



ORIGINAL ARTICLE

The SAFIRA study: A reflection on the prevalence and treatment patterns of atrial fibrillation and cardiovascular risk factors in 7500 elderly subjects[☆]



Pedro Monteiro, on behalf of the SAFIRA study investigators

Serviço de Cardiologia A do Centro Hospitalar e Universitário de Coimbra, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal

Received 9 December 2016; accepted 16 August 2017
Available online 23 April 2018

KEYWORDS

Atrial fibrillation;
Elderly;
Prevalence

Abstract

Introduction and Aim: Atrial fibrillation (AF) is a common arrhythmia and an important risk factor for ischemic stroke. The current ESC guidelines state that all patients aged 65 and over should be regularly screened for AF. The SAFIRA study aimed to determine the prevalence, epidemiology and clinical and therapeutic characterization of AF in the Portuguese elderly population.

Methods: The study population (7500 subjects) were recruited from all Portuguese administrative regions. Demographic, clinical and drug treatment data were collected, risk scores were calculated, and an electrocardiogram (ECG) was performed in all subjects. In those not found to have AF on the resting ECG, a randomized subset (400 subjects) underwent 24-hour Holter monitoring and 200 subjects were fitted with an event recorder for two weeks, in order to identify patients with paroxysmal AF. The primary endpoint was AF prevalence; secondary endpoints (in the AF population) included prevalence of paroxysmal AF, mean and median CHA₂DS₂-VASc and HAS-BLED scores, rates of anticoagulant and antiplatelet therapy, previous stroke, previous stroke/transient ischemic attack, previous bleeding, and time in therapeutic range (if on vitamin K antagonists).

Results: The prevalence of AF was 9.0%. Of these, 35.9% were unaware of the diagnosis and 18.6% had paroxysmal AF. Median CHA₂DS₂-VASc score was 3.5±1.2 and 56.3% of patients were not anticoagulated. In the AF subpopulation, the stroke rate was 11.2%. Overall, only 25.8% of the anticoagulated patients were considered to be adequately treated.

Conclusions: This study shows the high prevalence of AF in the elderly population, as well as suboptimal rates of diagnosis, anticoagulation and effective control of cardiovascular risk factors.

© 2018 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. All rights reserved.

[☆] Please cite this article as: Monteiro P. Estudo Safira: reflexões sobre a prevalência e os padrões de tratamento de fibrilhação auricular e risco cardiovascular em 7.500 indivíduos com 65 ou mais anos. Rev Port Cardiol. 2018;37:307–313.

E-mail address: pedromonte@gmail.com

PALAVRAS-CHAVE

Epidemiologia;
Fibrilhação auricular;
Idosos

Estudo Safira: reflexões sobre a prevalência e os padrões de tratamento de fibrilhação auricular e risco cardiovascular em 7.500 indivíduos com 65 ou mais anos

Resumo

Introdução: A fibrilhação auricular (FA) é um dos mais importantes problemas de saúde pública em Portugal, representa simultaneamente um importante fator e marcador de risco cardiovascular.

Objetivo: Avaliar, numa população representativa com 65 ou mais anos, a prevalência, epidemiologia e caracterização clínica e terapêutica da FA.

População e métodos: Foram avaliados 7.500 indivíduos de 65 anos ou mais, recrutados em todas as regiões administrativas e representativos da população idosa residente em Portugal continental. A todos eles foi feito um ECG e, na ausência de FA, um subgrupo fez ainda Holter de 24 h ou implantou um registador de eventos durante sete dias. Em toda essa população foram avaliados dados epidemiológicos, clínicos e farmacológicos.

Resultados: A população estudada (41,9% do sexo masculino e 58,1% feminino), com média de 68,9 anos, apresentou uma prevalência global de FA de 9,0%. Desses 35,9% desconheciam ter FA e 18,6% apresentavam FA paroxística. Nessa população, a prevalência de HTA foi de 85,3%, de dislipidemia foi de 75,4% e de diabetes de 22,7%. O valor mediano do score de Chads-vasc foi de 3,5 +/-1,2. Em termos de abordagem terapêutica, 56,3% dos doentes não estavam anticoagulados (29,8% dos doentes estavam antiagregados) e, de entre os medicados com antitrombóticos K, o valor médio de TTR foi de 41,7%.

Conclusões: Este estudo mostra a muito elevada prevalência de FA na população idosa portuguesa, bem como uma taxa subótima de diagnóstico, anticoagulação e controlo efetivo dos fatores de risco cardiovasculares.

© 2018 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L.U. Todos os direitos reservados.

Introduction

Atrial fibrillation (AF) is one of the most significant public health issues in Portugal. It is important both as a cardiovascular risk factor and a risk marker.¹⁻⁴

It is thus important to determine the prevalence of AF in the Portuguese population, especially the elderly, in order to establish and implement realistic and effective strategies for diagnosis, treatment and risk control.

Aim

This article aims to provide a detailed analysis of the results of the SAFIRA study,⁵ especially regarding the following aspects: screening and diagnosis of AF in the elderly; patterns of antithrombotic treatment; efficacy of antithrombotic treatment; patterns of cardiovascular risk factor control; what patients tell us; study limitations; and what should be done with these results.

Methods

The SAFIRA study aimed to determine the prevalence, epidemiology, and clinical and therapeutic characterization of AF in a representative population aged 65 years and over from all administrative regions of mainland Portugal. As this was a population-based study, in order to avoid selecting a population with an overexpression of the disease,

recruitment was mostly performed outside of health centers (93.7%; n=7027), through partnerships with civil society, including charitable organizations, parish councils, senior centers and retirement homes. The latter two groups provided 2225 individuals (29.7%), so as to include a portion of the elderly population that is often excluded from this type of study (Table 1). No inpatients or emergency department patients were included.

The institutions themselves invited the individuals in the sample to participate voluntarily in the study, up to a limit set for each institution to fulfill the quota of subjects required in a given administrative region. Each institution was asked to apply no selection criteria (particularly known AF), so as to minimize sample bias. To obtain this sample (n=7500), 9765 individuals were contacted. Recruitment began in October 2013 and ended in September 2015.

The subjects in the sample were assessed by a multidisciplinary health team, which included two permanent physician members (at least one of whom was present at all times). Subjects were given a questionnaire (Appendix 1) covering all the required information, administered by nurses with cardiovascular experience.

An electrocardiogram (ECG) was performed in all subjects. Of those in whom the ECG did not reveal AF, a randomized subset of 400 subjects underwent 24-hour Holter monitoring, and a second randomized subset of 200 subjects received an event recorder for two weeks, to increase the likelihood of detecting paroxysmal AF. The Holter monitors and event recorders were read centrally

Table 1 General characteristics of the study population.

Total population, n	7500
Recruited from health centers, n (%)	473 (6.3)
Recruited outside health centers, n (%)	7027 (93.7)
Recruited in senior centers and retirement homes, n (%)	2225 (29.7)
Mean age, years	68.9±4.5
Female, %	58.9%
Hypertension, %	85.3%
Diabetes, %	22.7%
Dyslipidemia, %	75.4%

by the same team of technicians and clinicians, and the effectiveness of these tests was compared, as specified in the study protocol.⁵ Subjects were assigned to each subset by block randomization (blocks of 30 individuals in the case of Holter monitoring and of 15 individuals for the event recorder). The prevalence of AF in these subpopulations was then added to the prevalence detected by the ECG and the unweighted mean prevalence was calculated in order to estimate the overall prevalence of AF in the study population.

All subjects were asked to bring a list of their medications and any recent test results on the day of assessment. In subjects with renal function results within the previous six months, creatinine clearance was calculated (according to the Cockcroft-Gault formula) to assess renal function, while for subjects being treated with a novel oral anticoagulant (NOAC), it was determined whether they were receiving the correct dosage on the basis of age and weight when these were included in the dose reduction indications approved by the Portuguese National Authority for Medicines and Health Products (Infarmed). For individuals treated with vitamin K antagonists (VKAs), time in therapeutic range (TTR) was calculated using the Rosendaal method whenever at least five international normalized ratio (INR) values from the last six months were available (considering therapeutic values to be 2.0 through 3.0).

The primary endpoint of the SAFIRA study⁵ was the prevalence of AF in the elderly population. The secondary endpoints were prevalence of paroxysmal AF, mean CHA₂DS₂-VASc and HAS-BLED scores, rates of anticoagulant and antiplatelet therapy, previous stroke, previous stroke or transient ischemic attack, previous bleeding, and TTR (in subjects treated with VKAs).

The results of this study showed a very high AF prevalence in this elderly population (9.0%), previously unknown in many cases (35.9%). The study also assessed treatment patterns for AF, stroke and cardiovascular risk factors. The results⁵ show the need for better understanding and for more effective strategies for the diagnosis and management of AF and risk of stroke in the elderly Portuguese population. In this context, we identified some of the overall outcomes that we felt required more in-depth analysis. These will be discussed below.

Statistical analysis

The sample size was calculated based on the Portuguese population over 65 years of age in the 2011 census (2 010 000

individuals), and assuming that 20% of those requested would not agree to participate in the study. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentage or median, as indicated.

Results

Screening and diagnosis of atrial fibrillation in the elderly

The SAFIRA study results revealed an estimated overall AF prevalence of 9.0% in elderly subjects, similar in men (8.9%) and women (9.1%). The prevalence was 9.3% in the subset that underwent Holter monitoring and 10.6% in the subset fitted with an event recorder (Table 2). The estimated prevalence stratified by age was 6.8% among those aged 65-69 years, 11.1% in those aged 70-89, and 15.2% in those aged 80 years or older.

Patterns of antithrombotic treatment

The median CHA₂DS₂-VASc score in the SAFIRA study was 3.5±1.2. The study revealed that 56.3% of subjects with known AF were not on oral anticoagulation therapy (including 29.8% treated with antiplatelet agents alone), while 43.7% were anticoagulated. The anticoagulation rate was 34.3% among individuals at senior centers and retirement homes. When the anticoagulation rate was stratified based on ischemic risk, the results were as follows: 25.3% for subjects with CHA₂DS₂-VASc score between 1 and 3; 50.1% with score 4-5; and 18.6% with score 6 or higher.

Efficacy of antithrombotic treatment

Among the subjects for whom data on anticoagulation were available, 65.7% were treated with VKAs and 34.3% were on NOACs.

In the former group, TTR was assessed whenever at least five INR values from the last six months were available. The median value was 41.7% (Table 2), this low figure being due in most cases (80%) to periods of subtherapeutic INR. In subjects treated with NOACs, we examined whether the drug, the dose level, and the number of daily doses were in line with the clinical presentation of each subject (including creatinine clearance when data to calculate it were available)

Table 2 Atrial fibrillation: main findings.

Overall estimated AF prevalence ^a (%)	9
Prevalence in those who only underwent ECG (%)	7.1
Prevalence in the subset who underwent Holter monitoring (%)	9.3
Prevalence in the subset fitted with an event recorder (%)	10.6
Overall estimated AF prevalence ^a – males (%)	8.9
Overall estimated AF prevalence ^a – females (%)	9.1
Paroxysmal AF (%)	18.6
CHA ₂ DS ₂ -VASc score (median)	3.5±1.2
Rate of anticoagulant therapy (%)	43.7
TTR (%)	41.7
Rate of previous bleeding in anticoagulated patients	4.6

^a Calculated as the mean of prevalences in subjects undergoing ECG only, those also undergoing Holter monitoring, and those also fitted with an event recorder.

AF: atrial fibrillation; ECG: electrocardiogram; TTR: time in therapeutic range.

and with the drug's Summary of Product Characteristics as approved in Portugal. It was found that 24.7% of the subjects were incorrectly treated (inappropriate dosage, inappropriate number of doses, or creatinine clearance incompatible with the use of NOACs). Using these criteria, 6.1% of anticoagulated subjects were overdosed (87.9% of them on VKAs) or did not have the creatinine clearance necessary to take the NOAC prescribed (93.1% of those treated with dabigatran) or the dosage prescribed (73.4% of them on rivaroxaban).

Overall, only 25.8% of anticoagulated subjects were found to be properly medicated (correct dosage for effective anticoagulation, including a TTR of at least 55% in those treated with VKAs).

The stroke rate in the AF population in the SAFIRA study was 11.2% (25.7% of whom had had two or more previous strokes).

Patterns of control of cardiovascular risk factors

The prevalence of cardiovascular risk factors in this population was very high (hypertension 85.3%, dyslipidemia 75.4%, and diabetes 22.7%) (Table 1). Control of these factors was also assessed, with control defined as blood pressure \leq 140/90 mmHg, low-density lipoprotein cholesterol <100 mg/dl and glycated hemoglobin <7%. When these criteria were applied, only 5.6% of patients with AF and data available had all risk factors in the target range and were on appropriate oral anticoagulation.

What patients tell us

As part of the SAFIRA study, subjects were also asked some questions concerning their knowledge of the disease, medical treatment, compliance with medication and side effects.

Answers to the question "What is most important to you about the medicines you take?" were as follows: safety (45.1%), efficacy (35.6%), cost (12.8%), and dosing convenience (6.7%).

To the question "What makes you stop taking long-term medication?", 88.7% responded "side effects". The main cause of discontinuing anticoagulants was bleeding (93.7%),

while cost was mentioned by 1.6% of subjects (reported almost exclusively by NOAC users, in 4.8% of subjects).

Regarding side effects, the rate of any degree of bleeding reported by subjects taking antithrombotics was 4.6% in the anticoagulated population and 12.3% in those treated with antiplatelets. Of these, 9.8% of bleeding cases were classified by the subjects as severe (89.3% of these cases occurred in subjects treated with VKAs), and only 1.9% of cases required hospitalization.

Discussion

Screening and diagnosis of atrial fibrillation in the elderly

When these prevalence rates are compared with those found by the FAMA study⁵ (2.5% prevalence of AF in the Portuguese population over 40 years of age), they may seem excessive. However, there are important differences between the two studies.

The FAMA study included subjects aged 40 years or older, recruited from the general population using a random-route method. By contrast, the SAFIRA study focused exclusively on the elderly population (aged 65 years or over) and sought to identify a more clinically varied population, including not only those usually treated in primary health care but also those in the non-governmental sector (senior centers and retirement homes), as well as some users of hospital care such as in day hospitals and emergency departments (although the latter were not used for recruitment of subject of the SAFIRA study). The FAMA study used the ECG as the only method to diagnose AF, whereas in the SAFIRA study, a subset of subjects underwent Holter monitoring or were fitted with an event recorder to improve detection of paroxysmal AF, which these devices identified in nearly three-fifths (58/102) of cases. This population has specific characteristics (Table 3). The results of other European studies, such as the Rotterdam study,⁶ which reported a prevalence of 8.3%, and a Spanish study by Cea-Calvo⁷ in which the prevalence was 8.5%, are within the same range as those of the SAFIRA study.

Table 3 Epidemiology of atrial fibrillation.

Population characteristics	With AF (n=548)	Paroxysmal AF (n=102)	Non-paroxysmal AF (n=446)	Without AF (n=6952)
Mean age (years)	69.8±6.7	68.8±4.6	70.7±4.4	68.7±4.2
Male (%)	44.5%	43.9%	45.1%	41.4%

AF: atrial fibrillation.

Despite these considerations, the SAFIRA study clearly shows a very high prevalence of AF in this elderly population, with similar figures for both sexes and increasing with age.

There is another finding that is at least as significant and challenging: 35.9% of the subjects were unaware that they had AF, which translates into a large population with unknown AF (in the 2011 census, one in five Portuguese were aged over 65). This makes stroke prevention very difficult in this subpopulation.

Patterns of antithrombotic treatment

Despite all the evidence of the efficacy, safety and cost-effectiveness of anticoagulation in the prevention of ischemic stroke, especially among the elderly,¹ the SAFIRA study showed that the rate of anticoagulation in subjects with known AF was low, seeing that, in this population aged 65 years or over, no subject had a CHA₂DS₂-VASc score⁸ of 0 and very few had a score of 1. Antiplatelet agents would not be recommended for the overwhelming majority of these subjects, and oral anticoagulation would be mandatory for almost all of them. However, the reality revealed by the SAFIRA study is quite different: 29.8% were treated with antiplatelets alone, and only 43.7% were anticoagulated. These figures are especially concerning for individuals at senior centers and retirement homes, even in those with relatively low HAS-BLED⁹ scores.

Regarding the relationship between CHA₂DS₂-VASc score and anticoagulation rate, the results were also not encouraging, with a low anticoagulation rate (25.3%) in those with a CHA₂DS₂-VASc score between 1 and 3, higher (50.1%) in those with a score of 4 or 5, but only 18.6% in those with a score of 6 or more.

Efficacy of antithrombotic treatment

Concerning the question of whether those under anticoagulation therapy were properly medicated, two findings warrant particular attention.

Firstly, in subjects treated with VKAs – the majority (65.7%) – the median TTR was only 41.7%, meaning that most of the time they were not properly anticoagulated, almost always due to the use of subtherapeutic doses. These individuals were thus not adequately protected against the risk of stroke,¹⁰ which is on average five times higher in patients with AF than in those without and which increases with age and duration of AF.

Secondly, around a quarter of subjects treated with NOACs were inadequately medicated (inappropriate dosage, inappropriate number of doses or creatinine clearance not compatible with the use of NOACs).

It is important to note that the results were much better in subjects treated with NOACs than in those treated with VKAs, even though NOACs were less often used in the elderly subjects of the SAFIRA study (34.3%) than in the general population (about 50%). Overall, only 25.8% of anticoagulated subjects were found to be properly medicated (correct dosing, with effective anticoagulation, including a TTR of at least 55% in those treated with VKAs). This indicates a potential for considerable improvement in this population, and means that the 11.2% stroke rate in the population with AF in the SAFIRA study (25.7% of whom had previously suffered two or more strokes) is hardly surprising.

Patterns of control of cardiovascular risk factors

It is well known that AF does not usually occur alone, especially in the elderly, but is almost always associated at least one cardiovascular risk factor, as clearly demonstrated by the composition of the CHA₂DS₂-VASc score⁸ itself. Control of cardiovascular risk is crucial to improving the prognosis for AF.^{11,12} With this in mind, the authors also assessed the presence and treatment of major cardiovascular risk factors. As expected, their prevalence was very high, as described in other studies.⁵⁻⁷ However, the degree of risk factor control was often inadequate; only 5.6% of subjects had all cardiovascular risk factors within target levels and were receiving appropriate oral anticoagulation.

What patients tell us

This may be one of the most important issues addressed by the SAFIRA study, and is one that will be the subject of a separate publication. Here, we highlight some of the main points.

The question of what is most important to patients about their medication is often raised and can lead to heated debate. The ranking revealed by the SAFIRA study (safety [45.1%], efficacy [35.6%], cost [12.8%] and dosing convenience [6.7%]) seems to indicate that, least among the medicated elderly, more importance is attributed to the quality of the treatment than to its cost and convenience. In the future, it would be interesting to ask healthcare professionals or policymakers the same question to see if the results are similar.

Responses to the question of what makes patients stop taking antithrombotic treatments indicate that, as expected, bleeding is at the top of the list, but the rate of any degree of bleeding reported by subjects was relatively low in the anticoagulated population (a third of that reported by those treated with antiplatelet agents, which is all the more important given that antiplatelet therapy is not an appropriate strategy for stroke prevention in the great

majority of these patients). The rate of discontinuation due to financial difficulties (found almost exclusively in subjects treated with NOACs, as expected) was lower than might be expected.

With regard to the safety of anticoagulation in the elderly, this is basically a question of the occurrence of bleeding. Subjects in the SAFIRA study classified only 9.8% of bleeding cases as severe (89.3% of these cases occurred in subjects treated with VKAs), and only 1.9% of cases required hospitalization. These results demonstrate the safety of this therapy (especially NOACs), even in these age ranges.

Still on the subject of safety, another finding to note is that according to data from the SAFIRA study, 6.1% of anticoagulated subjects were overdosed (especially those on VKAs) or did not have the necessary creatinine clearance to take the prescribed NOAC (almost always dabigatran) or the prescribed dose (almost always rivaroxaban). There is therefore also room for improvement in this regard.

Limitations of the study

Only a small proportion of the sample underwent Holter monitoring or were fitted with an event recorder. This may have limited the detection of paroxysmal AF, and may also have biased the results, since it was decided to use the unweighted mean of the prevalences to estimate the overall prevalence of AF in the sample population.

Subjects were mostly selected outside of healthcare institutions and did not include inpatients or emergency department patients, which may also have led to bias in the sample.

Only subjects who agreed to participate and provided written consent were enrolled, which may have led to selection of subjects who were more receptive to health care and may have had a greater degree of health literacy.

Attempts were made to ensure that the study was not consciously biased toward patients with a previous diagnosis of AF, but this cannot be absolutely guaranteed.

Not all subjects brought records of their previous medication and relevant recent tests for assessment. This limited the collection of certain information, including on treatment, renal function, suitability of medication and previous bleeding.

What should be done with these results

As with any scientific study, the publication of the SAFIRA study's results and analyses are not the end, but the beginning. These results, with all their nuances and limitations, are not to be overemphasized or downplayed, but more importantly, they should not be ignored. They should prompt analysis of the current situation, which calls for better understanding and positive action, for which there is an obvious need.

This article does not set out to present answers or definitive proposals, but rather to encourage a much-needed discussion of the situation concerning AF among the elderly in Portugal and of the ways in which it will be possible to intervene.

Conclusions

Analysis of these results leads to certain incontrovertible conclusions. There is a very high prevalence of AF in the elderly Portuguese population, with suboptimal rates of diagnosis, anticoagulation and effective control of cardiovascular risk factors. There are thus still enormous challenges in identifying and managing AF and cardiovascular risk in this population. It is imperative to optimize control of diseases (AF, stroke and systemic embolism) and health-promotion strategies by means of joint and ongoing efforts on the part of patients, caregivers, health professionals and educators, and the authorities responsible for health and socioeconomic wellbeing in the elderly, so that future studies in this important population will reveal a different situation, and one we can all be proud of.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

The SAFIRA study was funded by a research grant from Pfizer/Bristol Meyers Squibb, who had no involvement in the selection of study participants, data collection or analysis, or the preparation of this manuscript.

Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.repce.2017.08.006](https://doi.org/10.1016/j.repce.2017.08.006).

References

1. Kirchhof P, Benussi S, Kotecha D, et al., ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–962.
2. Hobbs FD, Fitzmaurice DA, Mant J, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess*. 2005;9, iii–iv, ix–x, 1–74.
3. Sposato LA, Cipriano LE, Saposnik G, et al. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:377–87.
4. Kishore A, Vail A, Majid A, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke*. 2014;45:520–6.
5. Bonhorst D, Mendes M, Adragão P, et al. Prevalence of atrial fibrillation in the Portuguese population aged 40 and over: the FAMA study. *Rev Port Cardiol*. 2010;29:331–50.
6. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949–53.
7. Cea-Calvo L, Redón J, Lozano JV, et al. Prevalence of atrial fibrillation in the Spanish population aged 60 years or more. The PREV-ICTUS study. *Rev Esp Cardiol*. 2007;60:616–24.

8. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–72.
9. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–100.
10. Connolly SJ, Pogue J, Eikelboom J, et al., on behalf of the ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029–37.
11. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222–31.
12. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;310:2050–60.