Hellenic Journal of Cardiology (2016) 57, 279–281

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

LETTER TO THE EDITOR

Anticoagulation management in non-valvular atrial fibrillation in rural and remote Crete. A single-center study from the region of Sitia

KEYWORDS
Atrial fibrillation;
Antithrombotic therapy;
Anticoagulants;
Registry

Anticoagulation therapy (AT) is the cornerstone of treatment in atrial fibrillation (AF) for the prevention of possible thromboembolic events. Until recently, vitamin K antagonists (VKAs) were the main class of oral drugs used in daily clinical practice. New oral anticoagulants (NOACs) were a revolution in the management of patients suffering from non-valvular atrial fibrillation (NVAF).

Epidemiological data for AF in Greece is limited.[1] This is especially true for rural and remote areas. There is uncertainty about the effectiveness and safety of NOACs in unselected elderly patients in primary care.[2] The purpose of this study is to evaluate the anticoagulation therapy with NVAF that was administered to patients in the remote and rural areas of Sitia, Crete.

Our study was a single-center, 1-year prospective (from January to December 2014), observational study that enrolled consecutive patients with NVAF under anticoagulation or dual antiplatelet therapy (aspirin and clopidogrel) from the emergency department or the outpatient clinics of the Health Center – General Hospital of Sitia in Crete. It was conducted in the area of the Municipality of Sitia, which has a population of approximately 20,000 inhabitants. 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 Health Center of Sitia and approved by the local ethics committee of our hospital.

The classification of AF as paroxysmal, persistent, or permanent was performed according to the latest ESC guidelines for AF.[3] In patients under therapy with VKAs, we retrospectively recorded the international normalized ratio (INR) values during the last six months prior to enrollment in the study. The target therapeutic range of INR was 2–3. Time in therapeutic range (TTR) was defined by two commonly used methodologies. In the first method, TTR was defined as the fraction of INRs the within target range (Method A). In the second, we used the Rosendaal linear interpolation of INR values[4] (Method B). TTR≥ 60% was considered effective anticoagulation with VKA.

A total of 356 consecutive patients (172 men) were enrolled in our study. The demographic and clinical characteristics of the patients are shown in Table 1. The mean CHA_2DS_2-VASc[3] and $CHADS_2$ scores[3] for stroke risk were 4.63±1.54 and 3.00±1.27, respectively, while the mean HAS-BLED score[3] was 3.00±1.05.

Ninety-six percent of patients with NVAF were treated with anticoagulant agents (Fig. 1). Four percent of patients received dual antiplatelet therapy. Acenocoumarol was the only VKA agent recorded in our region. Nineteen patients had changed the anticoagulation therapy from VKA to a NOAC. The reasons for this change of AT were unstable INR (8 patients), the occurrence of hemorrhagic stroke (6 patients), distance from the health care unit (3 patients) and food preferences of the patient (2 patients). Sixty-six percent of patients had regular follow-up of the arrhythmia (at least once a year), while 28% of patients had not revisited a cardiologist after the initial diagnosis of the arrhythmia.

Overall, 63.1% of patients treated with VKAs had regular measurements of INR on a monthly basis, while 2.6% of patients at the time of the enrollment were unaware of the need to measure the INR during treatment with VKAs. Appropriate data for the TTR analysis were available for 135 patients on VKA treatment. The mean TTR for all patients in our study was 43.72% and 52.36% with methods A and B, respectively. A TTR≥ 60% was observed in 30.4% of patients with method A and in 38.5% of patients with B method.

The study of rural and remote areas is interesting and challenging, as these regions usually have special cultural conditions in combination with limited access to healthcare

Peer review under responsibility of Hellenic Cardiological Society.

http://dx.doi.org/10.1016/j.hjc.2016.05.005

Table 1 Baseline demographic and clinical characteristics of patients.

	n = 356 (100%)	Mean ± SD
Age	356 (100%)	78.47 ± 9.1
Men	172 (48.3%)	
Hypertension	317 (89%)	
Smokers	142 (39.9%)	
Active smokers	38 (10.7%)	
Ex-smokers	104 (29.2%)	
Dyslipidemia	178 (50%)	
Diabetes Mellitus	121 (34%)	
Coronary artery disease	50 (14%)	
Heart failure	221 (62%)	
NYHA I	43 (12%)	
NYHA II	144 (40.4%)	
NYHA III	28 (7.9%)	
NYHA IV	6 (1.7%)	
History of TIA / stroke*	82 (23%)	
AF type		
Paroxysmal AF	117 (32.9%)	
Persistent AF	25 (7%)	
Permanent AF	214 (60.1%)	
Other Cardiac Medications heart**		
B-blockers	183 (51.4%)	
Diltiazem	16 (4.5%)	
Digoxin	15 (4.2%)	
Propafenone	22 (6.2%)	
Amiodarone	43 (12.1%)	
Sotalol	5 (1.4%)	

NYHA: New York Heart Association; TIA: Transient ischemic attack; AF: Atrial fibrillation

* The TIA / stroke was the initial manifestation of AF for 35 patients.

** Other cardiac medications include only drugs for controlling heart rate or heart rhythm

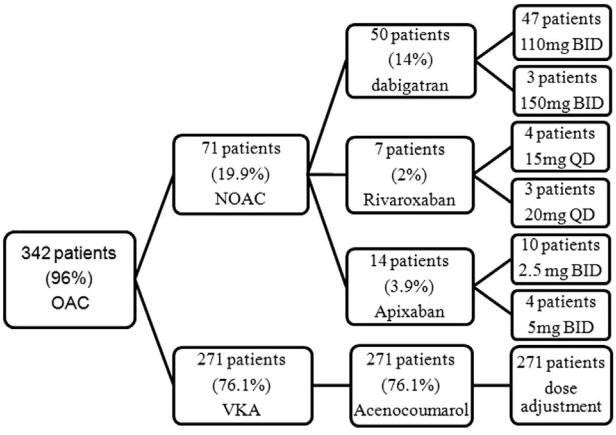

Figure 1 Anticoagulation drug therapy in study population. The percentages (%) are in reference to the total population of the study (356 patients). OAC: Oral anticoagulant; NOAC: New Oral Anticoagulant; VKA: Vitamin K antagonist; BID: bis in die; QD: quaque die.

services. RAFTING[5] and MANAGE-AF[1] are the two largest and most representative studies of the Greek population available for the treatment of AF at the national level. The MANAGE-AF[1] is the only Greek multi-center national registry to record the use of NOACs in AF. However, in this study only one NOAC (dabigatran) was included. To the best of our knowledge, ours is the first study concerning the anticoagulation management of NVAF in a rural and remote area of Greece where the three new available oral anticoagulant agents (dabigatran, rivaroxaban, apixaban) were available.

In our registry, dabigatran at a reduced dose (110 mg BID) ranked first among the NOACs. Not surprisingly, the above data were expected, as dabigatran was the first NOAC approved for the treatment of NVAF. Until recently, it was not available in Greece at a dose of 150 mg. Edoxaban was not available in Greece during the registration period of the study.

Some of the most recent data in the literature concerning the use of NOACs in AF were recorded in the American PINNACLE-AF registry[6] for a total of 150,000 patients. In this study, NOACs were used in 13% of AF patients in 2011. However, the PREFER[7] and EORP-AF19[8] studies recorded a smaller percentage of patients receiving NOACs (6.1% and 8.4% of patients, respectively). In the GARFIELD registry,[9] increased use of NOACs was observed over time, with a reduction in the use of VKAs.

The average TTR observed in participating Greek patients in the RE-LY[10] study was 56%. In MANAGE-AF,[1] the TTR of patients was not calculated, but indirect conclusions can be derived from the baseline mean INR value in the study population, which was 1.7±0.8. In our study, the majority of patients had TTR <60%, which shows poor adherence to treatment with VKAs.

In conclusion, most of the patients in our study were under treatment with VKAs, which require strict control to maintain the INR values in the therapeutic range. Possible reasons why this problem is not remedied by converting to NOACs may be either the reluctance of doctors to prescribe them or the unwillingness of patients in previously established therapy with VKA to convert to newer treatments. Another important factor, especially in a country in economic crisis such as Greece, is the high cost of NOACs. In our view, we believe that the establishment of national guidelines, especially in a country like Greece with its unique characteristics, will lead to a gradual harmonization of clinical practice in primary care with current European recommendations.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. 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.
2. Opstelten W, van den Donk M, Kuijpers T, Burgers J. New oral anticoagulants for nonvalvular atrial fibrillation in the elderly:

limited applicability in primary care. *Eur J Gen Pract*. 2015;21:145—149.
3. 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.
4. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thrombosis and Haemostasis*. 1993;69:236—239.
5. 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.
6. Chan PS, Maddox TM, Tang F, Spinler S, Spertus JA. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). *Am J Cardiol*. 2011;108:1136—1140.
7. 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.
8. 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.
9. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PloS One*. 2013;8:e63479.
10. 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.

Panteleimon E. Papakonstantinou*
Natalia I. Asimakopoulou
Anastasia Gargeraki
Konstantinos S. Gaitanis
Emmanouil Mintzaridis
Department of General Practice, Health Center-General Hospital of Sitia, Sitia, Lassithi, Crete, Greece

*Corresponding author. Panteleimon Papakonstantinou, Kapetan Gianni Papadaki 3, Xerokamares 72300, Sitia, Lassithi, Crete, Greece. Tel.: +30 2843340100, +30 6948050600 (mobile); fax: +30 2843 3 40 200.
E-mail address: pantelispapakon@gmail.com
(P.E. Papakonstantinou)

7 August 2015
Available online 26 August 2016