke or transient ischemic attack was present in 9.2% of the patients, while 6.2% had a history of gastrointestinal bleeding disorders. Six percent of the patients reported chronic renal dis-

Table 1. Baseline demographic and clinical characteristics of patients.

Demographics	n	(%)	Mean ± SD
Age (years)	603		68.5 ± 12.1
Age ≥75 (years)	198		
BMI (kg/m^2)	602		28.4 ± 4.4
Sex (male)	317/603	52.5	
Family status (married, %)	457/603	76.2	
Education			
Primary	290	48.6	
Secondary	187	31.3	
Higher	72	12.6	
Smoking			
No	355	58.9	
Ex-smoker	174	28.9	
Heart Rate (bpm)			88.9 ± 31.7
SAP (mmHg)			127.6 ± 18.1
DAP (mmHg)			77.2 ± 10.3
Type of AF			
First-diagnosed	83	13.8	
Paroxysmal	241	39.9	
Permanent	145	24.1	
Persistent	105	17.4	
Long-standing persistent	29	4.8	
Stroke risk factors			
Hypertension	424	70.3	
Heart failure	137	23.3	
Diabetes	132	21.8	
CAD	124	20.5	
Stroke/TIA	56	9.2	
Interventions			
Pacemaker	27	4.5	
Catheter ablation	29	4.8	
Co-morbidities			
Chronic renal disease	36	6.0	
Chronic hepatic disease	6	1.0	
History of gastrointestinal bleeding	37	6.2	

BMI – body mass index; SAP – systolic blood pressure; DAP – diastolic blood pressure; AF – atrial fibrillation; CAD – coronary artery disease; TIA – transient ischemic attack.

Table 2. Echocardiographic and laboratory baseline data.

	mean ± SD
Echocardiographic measurements	
Left ventricular end-diastolic diameter (mm)	50.9 ± 6.6
Left ventricular end-systolic diameter (mm)	35.1 ± 7.1
Ejection fraction (%)	56.6 ± 10.1
Left atrial diameter (mm)	44.2 ± 7.8
Laboratory measurements	
AST (mg/dL)	23.5 ± 13.2
ALT (mg/dL)	24.4 ± 14.0
γ-GT (U/L)	38.6 ± 54.5
Urea (mg/dL)	44.6 ± 20.2
Creatinine (mg/dL)	1.0 ± 0.3
GFR (mL/min)	80.3 ± 32.4
Glucose (mg/dL)	114.2 ± 34.1
TC (mg/dL)	184.8 ± 41.5
LDL-C (mg/dL)	114.4 ± 33.8
HDL-C (mg/dL)	46.3 ± 13.6
TG (mg/dL)	134.9 ± 65.7
Baseline INR (mg/dL)	1.7 ± 0.8

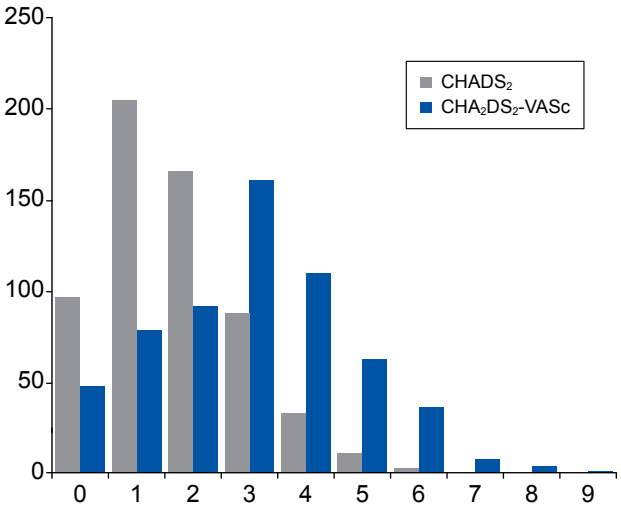

Figure 1. Distribution of both $CHADS_2$ and CHA_2DS_2-VASc scores in the study population.

Table 3. Medication at baseline.

Medication	n	(%)
Anticoagulant	297	49.3
Vitamin K antagonists	283	46.9
Dabigatran	6	1.0
Fondaparinux	6	1.0
Low molecular weight heparin	6	1.0
Antiplatelet	206	34.2
Aspirin	177	29.4
Clopidogrel	69	11.4
Triflusal	3	0.5
Beta-blockers	270	44.8
Calcium channel blockers	155	25.7
Antiarrhythmic	219	36.3
Propafenone	77	12.8
Amiodarone	60	9.9
Sotalol	47	7.8
Digoxin	34	5.6
Flecainide	10	1.7
Statin	232	38.4
Angiotensin-converting enzyme inhibitor	139	23.1
Angiotensin II receptor antagonist	207	34.3
Diuretics	240	39.8
Nitrates	32	5.3
Aldosterone antagonists	48	7.9

ease, while about 1% suffered from chronic hepatic disease. Only a few patients (4.8%) had undergone AF ablation or had a permanent implanted pacemaker (4.5%).

Table 2 shows the echocardiographic and laboratory measurements at baseline, as provided by the patients. The average ejection fraction was 56.6 ± 10.1% and left atrial diameter was 44.2 ± 7.8 mm. The baseline mean INR value in the total study population was 1.7 ± 0.8, significantly lower than the established therapeutic range of 2.0 to 3.0. More specifically, patients with permanent, persistent and long-standing persistent AF had mean INR values 1.7 ± 0.7, 1.8 ± 0.8 and 2.0 ± 0.7, respectively. As regards renal function, the mean value of glomerular filtration rate (GFR) was above normal levels, about 80.3 ± 32.4. Only 1.9% and 14.2% of the patients had GFR values <30 and between 30 and 50, respectively.

The medications used by the patients are summarized in Table 3. Half of the total patients (49.3%) were treated with anticoagulants, receiving mainly VKAs (46.9%). About 34.2% were on antiplatelet antithrombotic therapy, with aspirin and/or clopidogrel. About half of the patients (44.8%) were receiving beta-blockers, while significantly fewer (36.3%) were on antiarrhythmic drugs.

Regarding the thromboembolic risk, as shown in Figure 1, the majority of patients had $CHADS_2$ and CHA_2DS_2-VASc scores 2 or 3, with mean values 1.6 ± 1.2 and 3.0 ± 1.7, respectively. The prevalence of individual stroke risk factors is shown in Table 4. The median value of the HAS-BLED score was 2.1 ± 1.2 in the total study population. Most of the patients presented with mild or more severe symptoms (>2) according to the European Heart Rhythm Association (EHRA) score (Table 5).

Table 4. Prevalence of stroke risk factors-components of $CHADS_2$ and CHA_2DS_2-VASc scores.

Parameters	Prevalence (%)
Congestive heart failure (C)	135 (22.3%)
Hypertension (H)	423 (70.1%)
Age ≥75 years (A or A_2)	396 (65.6%)
Diabetes (D)	132 (21.9%)
History of stroke or TIA (S_2)	59 (9.7%)
History of vascular disease (V)	133 (22.1%)
Age (65 to 74 years) (A)	198 (32.8%)
Sex category (Sc)	286 (47.4%)

Table 5. Assessment of symptoms according to EHRA score.

EHRA score	N	%
1	238	39.47
2	254	42.12
3	6	1.00
4	96	15.92

Discussion

Atrial fibrillation is the most common arrhythmia and is associated with high morbidity and mortality. Registries provide valuable data regarding the special characteristics and the management of AF in certain cohorts. In the MANAGE-AF study we recorded these data from a representative sample of 603 Greek patients with AF from the outpatient clinics or emergency departments of 35 secondary or tertiary Greek hospitals. Since epidemiological data about AF patients in our country are limited, MANAGE-AF aims to reflect the characteristics of the Greek patients regarding their clinical profile and subsequent medical management.

The average age of patients in the MANAGE-AF study was 68.5 years, which is consistent with the average age of German patients (68.4 years) enrolled in the Registry of the German Competence NETwork on Atrial Fibrillation (AFNET).[8] Most of the patients in our study (60%) presented with non-paroxysmal AF and the most frequent stroke risk factor was hypertension (70.3%). This is in agreement with the results from the AFNET registry, where most of the patients who suffered from persistent and permanent AF also had arterial hypertension (69.2%).[8] Other cardiac and non-cardiac comorbidities, such as heart failure, coronary heart disease and diabetes mellitus, had similar prevalence in the AFNET and MANAGE-AF registries (29% vs. 23.3%, 28% vs. 20.5% and 21.7% vs. 21.8%, respectively).[8] Furthermore, 9.2% of the patients had a history of stoke and/or transient ischemic attack, quite similar to the 8.6% reported in the AFNET registry for German patients.[8] Recently published data from the RAFTING trial, which was conducted in Greece, showed a lower stroke rate around 5.3%.[6]

Regarding the antithrombotic therapy in our study, only half of the patients were treated with anticoagulation therapy, mainly VKAs, and a high rate of antiplatelet therapy prescription (aspirin and/or clopidogrel) was recorded in the total population. These findings are in line with previously reported data and reconfirm the low rate of appropriate anticoagulation management in patients with AF in Greece.[9-12] In comparison, the AFNET registry reported a rate of 71% of patients with AF treated with anticoagulants, which is consistent with the rates recorded in the EuroHeart Survey (67%).[8,13] A recently published meta-analysis performed in the United States reported anticoagulation rates similar to the ones in our study.[14]

The median values of $CHADS_2$ and CHA_2DS_2-VASc scores in our study were comparable to other similar registries, such as the Realise-AF and AFNET.[15,8] According to the guidelines and the $CHADS_2$ and CHA_2DS_2-VASc score values, the risk of stroke in our study population is between 3% and 4% per year, and anticoagulation therapy with either VKAs or NOACs is recommended unless contraindicated.[5] However, in our cohort, as mentioned above, about half of the patients did not receive the appropriate anticoagulation therapy. Moreover, the low mean value of INR in patients with non-paroxysmal AF who were receiving VKAs is indicative of a low time in therapeutic range (TTR), which is nowadays the index that indicates the efficacy and safety of VKAs. In line with our results, the assessed mean TTR in Greek patients under warfarin therapy in the RELY study was 56%, thus confirming the need for improved management of anticoagulation in patients with AF.[16]

Chronic kidney disease (CKD), with a creatinine clearance <60 mL/min, seems to be an independent risk factor for bleeding and stroke episodes in patients with AF.[17,18] The majority of patients in the MANAGE-AF study presented without renal impairment and only a few patients had mild to moderate CKD, which is associated with increased bleeding risk, while receiving either VKAs or NOACs. Therefore, according to the recently published recommendations from the ESC, a careful assessment of renal function is required, especially for patients who are going to receive NOACs.[19]

In our study, one third of the patients were re-

ceiving antiarrhythmic drugs, mostly propafenone and amiodarone, and about the half of them were on beta-blockers. These results are consistent with those derived from the EuroHeart Survey. In the AFNET registry, beta-blockers and digitalis were the most frequently used drugs and only 21% of the patients, primarily those with paroxysmal and persistent AF, were receiving class I and III antiarrhythmic drugs.[8] Similarly, data from another German registry based on the Gutenberg Health Study show that antiarrhythmic therapy other than beta-blockers was reported by approximately 20% of participants with AF.[20] Since the majority of our patients presented with first-detected or non-paroxysmal AF episodes, the mean heart rate seems to be high; this is consistent with the data from the AFNET registry, where similarly classified patients had a heart rate above 100 beats per minute.

The present study aims to reflect the clinical profile of patients suffering from AF in various Greek geographic regions. A larger study, enrolling more health centers, could probably offer more data in this field in the future. Moreover, the majority of the reported laboratory data were provided by the patients themselves, which could affect the accuracy and the proper validation of the values measured. According to these preliminary results, the management of anticoagulation to reduce the risk of stroke and its consequences in Greek patients with AF is suboptimal. Better compliance of attending physicians with the contemporary guidelines for the management of AF is clearly required.

Acknowledgements

We would like to thank everyone who was involved in the MANAGE-AF study, primarily the physicians whose names are listed in the Appendix. The study was organized under the auspices of Hellenic Cardiovascular Research Society and was supported by an unrestricted grant from Bayer Hellas.

References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285: 2370-2375.
2. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998; 82: 2N-9N.
3. Le Heuzey JY, Breithardt G, Camm J, et al. The RecordAF study: design, baseline data, and profile of patients according to chosen treatment strategy for atrial fibrillation. Am J Cardiol. 2010; 105: 687-693.
4. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke. 2001; 32: 392-398.
5. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31: 2369-2429.
6. Farmakis D, Pipilis A, Antoniou A, et al. Clinical profile and therapeutic management of patients with atrial fibrillation in Greece: results from the Registry of Atrial Fibrillation to Investigate New Guidelines (RAFTING). Hellenic J Cardiol. 2013; 54: 368-375.
7. Andrikopoulos G, Pipilis A, Goudevenos J, et al. Epidemiological characteristics, management and early outcome of acute myocardial infarction in Greece: the HELlenic Infarction Observation Study. Hellenic J Cardiol. 2007; 48: 325-334.
8. Nabauer M, Gerth A, Limbourg T, et al. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. Europace. 2009; 11: 423-434.
9. Vemmos KN, Takis CE, Georgilis K, et al. The Athens stroke registry: results of a five-year hospital-based study. Cerebrovasc Dis. 2000; 10: 133-141.
10. Vassilikos VP, Mantziari A, Goudis CA, et al. Differences in management of atrial fibrillation between cardiologists and non-cardiologists in Greece. Hellenic J Cardiol. 2010; 51: 113-121.
11. Ntaios G, Manios E, Synetou M, et al. Prevalence of atrial fibrillation in Greece: the Arcadia Rural Study on Atrial Fibrillation. Acta Cardiol. 2012; 67: 65-69.
12. Korantzopoulos P, Andrikopoulos G, Vemmos K, Goudevenos JA, Vardas PE. Atrial fibrillation and thromboembolic risk in Greece. Hellenic J Cardiol. 2012; 53: 48-54.
13. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2005; 26: 2422-2434.
14. Baczek VL, Chen WT, Kluger J, Coleman CI. Predictors of warfarin use in atrial fibrillation in the United States: a systematic review and meta-analysis. BMC Fam Pract. 2012; 13: 5.
15. Alam M, Bandeali SJ, Shahzad SA, Lakkis N. Real-life global survey evaluating patients with atrial fibrillation (REALISE-AF): results of an international observational registry. Expert Rev Cardiovasc Ther. 2012; 10: 283-291.
16. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010; 376: 975-983.
17. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2) CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation. 2013;

127: 224-232.
18. Camm AJ, Savelieva I. "R" for "renal" and for "risk": refining risk stratification for stroke in atrial fibrillation. Circulation. 2013; 127: 169-171.
19. Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013; 15: 625-651.
20. Schnabel RB, Wilde S, Wild PS, Munzel T, Blankenberg S. Atrial fibrillation: its prevalence and risk factor profile in the German general population. Dtsch Arztebl Int. 2012; 109: 293-299.

Appendix

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