AIHEMAF - P

“An Innovative Healthcare Model for AF Patients”

Non-profit observational study on the role of the community pharmacist and services pharmacy in the case management of patients suffering from atrial fibrillation and being treated with new generation oral anticoagulants

PROTOCOL

Version n. 3 - 05/10/2021

PAGE SIGNED BY PROMOTERS

Approved by:

dr. Raffaele La Regina

I, the undersigned Raffaele La Regina, declare that I have read this study protocol and accept the procedures. I undertake to conduct the study according to the ethical principles expressed in the Declaration of Helsinki, as amended, and in the Good Clinical Practice - GCP.

Any deviation from the study procedures will take place only if necessary, in order to safeguard the health and well-being of patients.

I agree to personally conduct or supervise the study.

I also declare that my study collaborators will have access to the study protocol and its amendments and that they are aware of their obligations.

Dr. Raffaele La Regina

Study Coordinator

Date 14.06.2021 *Signature*

KEY STAFF

Study Coordinator	**Dr. Raffaele La Regina**

Researchers

Study Coordinator of the observational study is Dr. Raffaele La Regina, community pharmacist at Farmacia La Regina s.r.l., located in San Rufo (SA).

The study is promoted by the same in collaboration with:

- Istituto Superiore di Sanità – Centro Nazionale per la telemedicina e le nuove tecnologie assistenziali
- Università degli Studi di Brescia
- Nova Biomedical Italia s.r.l.
- HTN – Health Telematic Network S.r.l.
- Centro Studi Federfarma

Conflict of interest

The promoter of the study declares that, in the period between the two years preceding the start of the study and the end of the same, there was no conflict of interest. The subjects involved were able to collaborate for teaching, training and non-profit research activities.

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1. Introduction

Title of the study

AIHEMAF – P "An Innovative Healthcare Model for AF Patients"

Non-profit observational study on the role of the community pharmacist and services pharmacy in the case management of patients suffering from atrial fibrillation and being treated with new generation oral anticoagulants.

1.1 Study background and rationale

Atrial fibrillation is one of the most common cardiac arrhythmias, from which, in Italy, more than a million people are affected and estimates speak of an increase of up to 70% in the coming years. Due to its ability to increase the thrombo-embolic risk, the affected people are subjected to anticoagulant and antiarrhythmic pharmacological interventions in order to protect the patient from highly disabling events such as cerebral stroke or other arterial embolisms.

However, these pharmacological therapies require a dynamic approach over time, as the choice of active ingredients and the relative dosages depend on the patient's overall health status and for this reason it is important that he adheres to the monitoring plan, prepared by the Specialist in Cardiology, so that therapeutic appropriateness is always guaranteed.

In daily clinical practice, the follow-up activities, defined by the guidelines of the European Society of Cardiology (ESC), consist in the evaluation of:

- General health status
- Bleeding events and related risk
- Therapeutic adherence
- Kidney function
- Drug interactions
- Control of heart rhythm and related symptoms
- Progression of the pathology

In the recent past, these activities were carried out only and exclusively by the Specialist in Cardiology, as the only person authorized to prescribe the new oral anticoagulant drugs. Only recently, with the introduction of the AIFA 97 note, the General Practitioner was given the

opportunity to prescribe these drugs to the patient suffering from Non-Valvular Atrial Fibrillation and to carry out the necessary monitoring. Consequently, the visit to the Specialist is reduced to once a year or whenever the General Practitioner deems it appropriate.

However, the recent epidemiological emergency has highlighted the need to redesign the follow-up pathways of these patients in order to reduce interpersonal contacts today and to simplify those pathways tomorrow. In fact, nowadays, patients suffering from atrial fibrillation and on anticoagulant therapy must carry out a series of interminable steps to comply with all the activities provided for in their follow-up plan. This, as the National Health System is organized today, therefore, translates into a lose-lose scenario, due to the lack of reconciliation between the diagnostic and therapeutic activities to be carried out and the rhythms of life.

On the basis of this, it is necessary to design follow-up models, which, thanks to the territorial integration of all the care settings and the related health professionals available, allow the patient to be able to enjoy 0 km assistance models, which allow him to carry out the activities provided for in the treatment plans in the simplest and most immediate way possible in order to be able to guarantee in a timely manner the most suitable treatments for your state of health, foreseeing and preventing complications and responding effectively and efficiently to the needs emerging.

Among the health professionals available to date, that of the Community Pharmacist is little considered, which represents, due to the position in which it is located within the National Health Service, a potential that has not yet been fully exploited. In fact, he could take on the role of case manager (professional who manages one or more cases entrusted to him according to a predetermined path, such as the PDTA, in a defined space-time context) of the patient suffering from atrial fibrillation and in therapy with oral anticoagulants of new generation thanks to the capillarity on the territory, the hourly availability higher than any other territorial health facility, the health skills in its possession and what it can offer in terms of services within the so-called "services pharmacy". In this scenario, the pharmacist would not replace any of the other actors already present in the multidisciplinary care team but would integrate into it and, moreover, being already affiliated with the National Health Service, the conferral of this role would not cause a excessive cost increases, such as that which would result from hiring new staff to achieve the same goals. The involvement of community pharmacists in the case management of these patients could represent the "sustainable" key for de-hospitalization of chronic patients, which has been talked about for some time without being able to find concrete and at the same time not particularly costly solutions, and the gateway to

the National Health Service that allows them to monitor their state of health, be supported in their activities and remain connected with all the other actors in the care process.

2. Literature review

After confirming the diagnosis, the patient with non-valvular atrial fibrillation is subjected to anticoagulant and antiarrhythmic drug therapy (1-2). Usually, for this therapeutic indication, new generation oral anticoagulant drugs based on edoxaban, rivaroxaban, apixaban and dabigatran are used.

When these drugs were introduced as an alternative to the now well-known warfarin, their spread was very fast due to the non-need for continuous blood monitoring and the fewer drug-food and drug-drug interactions.

However, it soon became evident the need to develop new monitoring models, which even if with a lower frequency than those used for warfarin, would allow an evaluation over time of the therapy practiced to confirm or not the appropriateness, safety and effectiveness. In this regard, in countries where there is already a widespread use of the electronic health record, studies were immediately conducted on what could be the elements to monitor and reassess during the follow-up phase through the implementation of dedicated dashboards (3) and ad hoc protocols in order to expand the services provided by anticoagulation clinics (4).

In defining the follow-up plans for this type of patient, much attention has always been placed on renal function (5) and the related haemorrhagic consequences. In fact, people with renal insufficiency are more at risk of haemorrhagic and / or thrombo-embolic events and this risk increases over time. For this reason, a continuous reassessment of renal function is necessary to ensure that the patient is constantly given the correct dose of the anticoagulant (6).

The activity of community pharmacists is particularly useful for this purpose, as evidenced by numerous evidences in the literature. In fact, the intervention of the community pharmacist allows, thanks to continuous contact with patients and specific training received, to ensure the appropriateness, safety and effectiveness of the drug therapy practiced (7-13).

However, the involvement of community pharmacists is the result of care models that provide for the complete integration of the various actors involved. Scenarios of this type are now consolidated in various countries of the world, while in Italy they still struggle to have a full realization.

With regard to the monitoring of the disease, no innovative follow-up models have been found in the literature, which are therefore based on the classic specialist check-up visit.

3. Objectives of the study

Primary Endpoint

The primary objective of the study is to describe the implementation and outcomes of an innovative Smart Clinic model useful for the clinical and pharmacological monitoring of the patient suffering from non-valvular atrial fibrillation treated with new generation oral anticoagulants, in which a community pharmacist, adequately trained, takes on the role of case manager and the patient has the possibility to perform the checks provided in telemedicine and in self-analysis, in the services pharmacy regime, the results of which will be shared in real time with the treating physician and reference specialist of the same.

Secondary Endpoints

The secondary objectives of the study are:

- assessment of adherence to the required controls;
- assessment of the prescriptive appropriateness of the dosages and molecules used;
- assessment of adherence to prescribed therapy;
- assessment of the occurrence of pharmacological problems related to drug-drug interactions;
- assessment of the occurrence of bleeding and / or thrombo-embolic complications;
- evaluation of the acceptance by the General Practitioner and / or the Specialist in Cardiology of the reports made by the pharmacist and the subsequent actions taken;
- assessment of the economic and social impact of this model on the National Health Service and on the patient;
- assessment of the impact on quality perceived by patients in carrying out this innovative monitoring process.

4. Study Procedures

The study, whose duration will be equal to 12 months (September 2021 - August 2022), which does not include any cost for the National Health Service and for the participating patients themselves, is of the following type:

- observational,
- perspective,
- monocentric,
- no profit.

The main phases of the research project are indicated below.

Phase 1: Patient enrollment (September 2021)

In the first phase, lasting a total of one month, patients are enrolled, with the characteristics indicated below, in a number equal to 50.

Phase 2: Review, database validation and definition of Individual Care Plans (September 2021)

In September 2021 we proceed with the validation of the database and with the definition, by the general practitioners involved, of the Individual Care Plans.

Phase 3: Case Management and follow up (September 2021 - August 2022)

In the remaining months, the Case Manager follows the patients in carrying out the checks required by the guidelines in force, relating to non-valvular atrial fibrillation and concomitant anticoagulant therapy, and by the Individual Care Plan drawn up by the attending physician, in case a personalization of the path is necessary. follow-up dictated by the patient's particular clinical conditions (e.g. impaired renal function). 12-lead ECG (performed with Microtel BT electrocardiograph and reported by the HTN Srl control unit), Holter ECG (performed with Cardioline WALK400H and reported by HTN Srl) self-analysis (hemoglobin, hematocrit and creatine, performed with the Allegro device from Nova Biomedical Italia Srl) will be carried out directly in the pharmacy through the use of the equipment and reporting platforms mentioned above. The control of drug interactions will be performed using the INTERcheck Web platform of the Mario Negri IRCCS Institute for Pharmacological Research.
The follow-up agenda includes the following activities:

Timing	Attività	Note
Enlistement	General health status	
	Pharmacological Therapy	- evaluated at each therapeutic insertion
	12-lead ecg	
	Dynamic ecg sec. Holter	- if not performed within the previous 12 months - if in the FVM ecg> 90 or <60bpm during AF
	Blood chemistry tests	
	Blood pressure and heart rate	
Frequency Monthly	General health status	
	Blood pressure and heart rate	
	12-lead ecg	- if specific symptoms are reported
Quarterly frequency	Single-track ecg	
	Blood chemistry tests	- if clearance ratio creatininemia / 10 = 3
Six-monthly frequency	12-lead ecg	
	Blood chemistry tests	- if patient over 75 and patients with cl cr/10 = 6
Annual frequency	12-lead ecg	
	Dynamic ecg sec. Holter	
	Blood chemistry tests	

After each follow-up meeting, a report including all the measurements made will be sent, through a special telemedicine platform, to a cardiology specialist for an initial analysis. The latter, after a careful evaluation of the documentation received, will forward a feed-back report with any

suggestions for the treating physician and / or the reference specialist, who, based on the knowledge of the patient in question, will define the actions to be taken. .
For the requested services that cannot be carried out in the pharmacy, the pharmacist proceeds with the execution of the prescription from the General Practitioner, the booking of the examination through the CUP service and the execution of a telephone reminder service that reminds the patient when to carry out the 'examination.

5. Expected duration of the study

The study will run for 12 months, from September 2021 to August 2022.

6. Inclusion and exclusion criteria

ARRUOLABLE patients:

- age> 18 years,
- patients suffering from Non-Valvular Atrial Fibrillation and being treated with new generation oral anticoagulants;
- able to express consent to the study;
- regularly related to the trial site (Farmacia La Regina S.r.l.)
- AntiCovid19 vaccination performed

7. Case Report Form (CRF)

Electronic data collection forms are provided (Case Report Form - CRF) necessary for the collection of the patient's clinical information, together with those of an organizational and managerial nature.
The detail of the information to be collected is defined in the data collection forms.
For the purpose of a homogeneous data collection, for each patient belonging to the target population, the compilation of a form is envisaged, the structure of which generally includes the following macro-areas:

- general information about the patient (ID, sex, age, etc.);
- information relating to the family setting (spouse, children, care giver, etc.)
- proximate and distant pathological history
- drug therapy practiced

- vital signs and entry blood tests
- examinations and procedures required for follow up
- results and reports of the checks carried out during the follow-up;
- perceived quality questionnaire.

8. Sample size and statistical analysis

A simple size of 50 patients was defined for the conduct of this study.

The statistical analysis of the collected data will be developed through descriptive analysis.

The economic evaluation will be performed by comparing the costs incurred in the traditional path and the costs resulting from the application of the model under study, calculated by referring to the regional tariff where appropriate.

The assessment of the perceived quality will be carried out through a short anonymous questionnaire administered at the end of the study to all the subjects enrolled.

All categorical variables measured in this study will be expressed as absolute numbers and percentages. Continuous variables will be expressed as mean and standard deviation or median and interquartile range [IQR], depending on the normal or non-normal distribution of the data.

Differences will be analyzed by chi-square test, unpaired t-test or Mann-Whitney U test, depending on the nature of the variable.

Any difference with a $p < 0.05$ will be considered statistically significant.

9. Results expected from the study

The patient suffering from non-valvular atrial fibrillation and being treated with oral anticoagulants needs his state of health to be in a condition of equilibrium between the risk of bleeding on the one hand and the risk of thrombo-embolism on the other.
For this reason, it is important that this type of patient undergoes constant checks over time to verify that his clinical conditions are always balanced, however, the daily rhythms of life hinder full adherence to the controls.

This study by overcoming this and other critical issues, thanks to the use of the unexpressed potential of the service pharmacy (remote execution of the services provided by the follow-up paths) and of the pharmacist, as case manager, alongside medicine basic and specialized, will allow to improve the current quality of care for the type of patients examined, with a view to safety, efficacy and appropriateness of care on the one hand and sustainability on the other.

10. Ethical considerations

To protect privacy, patients in the group described above will be identified only by means of progressive numerical codes (ID).

The data will be treated with confidentiality and confidentiality and disclosed only in aggregate and anonymous form.

The protection of individuals will be guaranteed as recommended in the Oviedo Convention (Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine - April 4, 1997) and in the Declaration of Helsinki relating to ethical principles for medical research and whose aim is to provide advice to doctors and other participants in medical research.

All patients will be required to sign a written Informed Consent, with particular reference to the processing of personal data.

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