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Murcia atrial fibrillation project II: protocol for a prospective observational study in patients with atrial fibrillation

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ABSTRACT

Introduction Atrial fibrillation (AF) is characterised by a high stroke risk. Vitamin K antagonists (VKAs) are the most commonly used oral anticoagulants (OACs) in Spain, but their efficacy and safety depend on the time in therapeutic range of International Normalized Ratio (INR) 2.0–3.0 over 65%–70%. Unfortunately, the difficulties of maintaining an optimal level of anticoagulation and the complications of VKAs (particularly haemorrhagic ones), frequently lead to cessation of this therapy, which has been associated with higher risk of adverse events (AEs), including ischaemic stroke. Our aims are as follows: (1) to evaluate the quality of oral anticoagulation with VKAs, the prevalence of poor quality of anticoagulation, and to identify factors predisposing to poor quality anticoagulation; and (2) to identify patients who will stop OAC and to investigate what factors influence the decision of OAC withdrawal.

Methods and analysis Prospective observational cohort study including outpatients newly diagnosed with AF and naïve for OACs from July 2016 to June 2018 in an anticoagulation clinic. Patients with prosthetic heart valves, rheumatic mitral valves or valvular AF will be excluded. Follow-up will extend for up to 3 years. During this period, the INR results and changes in the anticoagulant therapy will be recorded, as well as all AEs, or any other information that would be relevant to the proper conduct of research.

Ethics and dissemination All patients were informed about the nature and purpose of the study, and the protocol was approved by the Ethics Committee of Hospital General Universitario Morales Meseguer (reference: EST:20/16). This is an observational study focusing on 'real life' practice and therefore all treatments and follow-up will be performed in accordance to the routine clinical practice with no specific interventions or visits. The results of our study will be disseminated by presentations at national and international meetings, and publications in peer-reviewed journals.

Strengths and limitations of this study

- This will be one of the largest prospective observational cohort studies including non-valvular atrial fibrillation patients investigating the quality of anticoagulation with vitamin K antagonists in Spain.
- During the follow-up, physical examination data, comorbidities, concomitant therapies and results of laboratory tests, as well as INR results, changes in the anticoagulant therapy, efficacy and safety outcomes and other adverse events, will be recorded.
- All patients will be carefully and prospectively followed-up in an observational manner, and no interventions will be performed in relation to the study, thus providing an accurate insight from the real clinical practice.
- This study is limited by its observational design, the inclusion of mostly Caucasian patients and the way patients will be managed according to our standard protocol of care.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, with a prevalence of ~2% in the overall population, and up to 15% in the elderly aged ≥80 years old.[1–3]

This arrhythmia is characterised by a high risk of stroke, but the risk of stroke in AF is not homogeneous, being associated with the presence of several risk factors that have been identified in randomised and observational studies.[4] The more common and validated risk factors are included in the CHA_2DS_2-VASc score, which is used for to determine recommendations for stroke prevention.[5–7]

Oral anticoagulation, either vitamin K antagonists (VKAs) or direct-acting oral anticoagulants (DOACs), is central for stroke prevention in patients with AF. In Spain, the most commonly used oral anticoagulants (OACs) are the VKAs (acenocoumarol and warfarin), since the use of DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) is still limited. Nevertheless, VKA therapy has a number of complications inherent to these drugs such as the interindividual variability (in relation to clinical and genetic factors), pharmacological and food interactions, or the need for systematic monitoring.[8] Therefore, the efficacy and safety of VKAs depends on the maintenance of an average

time in therapeutic range (TTR) within an INR 2.0–3.0 over 65%–70%.[9] However, this goal is often not achieved in real-world clinical practice. In addition, the initiation of VKAs in previously untreated patients is usually associated with an increased risk of thromboembolic and haemorrhagic complications during the initial period of treatment, when the patient is suboptimally protected by VKAs.[10]

Despite oral anticoagulation therapy, cardiovascular complications such as acute coronary syndrome and cardiovascular death are frequent, due to the coexistence of others cardiovascular risk factors such as high blood pressure or diabetes mellitus. In addition, thrombotic risk correlates with the bleeding risk, and unsurprisingly, patients with high CHA_2DS_2-VASc score also have higher risk of bleeding complications.[11]

Thus, integrated or holistic care of AF includes not only stroke prevention but also efforts to reduce cardiovascular risk factors, including broader approaches such as nurse-led interventions, education and lifestyle modifications (eg, obesity management, exercise and healthy lifestyle efforts).[12]

Unfortunately, the difficulties of maintaining an optimal level of anticoagulation and the complications of oral anticoagulation with VKAs (particularly haemorrhagic ones), frequently lead to cessation of this therapy, which has been associated with a higher risk of adverse events (AEs), including ischaemic stroke.[11] Therefore, new prospective studies are necessary to assess the quality of oral anticoagulation in VKA users, and second, to investigate what factors influence decisions on oral anticoagulation therapy and the occurrence of AEs. Third, we will determine the influence of a contemporary 'integrated management' approach to AF on clinical outcomes.

OBJECTIVES

The following objectives were defined for this study:

1. To evaluate the quality of oral anticoagulation with VKAs, the prevalence of poor quality of anticoagulation and to identify factors predisposing to poor quality anticoagulation.
2. To compare different methods for estimating the quality of anticoagulation therapy with VKAs (ie, Rosendaal method, the direct method, the SD of INR and so on).
3. To develop and refine a prediction scheme to identify those patients who will likely have poor anticoagulation quality with VKAs.
4. To analyse the complications and AEs that may arise with anticoagulant treatment during the follow-up and to find out the predisposing causes in order to establish potential preventive actions.
5. To identify patients who will stop OACs and to investigate what factors influence the decision of OACs withdrawal.
6. To assess whether the prediction of bleeding events by a strategy based on modifiable bleeding risk factors alone is superior to clinical risk scores.
7. To evaluate whether the change in CHA_2DS_2-VASc and HAS-BLED scores between baseline and follow-up, would be more predictive of ischaemic stroke and bleeding compared with scores assessed at baseline.
8. To investigate the impact of implementing the atrial fibrillation better care (ABC: A, avoid stroke with OACs; B, better symptom management; C, cardiovascular and comorbidity risk management) pathway, on clinical outcomes.

METHODS AND ANALYSIS

Study design

This is a prospective observational cohort study including outpatients newly diagnosed with AF and naïve for oral anticoagulation in the anticoagulation clinic of the Hospital General Universitario Morales Meseguer (Murcia, Spain).

Hospitals involved and anticoagulation clinic

The 'Hospital General Universitario Morales Meseguer' is a tertiary hospital located in Murcia City, capital of the Autonomous Community of Región de Murcia, in Southeastern Spain. It is a hospital with 400 beds and almost 2000 employees, covering an area of ~255 000 inhabitants. The 'Hospital General Universitario Reina Sofía' is also a tertiary hospital located in Murcia City. It has 330 beds and ~1800 employees, covering an area of about 200 000 inhabitants (data revised on January 2019).

The outpatient anticoagulation clinic in the Hospital General Universitario Morales Meseguer receives patients from both, this hospital and the Hospital General Universitario Reina Sofía. This anticoagulation clinic is the reference clinic for managing patients requiring anticoagulation from two different health areas, hence covering ~455 000 inhabitants (figure 1). Of these, 2% receive oral anticoagulation therapy with VKAs. Among the multiple indications for anticoagulation therapy, non-valvular AF is the most frequent, constituting 50% of patients, thus we manage approximately a population of 4000 patients

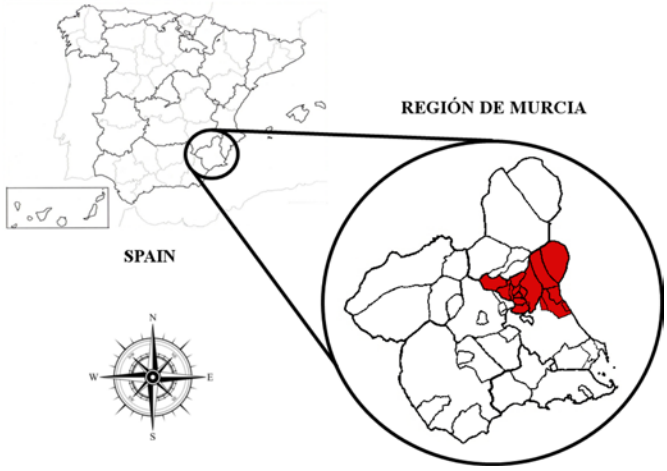

Figure 1 Map of Spain and Murcia.

with this diagnosis. All patients included in the study were derived from this anticoagulation clinic.

Participants

Eligible patients were those who started oral anticoagulation with VKAs for the prevention of thromboembolism due to permanent or paroxysmal AF. Only those patients older than 18 years with documented evidence of non-valvular AF on ECG and not previously anticoagulated for another reason were included. Patients with prosthetic heart valves, rheumatic mitral valves or other type of valvular AF were excluded from this study. In order to perform a study that reliably reflects the 'real world' clinical practice, no other exclusion criteria were established.

Recruitment

From 1 July 2016 to 30 June 2018, all consecutive patients referred to the anticoagulation clinic fulfilling the inclusion criteria were selected. Since sampling techniques were not used for this study, patients were considered included if they met all the selection criteria and accepted to participate by signing the informed consent.

Baseline assessment

At baseline, a complete medical history was obtained by collecting sociodemographic and anthropometric data, comorbidities, concomitant therapies and results of the most recent lab test. In addition, with the parameters recorded, stroke risk ($CHADS_2$ and CHA_2DS_2-VASc)[5 13] and bleeding risk ($HEMORR_2HAGES$, HAS-BLED, ATRIA and ORBIT)[14–17] were calculated. The risk of major adverse cardiovascular events (MACEs) was also assessed by the 2MACE score.[18] The SAMe-TT_2R_2 score[19] was used as an indirect clinical measure of the likelihood of achieving a good TTR. Assessment of functional independence was performed by the Barthel index for Activities of Daily Living[20] and the Lawton's Instrumental Activities of Daily Living scale,[21] whereas fragility was measured by the Clinical Frailty Scale.[22]

Interventions for the study

This is an observational study focusing on 'real life' practice; hence, all treatments and follow-up will be performed in accordance to the routine clinical practice with no specific interventions and no specific visits for study purposes. The fact that a patient accepted to participate or not in the study will not alter their treatment or management.

Outcome measures

Primary outcomes

Ischaemic stroke, major bleeding and all-cause mortality are the primary outcomes for this study. Ischaemic stroke will be defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery lasting >24 hours or resulted of an obstruction documented by imaging, surgery or autopsy. Major bleeding will be defined according to the 2005 International Society on Thrombosis and Haemostasis (ISTH)[23] criteria as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of ≥20 g/L (1.24 mmol/L) or more, or leading to transfusion of ≥2 units of whole blood or red cells.

Secondary outcomes

Several efficacy and safety secondary outcomes will be recorded for this study, including transient ischaemic attack (TIA), systemic embolism, venous thromboembolism (deep vein thrombosis and pulmonary embolism), acute coronary syndrome, acute heart failure, cardiovascular mortality, MACE, clinically relevant non-major bleeding (CRNMB) and minor bleeding.

TIA will be defined as a rapid development of clinical signs of focal or global cerebral function disturbance, lasting <24 hours, with no apparent non-vascular cause and confirmed as positive by cerebral imaging. Systemic embolism will be considered as any acute vascular occlusion of an organ or limb, documented by images and/or surgery. Acute heart failure will be determined as a gradual or rapid change in heart failure signs and symptoms resulting in a need for urgent therapy. A death will be classified as cardiac-related when there were unequivocal signs that the death occurred by a cardiovascular cause. MACE will be defined as the composite of fatal/non-fatal myocardial infarction, cardiac revascularisation or cardiovascular death. CRNMB will be defined according to the 2015 ISTH criteria as any sign or symptom of haemorrhage that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: (1) requiring medical intervention by a healthcare professional; (2) leading to hospitalisation or increased level of care; or (3) prompting a face-to-face (ie, not just a telephone or electronic communication) evaluation.[24] All bleeding reported by the patient that will not require medical attention or intervention will be considered as minor bleeding. Other outcomes will be defined according to the international guidelines. There will be no adjudication committee. The investigators will identify, confirm and record all AEs.

Sample size estimation

As we stated above, the recruitment was consecutive. We intended to include all patients fulfilling the inclusion criteria during 2 years but no sample size calculation was performed. We performed an estimation based on previous projects from our group and average of patients starting OACs per year in our clinic. Hence, ~1000 patients/year start anticoagulant therapy in our clinic, of which 60% correspond to patients with AF. We estimated an inclusion of at least 500 patients/year.

Statistical analyses

Categorical variables will be expressed as frequencies and percentages. Continuous variables will be tested for

normality by the Kolmogorov-Smirnov test or the Shapiro-Wilk test, and presented as mean±SD or median and IQR, as appropriate.

The Pearson χ^2 test will be used to compare proportions. Differences between continuous and categorical variables will be assessed using the Mann-Whitney U test or the Student's t-test, as appropriate, and correlations tested using the Spearman's Rho.

Multivariate Cox proportional hazard regression models will be performed to determine the association between patients' characteristics or clinical risk factors and AEs (or poor quality of oral anticoagulation). When multivariate Cox models will be performed, we will include only those variables that showed p value <0.15 in the univariate analyses. Goodness of fit will be evaluated using the Hosmer-Lemeshow test.

Kaplan-Meier estimates and analysis by the log-rank test will be carried out to assess differences in event-free survival.

Receiver operating characteristic (ROC) curves will be applied to evaluate the predictive ability (expressed as c-indexes). Comparisons of ROC curves will be carried out as reported by DeLong *et al* method.[25] Net reclassification improvement and integrated discriminatory improvement will be performed according to the methods described by Pencina *et al*.[26] Finally, clinical usefulness and net benefit of new predictive models will be estimated using decision curve analyses.[27 28]

A p value <0.05 will be accepted as statistically significant. Statistical analyses will be performed using SPSS V.22.0, MedCalc V.16.4.3, STATA V.12.0 and survIDINRI package for R V.3.3.1, for Windows.

Data collection at baseline and during the follow-up

As previously described, there will be no in-person visits in relation to the study. All the information will be captured from the electronic medical records, by personal interview using the patients' routine visits to the anticoagulation clinic and by telephone contact.

During the first visit to the anticoagulation clinic in order to start OAC therapy, all eligible patients were invited to participate in the study. If they agreed, they had to sign an informed consent. This visit was considered as the baseline visit. The information described in the Baseline assessment section was recorded during this visit.

Follow-up will be performed also by personal interview at each routine visit to the outpatient anticoagulation clinic or visits for the anticoagulation control (INR measurement). If the patient never attends to these visits, medical records and telephone calls will be used to obtain the information needed and vital status. In any case, patients will never have to attend in-person follow-up visits in addition to the routine clinical practice.

Follow-up will extend for up to 3 years, and 30 June 2021 is the expected date for the last follow-up in the last patient included. During this period, the INR results and changes in the anticoagulant therapy will be recorded, as well as all AEs, or any other information that would be relevant to the proper conduct of research.

Regarding the INR results, the therapeutic range for AF patients taking VKAs is an INR between 2.0 and 3.0. The TTR will be used as a way to assess the quality of anticoagulation control, and will be calculated by the method of Rosendaal[29] and by the Proportion of INRs within the therapeutic Range (PINRR, also known as direct method) at 6 months and 1 year of inclusion. The TTR by the method of Rosendaal will be calculated by adding INR measurement frequency and their values, and assuming that changes between consecutive INR measurements are linear over time. The PINRR will evaluate the percentage of INR measurements between 2.0 and 3.0 over the total number of INR measurements. Poor anticoagulation quality will be defined as a TTR <65% by the method of Rosendaal or PINRR <60%. The TTR and PINRR will be assessed avoiding the first month of anticoagulation since this period is largely influenced by the fluctuations due to treatment initiation rather due to the anticoagulant itself.

Access to patients' medical records will be carried out through the GOTA software (Systelab Werfen S.A.), which is the programme for the INR controls and is connected to the electronic medical records programme of the Health Service from Murcia (SMS), called SELENE (Siemens S.A.). The data records for this study will be made on an electronic database.

Premature termination

There are no specified premature termination criteria in this study. The management and follow-up will be performed according to the routine clinical practice and no additional medication, interventions or investigational medical devices will be applied in this observational study. Only those patients who explicitly state that they no longer want to be involved in the study, will be withdrawn.

Reporting of AEs

During the study, all AEs will be recorded. Serious AEs will be reported to the ethical committee in accordance to local regulatory requirements.

Ethical considerations and dissemination

All patients likely to be included in the study were informed about the nature of the study and received relevant information about the intended purpose. As this is an observational study, no visits have been scheduled in relation to the study, and no specific changes will be performed regarding the treatment, care or clinical management based on the results obtained from this research itself. All participants were provided with a unique study number. This study number allows the anonymisation of the information included in the study database.

The study protocol was carried out in accordance with the ethical standards established in the Declaration of Helsinki of 1964 and its subsequent amendments. The results of our study will be disseminated by presentation

at national and international meetings and publication in peer-reviewed journals.

Patient and public involvement

Patients and public were not involved in the design, recruitment nor conduct of the study.

DISCUSSION

AF is associated with impaired quality of life, and increased mortality and morbidity, mainly due to the embolic risk.[30] Oral anticoagulation is central for the prevention of stroke in patients with AF, but a poor quality of anticoagulation with VKAs (ie, a labile INR or a TTR <65%) results into a higher risk of AEs.[9]

Currently, the prescription of DOACs is increasing but still remains low in many countries where VKAs are the most frequent OACs.[31] Therefore, identifying factors that lead to poor quality of anticoagulation will allow us to identify high-risk patients and to establish clinical interventions that warrant optimal therapeutic management. On the other hand, there are some undesirable effects inherent to oral anticoagulation with VKAs (especially haemorrhagic ones). Often, these undesirable effects and complications of VKAs lead to lower persistence on this therapy, which has demonstrated to be associated with a higher risk of cardiovascular events, including ischaemic stroke.[11] For this reason, it is necessary to individually assess each patient to find out what factors determine decisions about anticoagulant therapy.

To date, the benefits of OACs in AF patients have been well demonstrated in randomised clinical trials (RCTs) and observational cohorts. However, there are few data, in particular from the real world about adherence to OACs and causes of poor OACs persistence. Similarly, evidence about a prediction strategy based only on modifiable bleeding risk factors, delta CHA_2DS_2-VASc and HAS-BLED scores for the prediction of ischaemic stroke and bleeding, and the performance of the ABC pathway is scarce, with limited data in a Spanish population.[32–38] Indeed, real-world data are of increasing interest, since patients included in the RCTs are, generally different from those in real life.[39]

This study will be limited by its observational design and the way the patients will be managed according to our standard protocol of care. Nevertheless, all patients will be carefully followed-up prospectively, and no interventions will be done in relation to the study. This will provide an accurate insight from the real-world clinical practice. Previously, the first phase of the Murcia AF Project resulted in relevant publications in several peer-reviewed journals, which have enhanced scientific knowledge about different aspects of AF. The present protocol paper aims to provide the methodology of the second phase of the Murcia AF Project in a stage in which four DOACs are available (dabigatran, apixaban, rivaroxaban and edoxaban) with prescription rates that are increasing, which will allow us to assess the paradigm shift in the management of patients with AF.

Current study status

The recruitment of patients started on 1 July 2016 and finished on 30 June 2018. During this period, 1291 patients were screened and 1094 patients were included in the study. However, the final sample size is still unknown since it will depend on the number of patients that allow being followed-up during the 3 years or until death, whichever will occur first. Data collection is expected to be completed (final follow-up of the last patient) in June 2021. This manuscript has been prepared following the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

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Contributors JMR-C and VR drafted the manuscript, contributed in the design and conduct of the study. JMR-C, FM, MAE-P, JG, VV and VR contributed in the data acquisition. FM and GYHL made critical revisions. All authors have read and approved the final version of the manuscript.

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