Original Research

A Greek Prospective Observational Study of Cardiovascular Morbidity and Mortality in Patients with Atrial Fibrillation

Panos Vardas[1], George Andrikopoulos[2], Barbara Baroutsou[3]; the ODYSSEY investigators*

[1]Cardiology Department, Heraklion University Hospital, Heraklion, Crete, [2]Department of Cardiology, Henry Dunant Hospital, Athens, [3]Sanofi, Medical Affairs Department, Athens, Greece

**Listed in Appendix 1*

Key words: **Cardiac arrhythmias, rate or rhythm control, cardiovascular morbidity, mortality.**

Introduction: Atrial fibrillation (AF) is the most common form of cardiac arrhythmia and represents a growing threat to public health. A representation of data among the private sector in Greece and an assessment of the correlation of different treatment strategies (rate or rhythm control) with annual cardiovascular (CV) morbidity and total mortality, are generally lacking.

Methods: Patients aged >18 years, diagnosed with AF verified by a standard electrocardiogram (ECG), were included in this observational study (n=1545). Information and data, including demographic characteristics, clinical profiles, therapeutic strategies and outcomes, were collected prospectively from each patient at 4 visits: baseline, 6±2, 12±2, and 24±2 months. Data were analyzed using descriptive statistics, quantitative and qualitative variables.

Results: The annual non-adjusted CV morbidity was 18.1% [95% CI 16.0–20.3%] and 17.2% [13.9–18.4%] in the first and second years, respectively. At the end of the first year, the non-adjusted CV morbidity was 17.1% [14.0–20.3%] for rhythm-control treatment and 18.9% [15.9–21.8%] for rate-control treatment (p=0.477). At the end of the second year, the non-adjusted CV morbidity was 14.9% [11.6–18.2%] for rhythm-control treatment and 17.2% [14.1–20.2%] for rate-control treatment (p=0.367). Overall non-adjusted mortality was 1.6% [0.9–2.3%] and 1.9% [1.1–2.7%] in the first and second years, respectively. At the end of the first year, the non-adjusted mortality was 0.7% [0.02–1.5%] for rhythm-control treatment and 2.3% [1.9–3.4%] for rate-control treatment (p=0.030). At the end of the second year, the non-adjusted mortality was 0.6% [0–1.4%] for rhythm-control treatment and 2.8% [1.5–4.1%] for rate-control treatment (p=0.009).

Conclusions: In this multi-centre, countrywide, 24-month observational prospective study, there were no statistically significant differences in CV morbidity between rhythm and rate control treatments, whereas there were statistically significant differences in total mortality in the first and second years. Rhythm- versus rate-control treatment showed a lower rate of total mortality in both the first and second years.

Manuscript received:
July 1, 2015;
Accepted:
October 14, 2015.

Address:
George Andrikopoulos

Department of Cardiology
Henry Dunant Hospital
107 Mesogion Avenue
115 26 Athens, Greece
andrikop@hotmail.com

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia and represents a growing threat to public health. Its incidence ranges from 0.4% to 1% in the general population, and can reach up to 10.7% in the elderly above 80 years old.[1,2]

In Greece, there are scarce and insufficient data on AF epidemiology and management because of geographical differences, methods of population sampling and analysis, as well as diversities of AF in different age groups of available epidemiological studies. An epidemiological study

from Epirus estimated that the annual incidence of paroxysmal AF was approximately 6 per 10,000 population and was higher for males.[3] In the Arcadia Rural Study, the overall prevalence of AF was 3.9%, showing an increasing trend with age.[4] In another study from rural Greece, the prevalence of permanent AF was 5% (6.6% among men and 3.6% among women) and again increased with age.[5]

AF often coexists with other cardiovascular (CV) diseases such as hypertension, coronary heart disease, and heart failure and is estimated to be one of the conditions that will evolve into epidemics in the 21st century.[6] AF increases CV morbidity and mortality, it is an independent risk factor for stroke, increasing its risk by 3- to 5-fold, and promotes the incidence of heart failure.[7-12]

AF also imposes a high economic burden on public health, as is shown by results from the Euro Heart Survey.[13] It accounts for approximately one third of hospitalisations for cardiac rhythm disturbances.[10] For instance, in Greece, the estimated health care cost of AF accounted for approximately €272 million, or 1.5% of total health care expenditures, in 2006.[14]

In addition, the presence of AF influences the quality of life of the patients involved, not only because it increases CV morbidity, but also because the adopted therapeutic strategies present side effects.[6]

The available data regarding the management of AF patients in the real world derive mainly from the data of the Euro Heart Survey,[13] a >10-year pan-European survey of AF management and the most recent European registries, such as the EURObservational Research Programme AF Registry and the PREFER Registry, designed to describe the management of AF patients in Europe after the release of the 2010 AF guidelines of the European Society of Cardiology (ESC).[15,16]

RECORD AF is another study that provided information regarding the rationale for the selection of different therapeutic approaches (rate or rhythm control), as well as the effect of these strategies on CV morbidity and mortality in patients with AF.[17]

The RAFTING registry is the most recent countrywide prospective observational study designed to depict the current clinical and management profile of AF patients in Greece.[18]

Different treatment strategies (rate or rhythm control) have been proposed for AF patients and have shown similar results in terms of reduction of morbidity and mortality, according to large randomised controlled trials RCTs.[19,20]

Although some studies and data have assessed the correlations among CV morbidity and mortality of AF, there is a shortage of data for Greek patients with AF.

The aim of this multi-centre, epidemiological, prospective observational study (ODYSSEY) was to assess CV morbidity and total mortality during two years of follow up of AF patients among the private sector on a countrywide basis, as well as to evaluate the effects of different treatment strategies (rate and rhythm control) on CV morbidity and mortality.

ODYSSEY study investigators also collected real-life information regarding the incidence of CV risk factors in relation to the morbidity and mortality of patients with AF, as well as recording pharmacological or non-pharmacological treatment, adverse events (AEs), and data regarding the management of patients with AF on an annual basis.

Methods

Study design

This study was conducted in 100 sites (private cardiologists) in Greece between October 2009 and October 2013. The site selection was performed following a relative feasibility questionnaire among the private sector in the entire Greek geographical territory, distributed in urban, suburban and rural areas that would be representative of available epidemiological patterns. The selection of cardiologists was reviewed by the National Coordinator of the study (P. Vardas), who was the final arbiter of site selection and distribution of the patient population. Each centre recruited a maximum of 20 consecutive patients who met the inclusion and exclusion criteria of the study.

The study protocol was approved by the National Coordinator's Hospital Scientific Committee and by the Greek National Organisation for Medicines. It was conducted in accordance with the Declaration of Helsinki and Good Epidemiological Practice Guidelines and subjects provided written informed consent.

Participants

Patients diagnosed with AF verified by a standard ECG, attending the physician's office seeking treatment or follow up of their disease, and older than 18 years, were eligible. The study did not interfere with clinical practice and only collected data from consecutive patients with AF, including their de-

mographic characteristics, clinical profiles, therapeutic strategies, anticoagulation therapy, estimated stroke risk (CHA_2DS_2-VASc score),[21] and outcomes, prospectively at 4 visits: baseline (Visit 0-V0), 6±2 months (site visit or phone contact) (Visit 1-V1), 12±2 months (Visit 2-V2), and 24±2 months (Visit 3-V3). Clinical data were retrieved from the medical records.

Exclusion criteria included patients with a life expectancy of less than 2 years, pulmonary hypertension (stage III or IV New York Heart Association [NYHA]/World Health Organisation), supraventricular arrhythmia other than AF, and reversible causes of AF (e.g. thyrotoxicosis).

In total, 1545 patients from 94 sites consented and were included in the baseline data, although full data on the clinical subtype of AF was available for only 1499 patients. Of the 1545 patients included at baseline, 1083 (70%) completed the study, 41 died (2%), and 421 were lost to follow up (27%).

More specifically, 1545 patients were included in V0, 1302 patients (84%) were included in V1, 1214 patients (78%) were included in V2 and 1083 patients (70%) were included in V3, as shown in Figure 1.

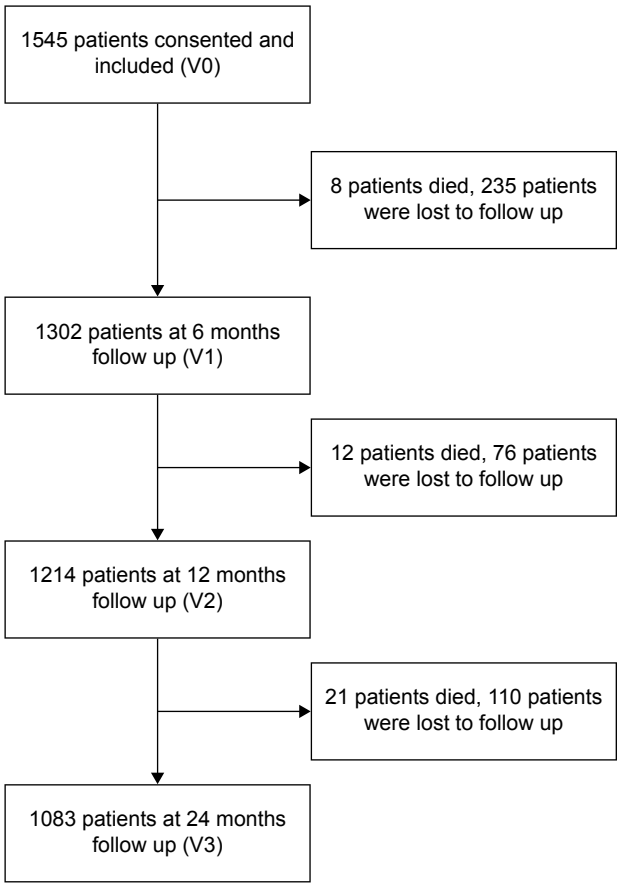

Figure 1. Study flowchart

Endpoints and safety measurements

The primary endpoint was the estimation of annual CV morbidity and total mortality in patients with AF and the evaluation of the correlation of different treatment strategies (rate or rhythm control) with CV morbidity and total mortality on an annual basis. CV morbidity was assessed by recording acute myocardial infarction, stable/unstable angina, stroke, transient ischaemic attack, heart failure (new onset or worsening), or hospitalisation for CV causes. Total mortality was adjudicated as death from any cause, whether CV or not, and was classified into four categories: deaths due to arrhythmia, to non-arrhythmic cardiac causes, to non-cardiac vascular causes, and to non-CV causes. The main causes of CV death were heart failure, cardiogenic shock, acute myocardial infarction or unstable angina, ventricular arrhythmia, sudden cardiac death, pulmonary or peripheral embolism, cardiac tamponade, aortic dissection or death during cardiac surgery (intracoronary bypass, coronary artery bypass surgery, pacemaker or defibrillator placement, ablation).

Secondary endpoints included the following: estimation of CV mortality for different treatment strategies (rate or rhythm control), percentage of patients with new onset heart failure on different treatment strategies (rate or rhythm control), percentage of patients with changes in NYHA functional classification of heart failure during follow up by therapeutic strategy (rate or rhythm control), hospitalisation rate due to recurrence of AF by therapeutic strategy, proportion of patients that changed therapeutic strategy (rate or rhythm control) during follow up, assessment of the impact of CV risk factors on CV morbidity and total mortality, relation of AEs to medications for AF, and collection of data regarding the management of patients with AF on an annual basis.

Sample population size

The planned number of 1642 patients was calculated based on the estimated evidence of the annual cardiac event incidence (about 10%), taking into account that 10% of the patients might be lost to follow up, leading to a final number of patients for analysis of 1478. Based on this sample size, the expected inci-

dence during the study can be calculated with an accuracy of 2%.

Statistical analysis

For the implementation of the statistical analysis, descriptive statistics were used for the following group of variables: demographics, clinical measurements, CV risk factors, medical history of CV disease, medical history of other disease and AF history.

For quantitative variables, mean, median, standard deviation, minimum, maximum, lower 5%, upper 5%, lower 25%, upper 25% were used. For qualitative variables the distribution table of the answers was presented.

To identify confounders, χ^2 and Kolmogorov–Smirnov tests, at the 95% significance level, were used. Paired t-tests were used for comparisons between endpoints versus baseline for the same subject. The population was split into two subgroups according to treatment strategy: the first subgroup contained patients who followed the rhythm-control treatment strategy and the second subgroup contained patients who followed the rate-control treatment strategy.

Logistic regression analysis was used with risk factors as independent variables and the odds of success as dependent variables. All statistical analyses were implemented at a significance level $\alpha=0.05$ using the statistical package SAS 9.3 – SAS Enterprise Guide 5.1.

Results

Baseline characteristics

Baseline and clinical characteristics of the study population according to treatment strategy are shown in Table 1. Overall, patients assigned to a rhythm-control strategy were younger and more likely to have fewer concomitant risk factors and diseases. The most common concomitant risk factors were hypertension, dyslipidaemia, smoking, abdominal obesity, family history of coronary heart disease, and diabetes. A statistically greater percentage of patients on rate control had hypertension and diabetes compared to patients under rhythm-control treatment.

The most common concomitant diseases were valvular heart disease, coronary heart disease, heart failure, myocardial infarction, stroke, transient ischaemic attack, and carotid stenosis. A statistically greater percentage of patients on rate control suffered from these diseases compared to patients under rhythm-control treatment.

The most common types of AF were permanent (45%), paroxysmal (35.7%), and persistent (10.7%), while first attack of AF (lone AF) was reported in only 8.6% of patients. The distribution of the rhythm-control treatment strategy was as follows: first episode (11.3%), paroxysmal (70.6%), persistent (15%), and permanent AF (3.2%). The distribution of the rate-control treatment strategy was as follows: first episode (5.3%), paroxysmal (5.9%), persistent (7.9%), and permanent AF (80.9%). In total, at baseline, a rhythm-control strategy was selected in 43% of patients and a rate-control strategy in 57% of patients.

Therapy

Drugs given for different types of AF at each visit

The distribution of the drugs that patients received at V0, V1, V2, and V3 per type of AF are shown in Figures 2-5. Treatment using various antiarrhythmic drug classes was similar between visits. B-blockers (excluding sotalol) were the most commonly used drugs, followed by Class III and Class Ic drugs and amiodarone for all types of AF.

Anticoagulation therapy

At baseline, 69.7% of patients received therapy with oral anticoagulants. In the rhythm-control treatment group 51.5% of patients received oral anticoagulants, while in the rate-control treatment group 83.6% of patients received oral anticoagulants, as shown in Table 2 (χ^2 test, $p<0.0001$).

At baseline, 92.8% of patients had a CHA_2DS_2-VASc score ≥2 and 7.2% of patients had CHA_2DS_2-VASc score<2.

At V3, 65.8% of patients received therapy with oral anticoagulants. In the rhythm-control treatment group 49.9% of patients received oral anticoagulants, while in the rate-control treatment group 76.9% of patients received oral anticoagulants, as shown in Table 3 (χ^2 test, $p <0.0001$).

The use of anticoagulation therapy and antiplatelet drugs in relation to CHA_2DS_2-VASc score at each visit is shown in Tables 4 and 5. Again the percentage of patients receiving oral anticoagulants decreased over the study period.

Table 1. Baseline and clinical characteristics of patients according to treatment strategy (n=1545)

Characteristics	Overall (N=1545)	Rhythm control Treatment (N=679)/ (43%)	Rate control Treatment (N=820)/ (57%)	p
Age mean (years)	68.8 ± 10.6	65.4 ± 11.4%	71.3 ± 9.0%	<0.001
Female sex (%)	634 (46.7%)	282 (48.1%)	352 (45.4%)	0.322
Height (cm)	168.1 ± 9.3	168.3 ± 9.6	168.0 ± 9.0	0.4550
Weight (kg) (SD)	80.9 ± 15.7	80.0 ± 14.2	81.4 ± 16.2	0.1854
Waist circumference (cm)	98.7 ± 15.2	98.4 ± 15.0	99.2 ± 15.3	0.2087
Blood pressure: Systolic (mmHg)	132.0 ± 16.7	132.0 ± 18.3	132.0 ± 15.2	0.8231
Blood pressure: Diastolic (mmHg)	80.4 ± 25.7	80.5 ± 26.1	79.4 ± 9.7	0.1956
Resting heart rate (bpm)	75.7 ± 20.8	73.4 ± 18.6	77.4 ± 22.4	<0.0001
Smoking status:				0.4335
Never	730 (53.4%)	306 (53.3%)	424 (55.7%)	
Active	191 (14.1%)	90 (15.7%)	101 (13.3%)	
No smoking Now- Previous	414 (30.3%)	178 (31.0%)	236 (31.0%)	
Hypertension	967 (67.7%)	399 (68.0%)	568 (73.4%)	0.03
Diabetes mellitus	239 (17.2%)	77 (13.1%)	162 (20.9%)	0.002
Dyslipidaemia	722 (52.1%)	317 (54.0%)	405 (52.3%)	0.539
Abdominal obesity	614 (45.0%)	265 (45.1%)	349 (45.1%)	0.9841
Family history of coronary heart disease	270 (19.6%)	123 (21.0%)	147 (19.0%)	0.3688
Coronary heart disease	267 (19.7%)	96 (16.4%)	171 (22.0%)	0.0089
Myocardial infarction	102 (7.4%)	31 (5.3%)	71 (9.2%)	0.0072
Stroke	96 (7.1%)	24 (4.1%)	72 (9.3%)	0.0002
Transient ischaemic attack	93 (6.5%)	35 (6.0%)	58 (7.5%)	0.2731
Peripheral artery disease	68 (4.7%)	23 (3.9%)	45 (5.8%)	0.1143
Carotid stenosis	103 (7.3%)	34 (5.8%)	69 (8.9%)	0.0320
Heart failure	321 (22.6%)	84 (14.3%)	237 (30.5%)	<0.0001
Valvular heart disease	553 (38.9%)	173 (29.5%)	380 (49%)	<0.0001
Peripheral embolic episodes	8 (0.8%)	2 (0.3%)	6 (0.8%)	0.3307
History of supraventricular or ventricular arrhythmia	73 (5.0%)	38 (6.5%)	35 (4.5%)	0.1122
History of cardiovascular interventions	246 (17.6%)	83 (14.1%)	163 (21.0%)	0.0011
Type of AF:				0.0001
First episode	104 (8.6%)	64 (11.3%)	40 (5.3%)	
Paroxysmal	445 (35.7%)	401 (70.6%)	44 (5.9%)	
Persistent	144 (10.7%)	85 (15.0%)	59 (7.9%)	
Permanent	625 (45.0%)	18 (3.2%)	607 (80.9%)	
ECG at visit:				
Atrial fibrillation	59.6%	144 (24.5%)	707 (91.2%)	<0.0001
Sinus rhythm	33.4%	404 (68.8%)	33 (4.3%)	<0.0001

Values are mean ± SD or n (%)

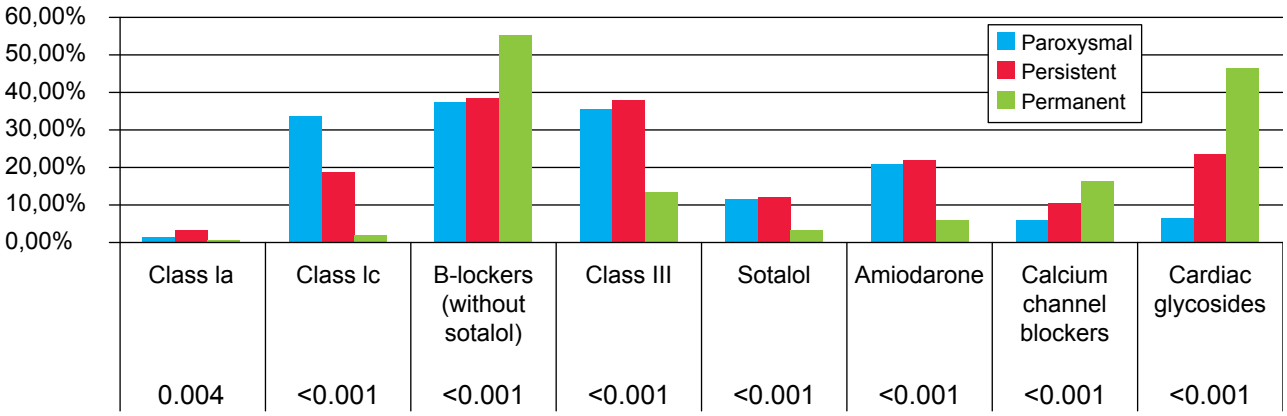

Figure 2. Drug regimen selected according to the type of atrial fibrillation at V0.

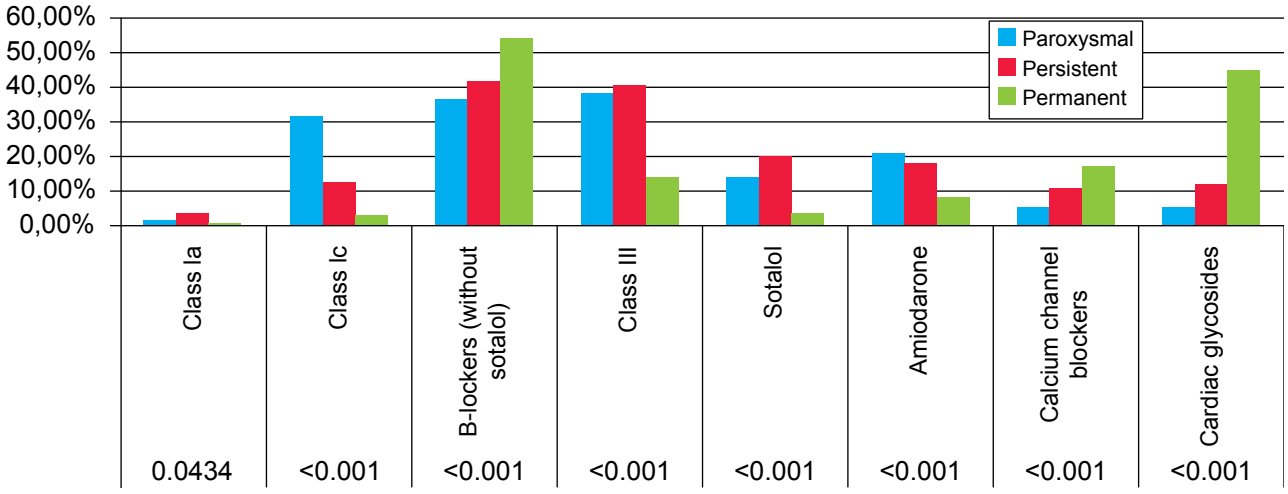

Figure 3. Drug regimen selected according to the type of atrial fibrillation at V1.

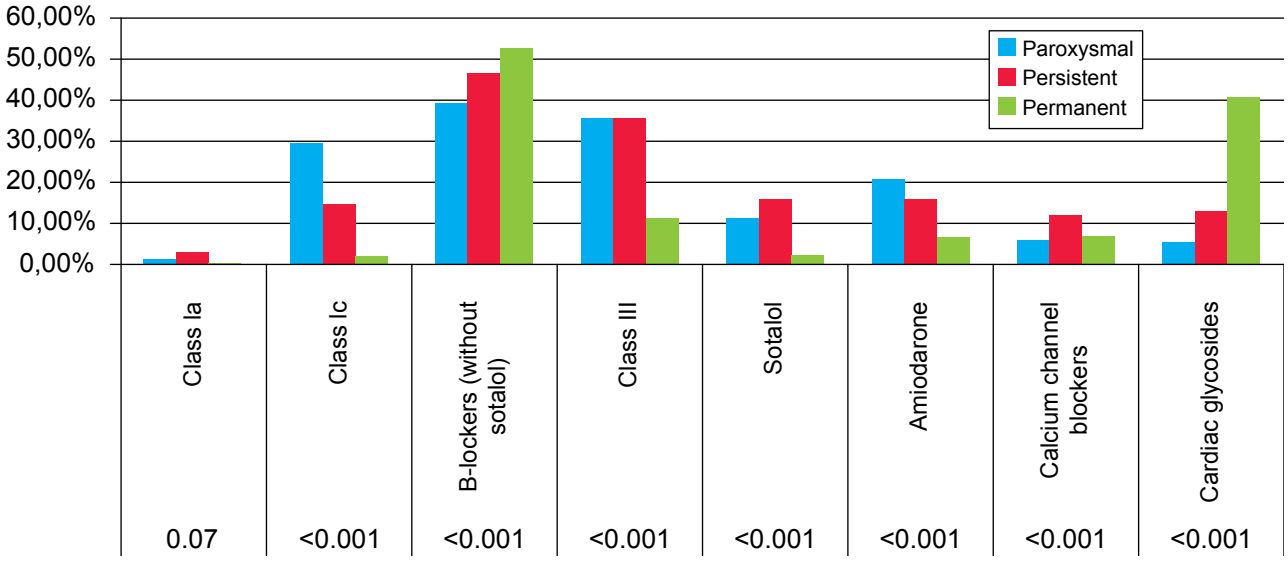

Figure 4. Drug regimen selected according to the type of atrial fibrillation at V2.

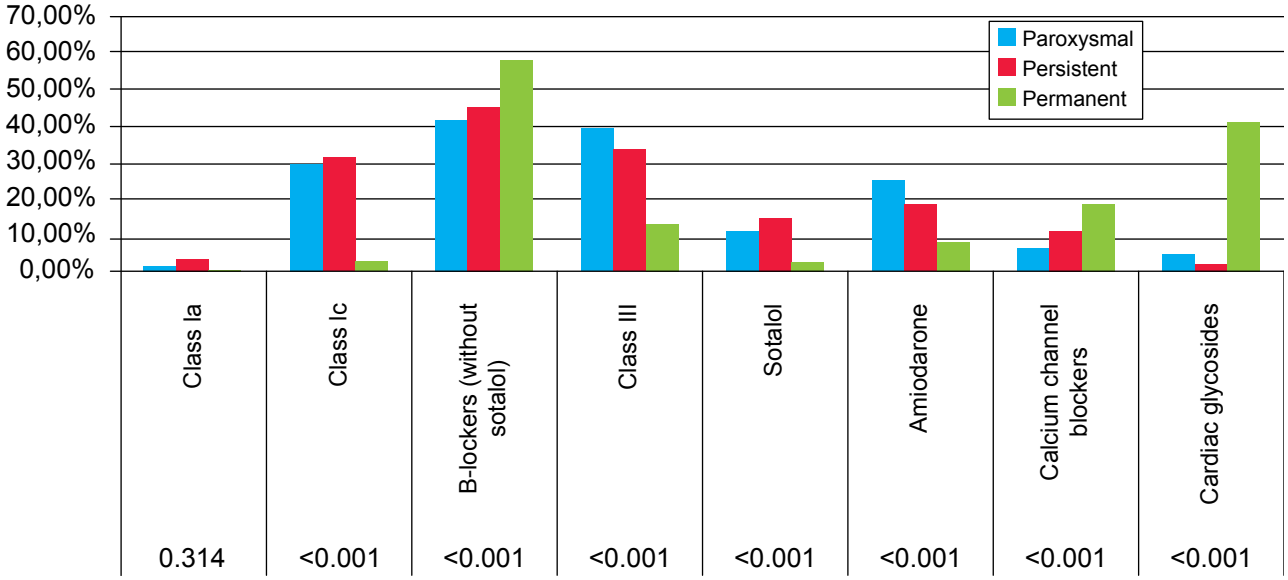

Figure 5. Drug regimen selected according to the type of atrial fibrillation at V3.

Table 2. Anticoagulation therapy at V0.

Receiving oral anticoagulant therapy (OACs)		Treatment		p
		Rhythm control	Rate control	
No	Frequency	285	127	<0.0001
	Col Pct	48.6%	16.4%	
Yes	Frequency	302	649	
	Col Pct	51.5%	83.6%	

Table 3. Anticoagulation therapy at V3.

Receiving oral anticoagulant therapy (OACs)		Treatment		p
		Rhythm control	Rate control	
No	Frequency	218	145	<0.001
	Col Pct	50.1%	23.1%	
Yes	Frequency	217	482	
	Col Pct	49.9%	76.9%	

Table 4. CHA_2DS_2-VASc Score and the use of Anticoagulation therapy.

Visit	CHA_2DS_2-VASc Score	anticoagulation therapy		p
		No	Yes	
V0	<2	60.9%	39.1%	<0.0001
	≥2	29.8%	70.2%	
V1	<2	43.1%	56.9%	0.1650
	≥2	36.4%	63.6%	
V2	<2	43.1%	56.9%	0.4307
	≥2	39.2%	60.8%	
V3	<2	41.9%	58.1%	0.3353
	≥2	36.9%	63.1%	

Table 5. CHA_2DS_2-VASc Score and the use of antiplatelet drugs.

Visit	CHA_2DS_2-VASc Score	anticoagulation therapy		p
		No	Yes	
V0	<2	64.6%	35.4%	0.5819
	≥2	67.1%	32.9%	
V1	<2	74.3%	25.7%	0.5322
	≥2	71.5%	28.5%	
V2	<2	76.5%	23.5%	0.5660
	≥2	73.9%	26.1%	
V3	<2	74.2%	25.8%	0.9313
	≥2	74.6%	25.4%	

Clinical outcomes

Clinical outcome events occurring per visit and therapy are presented in Tables 6, 7, and 8. More clinical events were observed in the rate-control treatment strategy group at all visits. Hospitalisations or prolongation of hospitalisation for CV reasons were the most common clinical events, similar for both strategies at all visits but with a declining rate from V1 to V3. The study showed no statistically significant relationship between stroke or transient ischaemic attack versus anticoagulation therapy for either therapeutic strategy (p=0.4118, p=0.9327).

Table 6. Clinical outcomes at V1.

Clinical events at V1	Rhythm control			Rate control			p
	n	N	%	n	N	%	
Any clinical event	60	649	9.4	121	789	15.3	0.005
Stroke	8	649	1.2	12	789	1.5	0.642
Transient ischaemic attack	4	649	0.6	13	789	1.7	0.071
Myocardial infarction							
Hospitalisation or prolongation of	1	649	0.2	1	789	0.1	--
hospitalisation for arrhythmia or proarrhythmia	50	649	7.7	19	789	2.4	<0.001
Hospitalisation or prolongation of hospitalisation	40	649	6.2	55	789	7	0.54
for other CV events or interventions							
Congestive heart failure	3	649	0.5	15	789	1.9	0.0146
Unstable angina	9	649	1.4	8	789	1.0	0.515
Other	24	649	3.7	33	789	4.2	0.640
Hospitalisation or prolongation of hospitalisation	0	649	0	3	789	0.4	---
for major complications of ablative procedure							

Table 7. Clinical outcomes at V2.

Clinical events at V2	Rhythm control			Rate control			p
	n	N	%	n	N	%	
Any clinical event	55	583	9.4	87	739	11.8	0.173
Stroke	7	583	1.2	7	739	1	0.655
Transient ischaemic attack	3	583	0.5	7	739	1	0.367
Myocardial infarction	0	583	0	1	739	0	-
Hospitalisation or prolongation of hospitalisation							
for arrhythmia or proarrhythmia	31	583	5.3	14	739	1.9	0.007
Hospitalisation or prolongation of hospitalisation for							
other CV events or interventions	22	583	3.8	36	739	4.9	0.333
Congestive heart failure	0	583	0	4	739	0.5	-
Unstable angina	2	583	0.3	5	739	0.7	0.407
Other	19	583	3.3	27	739	3.7	0.698
Hospitalisation or prolongation of hospitalisation for							
major complications of ablative procedure	0	583	0	2	739	0.3	-

Table 8. Clinical outcomes at V3.

Clinical events at V3	Rhythm control			Rate control			p
	n	N	%	n	N	%	
Any clinical event	39	521	7.5	9	697	13.1	0.0018
Stroke	1	521	0.2	22	697	3.2	-
Transient ischaemic attack	4	521	0.8	9	697	1.3	0.379
Myocardial Infarction	0	521	0	3	697	0.4	-
Hospitalisation or prolongation of hospitalisation							
for arrhythmia or proarrhythmia	27	521	5.2	15	697	2.2	0.004
Hospitalisation or prolongation of hospitalisation for							
other CV events or interventions	22	521	4.2	39	697	5.6	0.277
Congestive heart failure	6	521	1.2	10	697	1.4	0.668
Unstable angina	4	521	0.8	7	697	1	-
Other	8	521	0.5	24	697	3.4	0.039
Hospitalisation or prolongation of hospitalisation for							
major complications of ablative procedure	1	521	0.2	4	697	0.6	-

Table 9. Morbidity rates by treatment group (1st year).

End of 1st year		Treatment Group		p
		Rhythm control	Rate control	
No	Frequency	459	550	
	Col Pct	82.9%	81.1%	
Yes	Frequency	95	128	
	Col Pct	17.1%	18.9%	0.477

Primary endpoints

Annual CV morbidity and correlation with different treatment strategies

Non-adjusted ratio

The annual non-adjusted CV morbidity was 18.1% [95% CI 16.0–20.3%] and 17.2% [13.9–18.4%] in the first and second year. At the end of the first year, the non-adjusted CV morbidity was 17.1% [14.0–20.3%] for rhythm-control treatment and 18.9% [15.9–21.8%] for rate-control treatment (p=0.477) (Table 9). At the end of the second year, the non-adjusted CV morbidity was 14.9% [11.6–18.2%] for rhythm-control treatment and 17.2% [14.1–20.2%] for rate-control treatment (p=0.367) (Table 10).

After adjustment for potential confounders for morbidity (hypertension, diabetes, coronary heart disease, stroke, peripheral artery disease, carotid stenosis, heart failure, valvular heart disease, myocardial infarction), following a direct standardisation method, the confounder-adjusted morbidity rates were estimated for both AF treatment strategies. The 95% confidence interval (CI) was calculated and a Mandel–Haenszel χ^2 test was used to examine the hypothesis Ho: RR=1 vs. Ha: RR≠1 (or Ho: RRad=1 vs. Ha: RRad≠1).

Table 9A. Morbidity by therapy group and risk factor (1st year)

	Frequencies				Crude RR		Chi-Square test RR=1	Adjusted RR (Rrad)		Chi-Square test RRad=1
	Rhythm control		Rate control							
Morbidity:	No	Yes	No	Yes	95% CI of RR		p	95% CI of RR		p
Risk factor:	Blood pressure									
Yes	72	94	20	30	0.95		0.72	0.97		0.80
No	284	395	146	154	0.768592	1.167466		0.77244	1.16165	
Risk factor:	Diabetes mellitus									
Yes	20	31	72	93	0.95		0.72	0.98		0.89
No	52	104	378	445	0.768592	1.167466		0.772438	1.161654	
Risk factor:	Coronary heart disease									
Yes	31	41	60	85	0.92		0.59	0.99		0.93
No	53	113	377	436	0.748198	1.136405		0.754448	1.12699	
Risk factor:	Stroke									
Yes	1	16	90	110	0.92		0.59	0.94		0.63
No	16	52	414	497	0.748198	1.136405		0.747546	1.137396	
Risk factor:	Carotid stenosis									
Yes	8	17	83	109	0.92		0.59	0.95		0.68
No	24	43	406	506	0.748198	1.136405		0.751073	1.132054	
Risk factor:	Heart failure									
Yes	35	64	56	62	0.92		0.59	1.16		0.24
No	39	144	391	405	0.748198	1.136405		0.948332	1.407189	
Risk factor:	Valvular heart disease									
Yes	40	68	51	58	0.92		0.59	1.02		0.88
No	108	256	322	293	0.748198	1.136405		0.832048	1.248276	
Risk factor:	Myocardial infarction									
Yes	10	25	81	101	0.92		0.59	0.99		0.95
No	15	38	415	511	0.748198	1.136405		0.75169	1.131125	

Table 10. Morbidity rates by treatment group (second year).

End of 1st year		Treatment Group		p
		Rhythm control	Rate control	
No	Frequency	388	482	
	Col Pct	85.1%	82.8%	
Yes	Frequency	68	100	
	Col Pct	14.9%	17.2%	0.367

First year adjusted relative risk (RR)

Table 9A presents the results of the stratified analysis for the first year data. Frequencies, crude and adjusted RR, 95% CI and p-value from the Mandel–Haenszel χ^2 test are presented. There was no significant confounding for any confounder variables except heart failure. According to the Mandel–Haenszel χ^2 test, the hypothesis that relative risk is equal to 1 could not be rejected.

Second year adjusted RR

Table 10A presents the results of the stratified analysis for the second year data. Frequencies, crude and adjusted RR, 95% CI and p-value from the Mandel–Haenszel χ^2 test are presented. There was significant confounding for all confounder variables except blood pressure. According to the Mandel–Haenszel χ^2 test, the hypothesis that relative risk is equal to 1 could be rejected.

Table 10A. Morbidity by therapy group and risk factor (second year)

	Frequencies				Crude RR		Chi-Square test RR=1	Adjusted RR (Rrad)		Chi-Square test RRad=1
	Rhythm control		Rate control							
Morbidity:	No	Yes	No	Yes	95% CI of RR		p	95% CI of RR		p
Risk factor:	Blood pressure									
Yes	45	77	23	22	0.85		0.36	0.88		0.37
No	263	333	125	149	0.67033	1.08615		0.671992	1.083462	
Risk factor:	Diabetes mellitus									
Yes	9	23	59	76	0.85		0.36	0.88		0.40
No	50	93	338	389	0.67033	1.08615		0.671433	1.084365	
Risk factor:	Coronary heart disease									
Yes	21	31	46	69	0.83		0.29	0.89		0.43
No	47	81	341	401	0.653439	1.060169		0.658299	1.052343	
Risk factor:	Stroke									
Yes	3	17	64	83	0.83		0.29	0.89		0.44
No	14	44	374	438	0.653439	1.060169		0.652808	1.061194	
Risk factor:	Carotid stenosis									
Yes	9	17	58	83	0.83		0.29	0.87		0.33
No	23	32	365	450	0.653439	1.060169		0.656695	1.054912	
Risk factor:	Heart failure									
Yes	25	45	42	55	0.83		0.29	1.03		0.84
No	36	126	352	356	0.653439	1.060169		0.81786	1.294341	
Risk factor:	Valvular heart disease									
Yes	26	55	41	45	0.83		0.29	0.91		0.53
No	110	220	278	262	0.653439	1.060169		0.654346	1.058699	
Risk factor:	Myocardial infarction									
No	10	16	50	84	0.75		0.10	0.80		0.14
Yes	18	35	370	447	0.57977	0.958247		0.58354	0.952056	

Table 11. Mortality by Treatment Group (1st year).

End of 1st year		Treatment Group		p
		Rhythm control	Rate control	
Alive	Frequency	537	677	
	Col Pct	99.3%	97.7%	
Deaths	Frequency	4	16	
	Col Pct	0.7%	2.3%	0.030

Total mortality and correlation with different treatment strategies

Non-adjusted incidence ratio

Overall non-adjusted mortality was 1.6% [0.9–2.3%] and 1.9% [1.1–2.7%] in the first and second year. At the end of the first year, the non-adjusted mortality was 0.7% [0.02–1.5%] for rhythm-control treatment and 2.3% [1.9–3.4%] for rate-control treatment (p=0.030) (Table 11). At the end of the second year, the non-adjusted mortality ratio was 0.6% [0–1.4%] for rhythm-control treatment and 2.8% [1.5–4.1%] for rate-control treatment (p=0.009) (Table 12).

For total mortality, rhythm vs. rate control showed a lower incidence in both the first and second year. However, we have to underline the significant differences in patients' characteristics between the two different strategies, as mentioned before in baseline characteristics.

After adjustment for potential confounders for mortality (hypertension, diabetes, coronary heart disease, stroke, peripheral artery disease, carotid stenosis, heart failure, valvular heart disease, myocardial infarction), following a direct standardisation method, the confounder-adjusted mortality rates were estimated for both AF treatment strategies.

Table 11A. Mortality by therapy group and risk factor (1st year)

	Frequencies				Crude RR		Chi-Square test RR=1	Adjusted RR (Rrad)		Chi-Square test RRad=1
	Rhythm control		Rate control							
Death	No	Yes	No	Yes	95% CI of RR		p	95% CI of RR		p
Risk factor:	Blood pressure									
Yes	3	14	1	2	0.31		0.03	0.32		0.03
No	364	467	171	199	0.12	0.78		0.12	0.78	
Risk factor:	Diabetes mellitus									
Yes	3	4	1	12	0.31		0.03	0.37		0.05
No	70	141	467	534	0.13	0.78		0.16	0.87	
Risk factor:	Coronary heart disease									
Yes	1	3	3	13	0.32		0.03	0.32		0.03
No	88	138	448	539	0.13	0.79		0.13	0.78	
Risk factor:	Stroke									
Yes	1	0	3	16	0.32		0.03	0.33		0.03
No	18	68	518	611	0.13	0.79		0.13	0.75	
Risk factor:	Carotid stenosis									
Yes	1	0	3	16	0.32		0.03	0.32		0.03
No	31	50	505	627	0.13	0.79		0.13	0.78	
Risk factor:	Heart failure									
Yes	1	3	3	13	0.32		0.03	0.32		0.03
No	73	193	463	484	0.13	0.79		0.13	0.77	
Risk factor:	Valvular heart disease									
Yes	2	9	2	7	0.32		0.03	0.36		0.05
No	154	318	382	359	0.13	0.79		0.14	0.89	
Risk factor:	Myocardial infarction									
Yes	0	4	4	12	0.32		0.03	0.33		0.04
No	31	59	505	619	0.13	0.79		0.12	0.81	

Table 12. Mortality by treatment group (second year).

End of 1st year		Treatment Group		p
		Rhythm control	Rate control	
Alive	Frequency	465	618	
	Col Pct	99.4%	97.2%	
Deaths	Frequency	3	18	
	Col Pct	0.6%	2.8%	0.009

First year adjusted RR

Table 11A presents the results of the stratified analysis for the first year data. Frequencies, crude and adjusted RR, 95% CI and p-value from the Mandel–Haenszel χ^2 test are presented. There was no significant confounding for any confounder variables except diabetes mellitus and valvular heart disease. According to the Mandel–Haenszel χ^2 test, the hypothesis that relative risk is equal to 1 could be rejected for all the risk factors; the p-value for valvular heart disease was very close to the cut-off point of 0.05.

Second year adjusted RR

Table 12A presents the results of the stratified analysis for the first year data. Frequencies, crude and adjusted RR, 95% CI and p-value from the Mandel–Haenszel χ^2 test are presented. There was no significant confounding for any confounder variables except heart failure. According to the Mandel–Haenszel χ^2 test, the hypothesis that relative risk is equal to 1 could be rejected for all the risk factors.

Secondary outcomes

Estimation of CV mortality for different treatment strategies (rate or rhythm control)

Rhythm control vs. rate control showed a lower in-

Table 12A. Mortality by therapy group and risk factor (second year)

	Frequencies				Crude RR		Chi-Square test RR=1	Adjusted RR (Rrad)		Chi-Square test RRad=1
	Rhythm control		Rate control							
Death	No	Yes	No	Yes	95% CI of RR		p	95% CI of RR		p
Risk factor:	Blood pressure									
Yes	1	13	2	5	0.22		0.01	0.22		0.01
No	310	434	155	183	0.07967	0.613856		0.078421	0.623633	
Risk factor:	Diabetes mellitus									
Yes	0	8	3	10	0.22		0.01	0.24		0.02
No	57	120	408	497	0.07967	0.613856		0.075689	0.646141	
Risk factor:	Coronary heart disease									
Yes	1	7	2	11	0.22		0.01	0.24		0.01
No	72	120	392	498	0.079971	0.616175		0.079981	0.616101	
Risk factor:	Stroke									
Yes	0	1	3	17	0.22		0.01	0.22		0.01
No	16	61	448	557	0.079971	0.616175		0.079422	0.620436	
Risk factor:	Carotid stenosis									
Yes	0	1	3	17	0.22		0.01	0.23		0.01
No	31	50	433	568	0.079971	0.616175		0.079802	0.617485	
Risk factor:	Heart failure									
Yes	1	6	2	12	0.22		0.01	0.25		0.01
No	68	169	396	449	0.079971	0.616175		0.090342	0.673926	
Risk factor:	Valvular heart disease									
Yes	1	9	2	9	0.22		0.01	0.23		0.01
No	137	280	327	338	0.079971	0.616175		0.07909	0.623044	
Risk factor:	Myocardial infarction									
Yes	0	3	3	15	0.22		0.01	0.23		0.01
No	30	51	434	567	0.079971	0.616175		0.079156	0.622525	

Table 13. Cardiovascular mortality by treatment group (1st year).

End of 1st year		Treatment Group		p
		Rhythm control	Rate control	
Alive or death from other reason	Frequency	492	633	
	Col Pct	99.6%	99.0%	
Deaths	Frequency	2	7	
	Col Pct	0.4%	1.0%	0.038

Table 14. Cardiovascular mortality by treatment group (second year).

End of 1st year		Treatment Group		p
		Rhythm control	Rate control	
Alive or death from other reason	Frequency	470	632	
	Col Pct	100%	98.9%	
Deaths	Frequency	0	7	
	Col Pct	0%	1.1%	0.05

cidence of CV mortality in both the first (0.4% vs. 1.0% p<0.0038) and the second year (0% vs. 1.1%, p=0.05), as shown in Tables 13 and 14.

Percentage of patients with new-onset heart failure for different treatment strategies (rate or rhythm control)

Patients under rhythm control vs. rate control presented a lower incidence of new-onset heart failure (7.1% vs. 12.9%, p=0.0005), as shown in Table 15.

Percentage of patients with changes in NYHA functional class of heart failure during follow up by treatment strategy (rate or rhythm control)

Patients under rhythm control vs. rate control presented less change in NYHA class (8.9% vs. 15.4%, p=0.0005) in the overall period, as shown in Table 16. More specifically, patients under rhythm control vs. rate control, presented a lower incidence of worsening NYHA class (4.0% vs. 7.1%, p<0.0001) in the overall period, as shown in Table 17.

Hospitalisation rate due to recurrence of AF by therapeutic strategy

Patients under rhythm control vs. rate control showed a higher incidence of hospitalisations (8.6% vs. 4.2%, p=0.006, 95%CI: 5.4–11.8%) due to relapse of AF and subsequent need of rhythm restoration, as shown in Table 18. Overall, 13.7% of patients needed hospital admission during the 2-year interval. The mean number of admissions was 5.1 and the mean duration of hospital stay was 22.9 days, while 3% of the patients needed surgery. For the patients who needed surgery the mean number of operations was 1.2.

Proportion of patients who changed therapeutic strategy (rate or rhythm control) during follow up

Management of AF was considered a therapeutic success if the following conditions were met: [17]

- for the rhythm-control strategy, if the patient was in sinus rhythm on the ECG at the 12-month visit;

Table 15. Percentage of patients with new onset heart failure per treatment.

	Rhythm control				Rate control				
New	Percent	Std Err of Percent	95% Confidence interval for Percent		Percent	Std Err of Percent	95% Confidence interval for Percent		p
No	92.9%	1.4699	90.0%	95.7%	87.1%	1.6145	83.9%	90.2%	0.0005
Yes	7.1%	1.4699	4.3%	10.0%	12.9%	1.6145	9.8%	16.1%	

Table 16. NYHA change per treatment

	Rhythm control				Rate control				
NYHA Change	Percent	Std Err of Percent	95% Confidence interval for Percent		Percent	Std Err of Percent	95% Confidence interval for Percent		p
No	91.1%	1.6394	87.9%	94.30%	84.6%	1.7477	81.1%	88.0%	0.0005
Yes	8.9%	1.6394	5.7%	12.10%	15.4%	1.7477	12.0%	18.9%	

Table 17. NYHA change per treatment.

Overall period	Worsening	Stable	Improvement	p
Rhythm control	4.0%	88.8%	7.2%	
Rate control	7.1%	71.5%	21.5%	<0.0001

Table 18. Hospitalisation rate due to recurrence of AF by treatment strategy.

	Rhythm control				Rate Control				
Hospitalisation	Percent	Std Err of Percent	95% Confidence interval for Percent		Percent	Std Err of Percent	95% Confidence interval for Percent		p
No	91.4%	1.6117	88.2%	94.6%	95.8%	0.9713	93.9%	97.7%	0.006
Yes	8.6%	1.6117	5.4%	11.8%	4.2%	0.9713	2.3%	6.1%	

Table 19. Therapeutic success and change in treatment strategy per visit.

Visit	Therapeutic success	Rhythm control			Rate control			p
		n	N	%	n	N	%	
V1	Therapeutic success	558	637	90.3	617	789	78.2	
	Change in strategy between baseline and V1	54	679	8.0	37	820	4.5	0.004
V2	Therapeutic success	575	618	93.0	588	739	79.6	
	Change in strategy between V1 and V2	49	610	8.0	24	787	3.1	<0.001
V3	Therapeutic success	446	497	89.7	596	697	85.5	
	Change in strategy between V2 and V3	36	536	6.7	19	735	2.6	<0.001

Table 20. Changes of AF management strategy after each visit in different types of AF.

V1	Paroxysmal	Persistent	Permanent	p
Before the visit:				
Rhythm control	90.9%	74.2%	6.7%	
Rate control	9.1%	25.8%	93.3%	<0.001
After the visit:				
Rhythm control	92.5%	70.1%	2.9%	
Rate control	7.5%	29.9%	97.1%	<0.001
Change				
Yes	5.4%	10.3%	6.2%	0.181
V2	**Paroxysmal**	**Persistent**	**Permanent**	**p**
Before the visit				
Rhythm control	92.5%	70.1%	2.9%	
Rate control	7.5%	29.9%	97.1%	<0.0001
After the visit				
Rhythm control	88.4%	70.7%	2.5%	
Rate control	11.6%	29.3%	97.5%	<0.0001
Change				
Yes	11.0%	14.4%	5.2%	<0.0001
V3	**Paroxysmal**	**Persistent**	**Permanent**	**p**
Before the visit				
Rhythm control	91.9%	84.2%	4.2%	
Rate control	8.1%	15.8%	95.8%	<0.0001
After the visit				
Rhythm control	92.4%	71.8%	1.9%	
Rate control	7.6%	28.2%	98.1%	<0.0001
Change				
Yes	10.0%	21.5%	8.2%	0.0009

- for the rate-control strategy, if the patient had a resting heart rate of ≤80 beats/min on the ECG at the 12-month visit.

Table 19 presents the rates of therapeutic success and changes in strategy per visit.

The distribution of the therapeutic strategies per visit and AF type is given in Table 20. Rhythm control was the most used therapeutic strategy for the paroxysmal and persistent type, while rate control was chosen for the permanent type of AF. There were more switches in the therapeutic strategy of patients with paroxysmal and persistent type of AF than in the permanent type.

Assessment of the impact of CV risk factors on CV morbidity and total mortality on an annual basis

Logistic regression models showed that CV morbidity was affected mainly by dyslipidaemia and diabetes mellitus ($p<0.05$, odds ratio: 1.45 with 95%CI: 1.09–1.92, and odds ratio: 1.5 with 95%CI: 1.05–2.13, respectively), while total mortality was affected mainly by diabetes mellitus ($p<0.05$, odds ratio: 2.8 with 95%CI: 1.019–7.66).

Table 21. Adverse events at each visit related to medications for AF

Adverse Events		Visit V1			Visit V2			Visit V3			All Visits		
		Rhythm control	Rate control	p	Rhythm control	Rate control	p	Rhythm control	Rate control	p	% Frequency		
Cardiac AE s		4.8%	3.4%	0.291	4.0%	3.4%	0.760	3.3%	3.1%	0.941	21.2%		
	Palpitations	4.6%	3.7%	0.533	4.0%	2.8%	0.361	3.8%	3.8%	0.907		14.5%	
	Heart failure	1.2%	0.4%	0.289	0.2%	1.3%	0.115	1.0%	0.9%	0.899		3.7%	
	New onset	0.2%	0.3%	0.824	0.0%	0.3%	0.616	0.3%	0.9%	0.425			31.6%
	Worsening	1.0%	0.3%	0.269	0.2%	1.1%	0.173	0.0%	0.7%	0.246			68.4%
	Proarrhythmia	0.4%	0.1%	0.824	0.4%	0.5%	0.734	0.5%	0.2%	0.750		1.6%	
	Other	0.0%	0.7%	0.129	0.4%	0.3%	0.840	0.8%	0.2%	0.380		1.4%	
ECG		7.9%	2.7%	0.000	4.6%	2.1%	0.033	3.8%	3.1%	0.724	20.6%		
	QRS	0.8%	0.6%	0.995	0.4%	0.0%	0.352	0.8%	0.7%	0.777		2.6%	
	QT	1.0%	0.3%	0.269	1.1%	0.5%	0.430	1.0%	0.5%	0.626		2.5%	
	PR	0.6%	0.1%	0.446	0.7%	0.0%	0.152	0.8%	0.2%	0.380		1.2%	
	Sinoatrial bradycardia	4.6%	0.9%	0.000	3.8%	0.7%	0.001	2.5%	0.7%	0.039		7.4%	
	Sinoatrial tachycardia	0.6%	0.7%	0.995	0.0%	0.3%	0.616	0.0%	0.7%	0.246		1.7%	
	1st degree AV block	1.7%	0.1%	0.008	0.7%	0.2%	0.417	0.3%	0.2%	0.646		1.7%	
	2nd degree AV block	0.0%	0.0%		0.0%	0.0%		0.3%	0.0%	0.854		0.1%	
	3rd degree AV block	0.0%	0.1%	0.898	0.0%	0.2%	0.879	0.3%	0.2%	0.646		0.5%	
	Other	0.6%	1.9%	0.077	0.2%	0.8%	0.385	0.0%	1.0%	0.103		2.8%	
GI Disorders		3.1%	1.6%	0.145	2.4%	1.8%	0.616	1.0%	1.7%	0.499	15.8%		
	Nausea	1.9%	1.5%	0.726	1.5%	1.0%	0.582	1.0%	1.7%	0.499		5.5%	
	Vomit	0.2%	1.2%	0.101	0.4%	0.2%	0.792	0.3%	0.2%	0.646		1.9%	
	Dysgeusia	0.6%	0.4%	0.922	0.9%	0.3%	0.431	0.5%	0.5%	0.680		2.3%	
	Diarrhoea	0.0%	0.3%	0.595	0.2%	0.0%	0.879	0.3%	0.0%	0.854		0.7%	
	Constipation	1.7%	0.9%	0.306	0.7%	1.0%	0.826	1.5%	0.9%	0.540		4.4%	
	Other	0.0%	0.6%	0.208	0.0%	0.3%	0.616	0.0%	0.2%	0.854		1.0%	
Organ Toxicity		1.4%	1.3%	0.807	2.0%	0.8%	0.165	2.5%	1.2%	0.207	9.7%		
	Visual impairment	0.8%	0.3%	0.467	1.1%	0.5%	0.430	1.5%	0.2%	0.042		2.7%	
	Photosensitivity	0.6%	0.9%	0.773	0.2%	0.2%	0.616	1.0%	0.7%	0.872		3.2%	
	Neurological injuries	0.0%	0.0%		0.0%	0.2%	0.879	0.0%	0.0%			0.1%	
	Hyperthyroidism	0.0%	0.0%		0.0%	0.0%		0.8%	0.2%	0.380		0.4%	

	Hypothyroidism	0.8%	0.0%	0.076	1.8%	0.2%	0.013	1.5%	0.2%	0.042			2.1%	
	Lung disease	0.2%	0.3%	0.824	0.2%	0.0%	0.879	0.0%	0.0%				0.4%	
	Increase in liver enzymes	0.0%	0.1%	0.898	0.0%	0.0%		0.3%	0.2%	0.646			0.6%	
	Other	0.0%	0.0%		0.0%	0.2%	0.879	0.3%	0.2%	0.646			0.3%	
General AEs		5.4%	5.7%	0.939	3.5%	3.6%	0.906	3.5%	4.3%	0.624	27.3%			
	Dizziness	1.7%	2.8%	0.294	2.0%	2.3%	0.907	1.3%	2.3%	0.365			8.2%	
	Fatigue	5.4%	4.6%	0.637	2.9%	3.4%	0.738	3.3%	4.5%	0.411			15.3%	
	Erectile dysfunction	0.4%	1.0%	0.335	0.7%	0.7%	0.716	0.5%	0.7%	0.972			2.9%	
	Other	0.6%	0.1%	0.446	0.2%	0.0%	0.879	0.3%	0.0%	0.854			0.9%	
Bleeding due to anticoagulant treatment		0.2%	0.9%	0.235	0.0%	0.5%	0.365	0.8%	0.3%	0.680	5.3%			
	Bleeding leading to hospitalisation	0.2%	0.4%	0.804	0.0%	0.3%	0.616	0.5%	0.5%	0.680			1.3%	
	Transfusion	0.0%	0.1%	0.898	0.0%	0.0%		0.0%	0.0%				0.2%	
	Intracranial haemorrhage	0.0%	0.1%	0.898	0.2%	0.0%	0.879	0.3%	0.0%	0.854			0.4%	
	Other	0.8%	1.8%	0.208	0.7%	0.8%	0.943	0.8%	0.7%	0.777			3.5%	
Total											100.0%	100.0%	100.0%	

Adverse events related to medications for AF

Adverse events related to medications for AF are shown in Table 21. The safety profile was as expected.

Discussion

Accumulated trial data have shown that there are no remarkable differences with regard to various major CV endpoints between a rhythm-control and a rate-control treatment strategy.[22-24]

In the present study, there were no statistically significant differences in CV morbidity between the rhythm- and rate-control strategies in the first or second year. The annual non-adjusted CV morbidity was 18.1% and 17.2% in the first and second years, respectively.

However during the same period, patients under rhythm control versus rate control presented a statistically significantly lower total mortality in the first and second years. The annual non-adjusted mortality was 1.6% and 1.9% in the first and second years. Patients under rhythm control also presented a lower incidence of CV mortality and new-onset heart failure, a smaller percentage worsening in NYHA functional class, but a greater hospitalisation rate due to relapse of AF with subsequent need for rhythm restoration.

However, we have to underline that patients assigned to the rate-control treatment strategy were older and were more likely to have more risk factors and concomitant diseases, such as hypertension, diabetes, coronary heart disease, heart failure, myocardial infarction, valvular heart disease, stroke and carotid stenosis. The multivariate analysis demonstrated that CV morbidity was affected mainly by dyslipidaemia and diabetes mellitus. For dyslipidaemia, the odds ratio was 1.45 (95% CI 1.09–1.92) and for diabetes mellitus the odds ratio was 1.5 (95% CI 1.05–2.13). The multivariate analysis demonstrated that total mortality was affected mainly by diabetes mellitus, with an odds ratio of 2.8 (95% CI 1.019–7.66). This is in accordance with RECORD AF,[25] where patients under rate control were older and had more comorbidities, especially heart failure and valvular heart disease, while rhythm control was the main therapeutic strategy for patients with paroxysmal AF.

AF is independently associated with increased morbidity and mortality, mainly due to an increased incidence of thromboembolic events. Despite the

existence of various anticoagulation drugs and the knowledge of the beneficial effects of anticoagulation in preventing stroke, anticoagulation prophylaxis in patients with AF is underused.[16] Many patients with AF do not receive anticoagulation therapy or discontinue therapy within 1 year.[26] Indeed, in the present study, 70% of the patients used oral anticoagulant therapy, while the percentage continuing to take oral anticoagulants after 2 years of follow up was 65.8%. This is in accordance with other registries. In the Euro Heart Survey, 67% of eligible patients were on anticoagulation therapy.[13] In the RECORD AF study,[26] 61% were receiving oral anticoagulation, while in the AFFECTS study the proportion was 69%.[27] However, in the most recent European registries, such as the EURObservational Research Programme AF Registry and the PREFER Registry, oral anticoagulant use has increased to over of 80% of eligible patients, reflecting a rapid implementation of 2010 ESC guidelines.[15,16]

Underutilisation of anticoagulants at 40.6% of the eligible population was also found by a Greek prospective population-based study investigating the prevalence of permanent AF, its associated clinical conditions, and treatment status in the elderly population in rural Greece.[5] Moreover, a recent review from the Hellenic Cardiovascular Research Society highlighted the current significant real-world underuse of anticoagulation therapy.[28] However, in the RAFTING registry, the most recent countrywide observational study, 74.8% of all patients received antithrombotic therapy.[18]

In addition, several risk factors, such as diabetes mellitus, arterial hypertension and dyslipidaemia, seem to affect CV morbidity and mortality in these patients. Overall, the prevalence of risk factors in the present study was in accordance with recent international registries (Euroheart, RECORD AF, Realise AF, EORP-AF, PREFER) and local registries/reviews for AF. For example, the incidence of arterial hypertension was 70%, within the range of 50–90% reported in recent studies.[5,13,15,16,18,25,29,30]

Study limitations

Although data were collected from a broad geographical sample of cardiologists around Greece to present an overview of daily practice, several limitations of the study need to be mentioned. Of the patients included in V0, 27% were lost to follow up, more than the initially estimated 10%, which resulted in a smaller final number of patients for analysis. The non-randomised design can be considered a limiting factor because of selection bias and the lack of a control group. Participation in the study was voluntary. Thus, patients and practices enrolled may not have been entirely representative. In addition, participating in a study, particularly as part of a quality improvement effort, may alter practice patterns at a study site.[31]

The limitations of the study also include the risk of misclassification of the type or severity of AF. However, according to several prior studies, our current observations are comparable with those for general clinical practice.[32-34]

Generalisability

This observational study aimed to extend our understanding of the management of AF and incidence of CV morbidity and total mortality during a 2-year follow up of patients with AF among the private sector in Greece. As an observational study, it has its clear intrinsic limitations, but its results are reasonably representative of the available management of AF.

Conclusions

The ODYSSEY study demonstrated that rhythm control seems to be the preferred treatment strategy in younger AF patients with fewer comorbidities and risk factors such as hypertension, diabetes, coronary heart disease, heart failure, myocardial infarction, valvular heart disease, stroke, and carotid stenosis, as well as in patients with paroxysmal and persistent AF. There were no statistically significant differences in CV morbidity between the rhythm- and the rate-control treatment strategies. However, patients under rhythm control presented a lower incidence of the primary outcome of total mortality, which was statistically significant in both the first and second years but did not differ from the first to the second year, as well as a lower incidence of secondary outcomes, such as CV mortality and new-onset heart failure, and a smaller change in NYHA class, but presented more hospitalisations due to the relapse of AF. The multivariate analysis demonstrated that CV morbidity was affected mainly by dyslipidaemia and diabetes mellitus, while total mortality was affected mainly by diabetes mellitus.

Despite the fact that several studies with anticoagulants have shown promising results with improved

outcomes, the ODYSSEY study confirmed that oral anticoagulant therapy remains suboptimal in patients with AF.

These data confirm and complement results reported in previous trials and support the need for additional future research to estimate the current cost of AF,[35] to optimise AF treatment,[36] and to improve the quality of life and outcomes in patients with AF.

Acknowledgments

The study and the editorial support were funded by Sanofi, Greece.

Sincere thanks and appreciation for the valuable contribution of Kostas Milios and Emily Vassiliadis, who are employees of Sanofi, working as Medical Science Liaison and Clinical Project Manager, respectively, in Greece for the study conduct, data management and study report.

References

1. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997; 96: 2455-2461.
2. 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.
3. Goudevenos JA, Vakalis JN, Giogiakas V, et al. An epidemiological study of symptomatic paroxysmal atrial fibrillation in northwest Greece. Europace. 1999; 1: 226-233.
4. 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.
5. Ninios I, Bogossian H, Zarse M, et al. Prevalence, clinical correlates and treatment of permanent atrial fibrillation among the elderly: insights from the first prospective population-based study in rural Greece. J Thromb Thrombolysis. 2010; 30: 90-96.
6. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol. 2013; 167: 1807-1824.
7. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology. 2003; 22: 118-123.
8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22: 983-988.
9. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003; 107: 2920-2925.
10. Efremidis M, Pappas L, Sideris A, Filippatos G. Management of atrial fibrillation in patients with heart failure. J Card Fail. 2008; 14: 232-237.
11. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98: 946-952.
12. Vidaillet H, Granada JF, Chyou P, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med. 2002; 113: 365-370.
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. Ringborg A, Nieuwlaat R, Lindgren P, et al. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Europace. 2008; 10: 403-411.
15. Lip GY, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Europace. 2014; 16: 308-319.
16. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events—European Registry in Atrial Fibrillation (PREFER in AF). Europace. 2014; 16: 6-14.
17. Camm AJ, Breithardt G, Crijns H, et al. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). J Am Coll Cardiol. 2011; 58: 493-501.
18. 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.
19. Roy D, Talajic M, Nattel S, et al. Rhythm versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008; 358: 2667-2677.
20. Wyse DG, Waldo AL, DiMarco JP, et al; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002; 347: 1825-1833.
21. 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.
22. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002; 347: 1825-1833.
23. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA.

Rate vs. rhythm control in patients with atrial fibrillation: a meta-analysis. Arch Intern Med. 2005; 165: 258-262.
24. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008; 358: 2667-2677.
25. 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.
26. Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2010; 3: 624-631.
27. Kowey PR, Reiffel JA, Myerburg R, et al. Warfarin and aspirin use in atrial fibrillation among practicing cardiologist (from the AFFECTS Registry). Am J Cardiol. 2010; 105: 1130-1134.
28. Korantzopoulos P, Andrikopoulos G, Vemmos K, Goudevenos JA, Vardas PE. Atrial fibrillation and thromboembolic risk in Greece. Hellenic J Cardiol. 2012; 53: 48-54.
29. Chiang CE, Naditch-Brûlé L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. Circ Arrhythm Electrophysiol. 2012; 5: 632-639.
30. Manolis AJ, Kallistratos MS, Poulimenos LE. Recent clinical trials in atrial fibrillation in hypertensive patients. Curr Hypertens Rep. 2012; 14: 350-359.
31. Muller MP, Detsky AS. Public reporting of hospital hand hygiene compliance—helpful or harmful? JAMA. 2010; 304: 1116-1117.
32. Curtis LH, Greiner MA, Hammill BG, et al. Representativeness of a national heart failure quality-of-care registry: comparison of OPTIMIZE-HF and non-OPTIMIZE-HF Medicare patients. Circ Cardiovasc QualOutcomes. 2009; 2: 377-384.
33. Heidenreich PA, Fonarow GC. Are registry hospitals different? A comparison of patients admitted to hospitals of a commercial heart failure registry with those from national and community cohorts. Am Heart J. 2006; 152: 935-939.
34. Granger CB, Gersh BJ. Clinical trials and registries in cardiovascular disease: competitive or complementary? Eur Heart J. 2010; 31: 520-521.
35. Athanasakis K, Karampli E, Ollandezos M, et al. Estimating the cost of atrial fibrillation in Greece. Value in Health 2010 13: 7 (A350).
36. Andrikopoulos G, Pastromas S, Mantas I, et al. Management of atrial fibrillation in Greece: the MANAGE-AF study. Hellenic J Cardiol. 2014; 55: 281-287.

Appendix 1

National Study Coordinator and Principal Investigator

Prof. Panos Vardas, Cardiology Department, Heraklion University Hospital, Heraklion, Greece

Study Investigators

Dr. Georgios Afaras, Athens; Dr. Georgios Aggelopoulos, Aigio; Dr. Ilias Agrafiotis, Arta; Dr. Barbara Anastasaki, Athens; Dr. Fillipos Anastasiadis, Athens; Dr. Ilias Andreanidis, Larissa; Dr. Maria Apostolidou, Athens; Dr. Georgios Arvanitakis, Athens; Dr. Christos Athanasiou, Larissa; Dr Christos Avgerinos, Thessaloniki; Dr. Socrates Avlonitis, Kavala; Dr. Georgios Avrabos, Athens; Dr. Ilias Bofilis, Athens; Dr. Emmanouil Bountioukos, Kozani; Dr. Emmanouil Chalkiadakis, Crete; Dr. Georgios Chatzioakim, Athens; Dr. Ioannis Choursalas, Korinthos; Dr. Zaharias Christogiannis, Ioannina; Dr. Panagiotis Dalabiras, Larissa; Dr. Konstantinos Dimas, Athens; Dr. Vasilios Dimitriadis, Serres; Dr. Spiridon Dimitriou, Chalkida; Dr. Dimitrios Evaggelou, Larissa; Dr. Dimitrios Fanourakis, Crete; Dr. Symeon Gavrilidis, Giannitsa; Dr. Andreas Georgakis, Athens; Dr. Dimosthenis Georgariou, Athens; Dr. Anastasios Geramoutsos, Athens; Dr. Dimitrios Gikas, Athens; Dr. Dimitrios Ginopoulos, Thessaloniki; Dr. Athanassios Grekos, Athens; Dr. Eleni Hatzinikolaou, Thessaloniki; Dr. Petros Kalogeropoulos, Athens; Dr. Christos Kanatselos, Athens; Dr. Konstantinos Kanelopoulos, Patra; Dr. Ioannis Kantiloros, Athens; Dr. Alexandra Karasavidou, Thessaloniki; Dr. Emmanouil Kasotakis, Livadia; Dr. Georgios Kazianis, Athens; Dr. Agelos Kekes, Alexandroupolis; Dr. Konstantinos Klebetsanis, Thessaloniki; Dr. Dimitrios Kolonas, Trikala; Dr. Ilias Konstantinidis, Kozani; Dr. Georgios Korlos, Athens; Dr. Dimitrios Kostakis, Volos; Dr. Andreas Kotsalos, Patra; Dr. Avraam Kotsaridis, Katerini; Dr. Nikolaos Kounis, Patra; Dr. Georgios Koutsibanis, Alexandroupolis; Dr. Kyriakos Kyriakoulis, Athens; Dr. Dimitrios Lagatouras, Athens; Dr. Elpida Lazaridou, Kilkis; Dr. Ioannis Leontaridis, Ioannina; Dr. Marios Liapakis, Crete; Dr. Anastasios Markopoulos, Athens; Dr. Dimitrios Markou, Athens; Dr. Loukas Martsekis, Patra; Dr. Nikolaos Matsas, Patra; Dr. Ioannis Mavrepis, Thessaloniki; Dr. Aggelos Mavridis, Alexandroulis; Dr. Dimitrios Mitropoulos, Kalamata; Dr. Anestis Orkopoulos, Athens; Dr. Ioannis Paizis, Athens; Dr. Andreas Panourgias, Athens; Dr. Georgios Papadopoulos, Athens; Dr. Nikolaos Papadopoulos, Thessaloniki; Dr. Antonios Papaioannou, Chalki-

da; Dr. Pantelis Papoutsakis, Crete; Dr. Konstantinos Pissaridis, Volos; Dr. Vasilios Plastiras, Thessaloniki; Dr. Nikolaos Prokopakis, Crete; Dr. Damianos Routsakos, Athens; Dr. Andreas Samothrakitis, Patra; Dr. Alexandros Selianakis, Crete; Dr. Dionisios Simeonidis, Athens; Dr. Loukas Sinos, Lamia; Dr. Georgios Sofronas, Kalamata; Dr. Konstantinos Staboulidis, Thessaloniki; Dr. Christos Stathopoulos, Patra; Dr. Georgios Stavroulakis, Athens; Dr. Ioannis Stefanis, Thessaloniki; Dr. Leonidas Stergiou, Athens; Dr. Nikandros Stylianou, Ilia; Dr. Christos Tachmatzidis, Imathia; Dr. Panagiotis Tarenidis, Katerini; Dr. Sofia Terzi, Komotini; Dr. Konstantinos Travlos, Athens; Dr. Eleftherios Tsagaropoulos, Athens; Dr. Ilias Tsaglis, Athens; Dr. Nikolaos Tsamis, Xanthi; Dr. Charalabos Vassiliadis, Drama; Dr. Dimitrios Vassiliadis, Elassona; Dr. Vasilios Zahos, Athens; Dr. Ioannis Zavitsanos, Corfu.