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Persistence to rivaroxaban therapy for stroke prevention in clinical practice in Italy: Rationale and design of the RITMUS-AF prospective observational cohort study

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ABSTRACT

Background: Non-valvular atrial fibrillation (NVAF) is a cardiac rhythm disturbance that increases the risk of stroke and is highly prevalent in Europe and Italy, increasingly with advancing age. Oral anticoagulation is a key component of stroke prevention in patients with NVAF, yet withdrawal or interruption of anticoagulation may transiently increase the risk of embolic events. Treatment persistence to anticoagulation is an important metric but one that is not well studied in patients with NVAF in Italy. The RITMUS-AF study aims to evaluate the persistence with rivaroxaban treatment for stroke prevention in patients with NVAF in Italy.

Methods: RITMUS-AF is a prospective, observational cohort study of patients with NVAF in hospital cardiology departments with a non–vitamin K antagonist oral anticoagulant surveillance program across all 20 regions of Italy. The study population comprises consecutively screened, consenting patients with NVAF naïve to and newly treated with rivaroxaban for stroke prevention in routine clinical practice. The target enrollment is 800 patients; each patient will be followed for a maximum duration of 24 months. The primary endpoint is the proportion of patients who discontinue rivaroxaban treatment. Secondary endpoints are reasons for rivaroxaban discontinuation, dose changes and reasons for changes, switches to alternative therapies and the reasons for these decisions, and self-reported adherence. Data analyses will be exploratory and descriptive.

Conclusion: RITMUS-AF will help to address the limited data in Italian clinical practice on treatment persistence and reasons for drug interruptions in patients with NVAF on rivaroxaban.

1. Introduction

Non-valvular atrial fibrillation (NVAF) is a frequently diagnosed cardiac rhythm disturbance responsible for an increased risk of stroke and mortality.[1–4] It has a high prevalence, particularly in older individuals.[3,5,6] The prevalence of NVAF in Italy for those aged 65 years and older is estimated at around 7.3% (8.6% in men and 6.2% in women), rising to 16.1% in individuals older than 85 years;[7] this is reflective of the broader European landscape.[8]

NVAF increases the risk of stroke five-fold,[2] with an annual incidence of stroke of around 4%, although this varies significantly with age and underlying risk factors.[9] Stroke is a potentially severe consequence of NVAF and a leading cause of death and disability, with an estimated annual incidence that is similar in Europe and the Italian population.[1,10,11]

Oral anticoagulants (OACs) substantially reduce the risk of stroke in patients with NVAF and represent a cornerstone of the management of NVAF.[2,12–17] However, when OAC therapy is withdrawn, patients may be at an increased risk of stroke because of a prothrombotic rebound state.[17–21] In addition, when switching between anticoagulants, there is a potentially increased risk of bleeding during the transition, with any switch requiring a considered approach accounting for the pharmacokinetics and pharmacodynamics of both the current and future regimens.[22]

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As a result of these potentially increased risks, treatment continuity and patient adherence to OACs play a central role in stroke prevention. Non-persistence has long been a concern for patients with NVAF receiving OACs, with high rates of discontinuation (approximately 50%) and treatment interruption (12%) reported in the first year of treatment with a vitamin K antagonist.[23,24] Non–vitamin K antagonist oral anticoagulants (NOACs) had lower, but still notable, 1-year discontinuation (approximately 20%) and non-adherence (approximately 35%) rates.[25–29]

Limited information exists on the number of patients with NVAF stopping or changing treatment with anticoagulants, including rivaroxaban, and the underlying reasons for treatment changes. Although the Italian National Health System requires an online therapeutic plan to be recorded for patients with NVAF who are treated with a NOAC, no data on treatment persistence and non-adherence with respect to rivaroxaban or other NOACs are captured.

1.1. Study aims and objectives

The prospective, observational RITMUS-AF cohort study aims to investigate how many patients with NVAF change or discontinue rivaroxaban therapy in routine clinical practice in Italy and establish the reasons for these treatment decisions. The primary objective of this study is to evaluate the persistence of rivaroxaban treatment for prevention of stroke and non-central nervous system (CNS) systemic embolism in patients with NVAF. The secondary objective is to collect data on discontinuation of rivaroxaban therapy, dose changes, switches to other therapies, and patient adherence.

2. Methods

2.1. Study design

RITMUS-AF is a prospective, multicenter, observational cohort study in patients with confirmed NVAF who are newly treated with rivaroxaban to prevent stroke or non-CNS systemic embolism (Fig. 1). This study has been registered at ClinicalTrials.gov (NCT04174859).

2.2. Patient population, enrollment, and follow-up

The study population comprises eligible patients with NVAF aged at least 18 years who are new users of rivaroxaban, naïve or non-naïve to treatment with OACs, and have provided informed consent. Patients eligible for treatment with, and who are naïve to, rivaroxaban for the prevention of stroke or systemic embolism will be screened consecutively and enrolled according to inclusion and exclusion criteria (Table 1). No further selection criteria will be applied.

The study is based in hospital cardiology departments with a NOAC surveillance program in place, as per the requirements of the Italian National Health System. This setting is reflective of the clinical environment in which most patients with NVAF are managed in Italy. Study sites are evenly distributed throughout all 20 regions of Italy.

The enrollment target was 800 patients, and enrollment was completed on September 30, 2021. A total of 815 patients were enrolled in this study. The study start date was December 1, 2019, with final data collection planned for approximately 48 months from the date of first patient enrollment, currently anticipated to be September 2023, with study completion date anticipated to be March 2024. Follow-up during treatment with rivaroxaban will last until the end of data collection, up to a maximum of 24 months for each patient. Patients who elect to withdraw will not be replaced.

Table 1
Study eligibility criteria.

Inclusion criteria	Exclusion criteria
At least 18 years of age	Medical history of heart valve replacement
Diagnosed with NVAF	Patient participation in an investigational program with interventions outside of routine clinical practice
New user to rivaroxaban; naïve or non-naïve to treatment with oral anticoagulant	
Decision taken to initiate treatment with rivaroxaban per routine clinical practice for prevention of stroke and non-CNS systemic embolism	
Informed consent provided	

CNS, central nervous system; NVAF, non-valvular atrial fibrillation.

2.3. Medication

Rivaroxaban will be prescribed in accordance with its marketing authorization in Italy, with all treatment decisions made by the prescribing physician. Withdrawal from this study is independent of underlying therapy decisions and will not influence a participant's medical care.

2.4. Data collection and management

During the study period, visits will be performed as part of routine clinical practice and will be documented in an electronic case report form. The investigators will be asked to collect data during routine clinical consultations, which are anticipated to occur in person approximately once per year (at months 12 and 24) and during telephone contacts at regular intervals of approximately months 4, 8, 16, and 20. These follow-up visits will be performed per routine clinical practice and therefore should not influence patient adherence or persistence on rivaroxaban treatment. At month 24, or earlier if the patient exits the study for any reason, the end of observation will be documented in the electronic case report form. The patients' medical charts will be the data source, which will be updated by the treating physician at each visit. Variables collected will include demographics, vital signs, disease history, history of NVAF treatment, laboratory data, status of rivaroxaban treatment, and adherence. All medication taken in addition to rivaroxaban for any indication, either initiated prior to study start or during the study, will be documented. At visits performed for

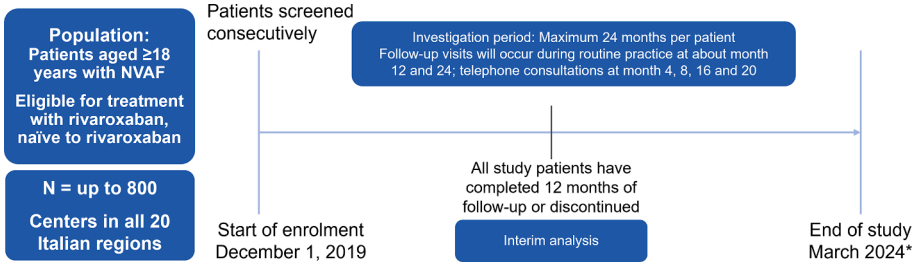

Fig. 1. Study Design. *Predicted. NVAF, non-valvular atrial fibrillation.

months 12 and 24, patients will be asked to complete the Morisky questionnaire.[30–32] Data will be managed by a contract research organization responsible for the electronic data-capturing system that includes the electronic case report form.

2.5. Study oversight and conduct

Given the observational nature of the RITMUS-AF study, no additional diagnostic or monitoring process on top of current clinical practice will be required for participation or during the study.

Documented central approval from each coordinating site's Institutional Review Board or Ethics Committee will be obtained. Informed, written consent will be obtained from each patient before the documentation of any data. The investigator must have the Institutional Review Board or Ethics Committee's written approval or favorable opinion of the informed consent form, data privacy form, Morisky questionnaire,[30–32] and any other documentation that will be provided to patients, prior to the beginning of observation.

Relevant guidelines and regulations, including those of the European Medicines Agency, Italian Regulatory Agency, European Federation of Pharmaceutical Industries and Associations, and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, as well as guidelines on good pharmacovigilance practices, will be followed during the conduct of the study. The International Conference on Harmonisation Good Clinical Practice guidelines will be adhered to.

During the study, in line with the Quality Review Plan in place for the study, telephone interviews and on-site quality review visits will be carried out randomly to verify compliance with study protocols and ensure the quality of the study.

2.6. Study endpoints

The primary endpoint is the proportion of patients who discontinue rivaroxaban treatment, defined as the duration of time from entry into the study until permanent discontinuation of therapy during a maximum follow-up period of 24 months. The secondary endpoints are reasons for discontinuation of rivaroxaban therapy, dose changes and reasons for dose changes, switching to another therapy and reasons for this decision, and self-reported adherence to rivaroxaban therapy (based on the Morisky questionnaire).[30–32]

2.7. Statistical analyses

Statistical analyses will be exploratory and descriptive, with no hypothesis testing. All variables will be analyzed descriptively with appropriate statistical methods: categoric variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e., mean, standard deviation, minimum, median, quartiles, and maximum).

The target sample size of 800 patients was based on the feasibility of the sites and the ability to fulfill the objective of the study, which is to assess persistence to rivaroxaban treatment for prevention of stroke and non-CNS systemic embolism in patients with NVAF at 12 and 24 months after study entry. Table 2 shows the limits of confidence depending on the frequency (%) of rivaroxaban discontinuation at 24 months from study entry based on a sample size of 800 patients.

Patients who die, withdraw informed consent, or are lost to follow-up without information on treatment status will be censored at that specific date or the last date of follow-up contact. The Kaplan–Meier product limit method will be used to estimate time to rivaroxaban discontinuation. The rate of treatment discontinuation will be shown as the number of permanent discontinuation events per 100 patient-years. Total treatment time with rivaroxaban will be calculated as the sum of days from rivaroxaban initiation until permanent discontinuation.

The analysis will include all enrolled patients who received at least one dose of rivaroxaban. Results of the primary and secondary endpoints will be stratified by age (<75 yrs vs ≥ 75 yrs), diabetes (yes vs no) and prior oral anticoagulant treatment (naïve or non-naïve patients). Results will be shown for additional subgroups where sufficient patient numbers are available. One interim analysis will be performed when all patients recruited into the study either have completed 12 months of follow-up or have discontinued study treatment before 12 months.

Table 2
Confidence in sample size regarding discontinuation frequency.

Patients with NVAF who discontinued rivaroxaban within 24 months from study entry (%)	50	20
Standard error (%)	1.77	1.41
95% CI	46.5–53.5	17.2–22.8

CI, confidence interval; NVAF, non-valvular atrial fibrillation.

3. Discussion

Stroke is a frequently encountered clinical consequence of NVAF, carrying significant risks of both disability and death.[5,10,11] Although prophylactic treatment with OACs is an effective method for reducing the risk of stroke, changes to a patient's treatment regimen may increase the risk of stroke or bleeding and thus require careful management.[17–22] Discontinuation, switching, and non-adherence are frequently encountered in patients with NVAF.[23–29] Despite this, in Italy, there is a limited body of work exploring the rate at which patients stop or change their anticoagulant regimen and the underlying reasons. RITMUS-AF is designed to evaluate the rate of discontinuation with rivaroxaban, to explore the reasons for discontinuation, and to establish which therapies patients switch to in clinical practice in Italy. This study will complement the limited number of previous estimates of treatment persistence in Italy by including patients from additional regions across the country, as well as endpoints that have not yet been explored in Italy.

3.1. Strengths of RITMUS-AF

The present study has several strengths. Because of its prospective study design, RITMUS-AF can capture more complete information on clinically relevant aspects of treatment persistence to rivaroxaban than non-prospective studies, which are limited by the parameters captured in the source data. RITMUS-AF includes centers from every region of Italy; therefore, it will generate data that are representative of routine clinical practice across the country. Another important strength is that the reasons for rivaroxaban discontinuation will be captured; this information is lacking in most other studies on this topic, yet it is highly important to understand. Gaining this knowledge may support clinicians in improving the care of their patients. The follow-up period that covers the first 2 years of rivaroxaban treatment should provide an overview of the temporal patterns of discontinuation, and the consecutive screening and enrollment of patients will reduce the risk of selection bias. In Italy, it is mandatory to record each treatment on a web-based therapeutic plan to prescribe NOACs according to the criteria for appropriate use from international guidelines and the summary of product information.

3.2. Limitations of RITMUS-AF

RITMUS-AF is an observational study, so certain limitations are expected: there is a possibility of selection bias, although consecutive screening will mitigate this to some extent, and the availability of medical history data may be limited. In addition, it is possible that some patients will be lost to follow-up, and their treatment status will remain unknown. Adherence will be based on a validated questionnaire; however, recall bias may reduce the accuracy of this self-reported measure. Furthermore, it is possible that regular telephone follow-up may potentially influence patient adherence and persistence on treatment,

however, we expect this effect to be minimal. Because there is no control group in this study, any reasons for discontinuation that are reported may not be attributable to therapy alone, and, as such, causal conclusions should not be drawn. From a statistical perspective, there is no control for multiplicity between subgroups, and because of the potential for non-controlled error, *p*–values should be interpreted as landmark analysis only. The study was conducted in the COVID-19 pandemic era, resulting in a reduction in the number of potentially eligible patients.

4. Conclusion

RITMUS-AF will provide important insights into the management of patients receiving rivaroxaban therapy appropriately prescribed for stroke prevention in those with NVAF. This study will help to address the scarcity of data on the discontinuation of and persistence to rivaroxaban in real-world clinical practice, as well as the underlying reasons for changes in treatment. RITMUS-AF could ultimately inform strategies to improve treatment persistence in patients with NVAF in Italy by providing insight into clinical scenarios leading to changes in anticoagulation therapy that may increase the risk of stroke and bleeding. Future studies could evaluate potential predictors of discontinuation in clinical practice and further investigate causal relationships behind any trends and reasons for discontinuation identified by RITMUS-AF. Discontinuation and persistence could also be further investigated in a long-term study beyond 2 years, or in any subgroups of interest that did not have sufficient patient numbers for analysis in RITMUS-AF, or in other countries where these aspects of stroke prevention have not yet been satisfactorily explored.

Author contributions

All authors were involved with the development and review of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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