Ricerca e Formazione Clinica
QUOVADIS
Associazione Riconosciuta

MAC PROJECT - MONITORING ANTICOAGULANT THERAPY

OBSERVATIONAL STUDY

Promotor: QUOVADIS no-profit Association
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Project **MAC** - Monitoring AntiCoagulant therapy

RATIONALE

Anticoagulant drugs have been used for more than 50 years for the prevention and treatment of venous thromboembolic (VTE) and arterial pathologies with wide support of high-quality scientific evidence (randomized and double-blinded multicentre studies) to support their safety and effectiveness.

In addition to traditional medicines, administered parenterally (heparins and heparinoids) or orally (vitamin K inhibitors), some "new" oral anticoagulants (direct inhibitors of Factor Xa and IIa) have become available on the market [1,2]. The latter combine a superimposable efficacy to that of “traditional” anticoagulants to a more favourable safety profile, as demonstrated by registrative trials, and subsequently confirmed by phase 4, "real-life" studies, prospective registers, and retrospective analyses of administrative databases [3-9]. Indeed, as registrative trials usually employ strict inclusion criteria, the generalizability and reproducibility of their results need to be subsequently confirmed by "real-life" studies in a broader spectrum of patients, or better, in unselected patients. Precisely, the Regulatory Authorities (EMA, FDA, etc.) may request that post-authorization security studies (PASS, Post-Authorization Safety Studies) be conducted.
Four of such studies are currently ongoing worldwide (edoxaban: ETNA-VTE, ETNA-AF; dabigatran: GLORIA-AF), and in Europe (apixaban: CV185365) whose results, however, will only be available in a few years. Three PASS have already been published, testing rivaroxaban in different clinical settings (XAMOS, in orthopaedic patients; XANTUS in patients with non-valvular atrial fibrillation; and XALIA, in patients with venous thromboembolism) [10-16].

Unfortunately, since the registration of direct oral anticoagulants was unduly delayed in our country, the Italian population is hardly represented in the above-mentioned trials (no patients in both XANTUS and XAMOS, and only 23 patients in XALIA). Therefore, no “real-life” data on the use of direct oral anticoagulants is currently available for the Italian population. Accordingly, a

prospective data collection, carried out in unselected consecutive patients, affected by both venous thromboembolism and atrial fibrillation, is expected to provide valuable information for the specific Italian context, accounting for potential differences linked to the genetic array and the typical diet/ lifestyle. This is all the more relevant if we consider some particular groups of patients, usually excluded or poorly represented in registrative studies, such as: patients with cancer, renal failure, body weight <50 kg or morbidly obese, transplant recipients, and those receiving multiple drug-treatments, being data on potential drug interactions still pending, or not even accounted for by the most-recent EHRA 2017 recommendations.

All of the above concepts also apply to the class of antiplatelet drugs, recently enriched with several new agents, that have already been included in the most influential European and American guidelines. Despite the availability of well conducted randomized trials, real-life data are also scarce on newer antiplatelet drugs.

Anticoagulant and antiplatelet drugs available in Italy

ATC	Substance
B01AC06	ACETYLSALICYLIC ACID
B01AA07	ACENOCUMAROL
BO1AF02	APIXABAN
B01AB12	BEMIPARIN
B01AC04	CLOPIDOGREL
B01AE07	DABIGATRAN
B01AC07	DIPIRIDAMOL
B01AF03	EDOXABAN
B01AB05	ENOXAPARIN
B01AX05	FONDAPARINUX
B01AB06	NADROPARIN
B01AB07	PARNAPARIN
B01AC22	PRASUGREL
B01AX06	RIVAROXABAN
B01AC24	TICAGRELOR
B01AC05	TYCLOPIDIN
B01AA03	WARFARIN

STUDY PURPOSE

Aim of the MAC Project is to prospectively collect reliable clinical information on patients treated with anticoagulants and antiplatelet agents, regardless of the underlying disease, duration of treatment, and the type of drug used.

Our goal is to verify the efficacy and safety of anticoagulant and antiplatelet drugs in a large cohort of unselected patients belonging to the participating clinical centres, during a medium-long term follow-up period. Specifically, we will gather information on:

- clinical outcomes;
- adverse events of anticoagulant and antiplatelet drugs;
- interactions with other concomitant medications;
- risk factors;
- concurrent diseases;
- survival.

Collected data, appropriately anonymized, will be used by the centres participating in the project for scientific purposes, to standardize clinical-pathways, and to plan targeted training events.

Among the strengths of the MAC Project are:

- lack of exclusion criteria (patients / drugs / pathologies), allowing for an assessment of the so-called "real-life setting" of patients treated with anticoagulant and antiplatelet drugs, regardless of the underlying pathology, duration of treatment, and type of used drug;
- long-term follow-up, with controls at 3, 6, 12 months from inclusion, and then annually up to 5 years;
- implementation of the most commonly used risk scores (events / haemorrhage);
- secure, efficient and widely tested electronic data-collection web platform.

STUDY DESIGN

This is an Italian Multicentre, prospective, cohort study, with observational "event driven" branches (i.e.: specific observational pathways of the various clinical events that may occur), in relation to the different types of treatments used (antiplatelet agents, parenteral anticoagulants, inhibitors of vitamin K and direct oral anticoagulants).

STUDY ORGANIZATION

CLINICAL COORDINATOR OF THE STUDY

The Clinical Coordinator of the study is Dr. Cristiano Bortoluzzi, from the Azienda ULSS 3 “Serenissima” (Venice).

PROMOTER

Promoter of the project is QUOVADIS, a recognized non-profit association, based in Padua (https://quovadis-ass.it/). QUOVADIS has as its object the study and scientific research in the field of diagnostic strategies, prevention and treatment of cardiovascular diseases, diseases of the liver and gastrointestinal system and other diseases of medical and surgical interest.

SETTING

The study will be held in clinical centres, either hospital-based or outpatient clinics, experienced in the management of patients with cardiovascular diseases requiring antiplatelet or anticoagulant treatment, either on short- (e.g. superficial venous thrombosis), medium- (e.g. deep-vein thrombosis, pulmonary embolism, acute coronary syndrome, etc.), and long-term (e.g. atrial fibrillation, mechanic heart valves, secondary prevention of recurrent VTE, obstructive arterial disease of the lower limbs, etc.).

All treatment options, including the choice of anticoagulant or antiplatelet drug, the duration, and dosage variations, will be at the discretion and under the responsibility of the attending physician and of the patient, according to good clinical practice.

The drugs will not be provided by the sponsor and will be prescribed according to current standards of care and regulations.

STUDY POPULATION

Subjects of both sexes, aged 18 years or older, requiring the prescription of, or already on anticoagulant or antiplatelet treatment will be eligible for the study, irrespective of the index event, of the intended treatment duration, and of the type of drug used.

Included subjects will be followed-up prospectively up to 5 years, as per current practice and according to local, national and international guidelines.

INCLUSION CRITERIA

- Legal age (>=18 years);
- mandatory anticoagulant or antiplatelet treatment;
- ability to understand the purposes of the study, as described in the information;
- ability to express a valid informed consent;
- simultaneous participation in other non-interventional studies is allowed.

EXCLUSION CRITERIA

- none

OBSERVATIONAL PLAN

Patients included in the study will be followed-up for maximum of 5 years.
In accordance with the most recent guidelines, each investigator will be asked to evaluate each patient at 3, 6, 12 months from the event, and then annually up to 5 years, except for in the case of any new adverse event, which will require a closer time-frame observation.

The occurrence of clinically relevant end-points, either concerning the efficacy and the safety of the ongoing treatment, will be recorded at each follow-up visit, along with information on the

management of such events, and their outcome. Additionally, data on treatment compliance / adherence, and on the patients' appreciation will be evaluated by a specific score (ACTS), as long as the use of concomitant therapies.

END OF TREATMENT

The patient's observation will continue until the predicted end of the study (5 years), regardless of any temporary or permanent discontinuation of antiplatelet / anticoagulant treatment.

EARLY DISCONTINUATION OF OBSERVATION (DROP-OUT)

Every possible effort will be made to assess if patients skipping the planned visits have experienced any of the outcomes of interest for the study, making them suitable for the end-point evaluation.

PRIMARY OBJECTIVE

To collect and evaluate safety and efficacy data of antiplatelet / anticoagulant treatment in a real-life setting, regardless of the underlying pathology, and of the duration of treatment.

SECONDARY OBJECTIVE

To separately evaluate safety and efficacy of antiplatelet and anticoagulant drugs for treatment of cardiovascular diseases, specifically considering treatment duration, as follows:

- short-term (e.g. superficial venous thrombosis);
- medium-term (e.g. deep vein thrombosis, pulmonary embolism, etc.);
- long-term (e.g. atrial fibrillation, prevention of recurrent VTE or long-term treatment of recurrent VTE, peripheral arterial obstructive disease, etc.).

SAFETY MEASURES

Treatment safety will be evaluated by the following outcomes:

- incidence of major bleeding;
- incidence of clinically relevant non-major bleeding;
- incidence of minor bleeding;
- incidence of serious adverse events;

- incidence of mortality (VTE-related, cardiovascular, and all-cause).

Major bleeding will be classified according to the ISTH definitions [17], as follows:

- fatal bleeding;
- bleeding associated with haemoglobin drop ≥ 2 gr/dL;
- bleeding needing transfusion of ≥ 2 units of PRBC;
- bleeding occurring in a critical area or organ:
  - intracranial,
  - spinal,
  - intraocular,
  - pericardial,
  - intra-articular,
  - intra-muscular with compartment syndrome,
  - retroperitoneal.

Clinically relevant non-major bleeding [18] is defined a clinically evident event, which does not meet the criteria for major bleeding, but requires medical treatment, such as:

- new hospitalization;
- delayed discharge in case of a hospitalized patient;
- laboratory evaluation;
- imaging studies;
- invasive diagnostic procedures (endoscopy, cystoscopy, bronchoscopy, etc.);
- nasal tamponade;
- manual compression;
- eco-guided compression or embolization of post-procedural pseudo-aneurysm;
- surgical intervention;
- temporary or permanent discontinuation of the antiplatelet / anticoagulant treatment, or change of concomitant therapy on the advice of a doctor.

EFFICACY MEASURES

Treatment effectiveness will be evaluated by the following outcomes:

- incidence of symptomatic recurrent VTE;
- incidence of symptomatic recurrent VTE in the various treatment subgroups;
- incidence of stroke (ischemic and haemorrhagic);
- incidence of systemic embolic events;
- number of hospital admissions related to cardio-vascular (either venous or arterial) disease;
- incidence of post-thrombotic syndrome.

INFORMATION COLLECTED

The information collected will concern:

- risk factors for venous thromboembolism, and atherosclerosis;
- calculation of thromboembolic and haemorrhagic risk-scores (normally used in clinical practice);
- comorbidities;
- anticoagulant / antiplatelet treatment in progress;
- concurrent treatments;
- clinical events;
- adverse events;
- survival;
- possible causes of death;

Further detail of the nature and type of data that will be prospectively collected is available from the document describing the eCRF (clinical data collection sheets), attached to this protocol.

ELECTRONIC DATA CAPTURE

All data will be recorded on an "Electronic Data Capture" (EDC) system, based on the "Research Electronic Data Capture" on-line platform (REDCap, produced and distributed by Vanderbilt University and "REDCap Consortium").

DATA PROTECTION

Personal data of enrolled subjects will be treated with the maximum confidentiality, according to the terms of the Italian law (D.L. 211/2003 and subsequent amendments and additions) and GDPR (REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016). In particular, the personal data of the subjects will be known only to the principal Investigator and his collaborators who follow the patient and collect consent to the treatment. Each enlisted subject will be distinguished by a unique numeric identifier.

Exercise of rights: in compliance with art. 13 of the GDPR, the retention period for personal data will be 10 years and may be transferred to an EU state. The enrolled person will have the right to ask the data controller to access and correct the personal data concerning him/her.

At any time, without giving any justification, he/she may revoke the consent to the processing of data, request their deletion or limitation of treatment or oppose their treatment, communicating this intention in writing to the Clinical Trial Centre study doctor. In this case, he/she will not be able to continue participating in the study. Furthermore, he/she will be entitled to the portability of data concerning him/her and to propose a complaint to the Supervisory Authority (Garante per la protezione dei dati personali, https://www.garanteprivacy.it).

The use and maintenance of the REDCap platform are guaranteed by an administrator who manages the users privileges with a flexible and granular authorization system. REDCap applies the permissions granted to each user who connects via a web browser and the protocol with SSL encryption (using a personal "username" and "password"), activating certain functions, tabs, links and buttons according to the privileges granted and to the group / centre.

REDCap allows a complete "audit" of the procedures performed by each user, by logging all operations on the data, including viewing and exporting. The operational control log (log) stores the date, time and the user performing the operation, allowing a complete overhaul and remote monitoring of the clinical study if necessary.

All users accessing the EDC platform (the investigators, the members of their staff, and the staff of the Promoter) must complete a training event, in order to increase the reliability, quality and integrity of the data recorded in the EDC platform.
REDCap implementations allow compliance with the most common industry standards and EMA requirements (GCP, Privacy-IT: D.L. 211/2003 and subsequent amendments and additions, GDPR and FDA (21-CFR2-Part 11).

Every effort is made to ensure compliance with the "GCDMP" guidelines (Good Clinical Data Management Practice, published by the Society for Clinical Data Management, 2013); especially concerning the reliability, quality, integrity and security of data registered in the EDC platform, both from a procedural and IT point of view using "state of the art" solutions.

SAMPLE SIZE

According to a recent paper published on the BMJ (comparative safety of direct oral anticoagulants and warfarin in venous thromboembolism: multicentre, population based, observational study [19]), the expected average frequency of serious adverse events (death, major bleeding) for the various anticoagulant treatments is around 1.7%; and that of other bleeding events is around 2.2% at 60 days (early events). By recruiting 4000 subjects over 5 years, we estimate to obtain a 95% confidence interval around the observed value for serious events of 0.4% and of 0.5% for other bleedings.
Hypothesizing that each study centre would recruit some 270 patients per year on average, at least 5 centres would be required to enrol the required patient sample within the first 3 years with at least 2 years of follow-up, for a total planned 5-year time-frame. If necessary, the total number of patients per Centre and the number of Centres may be adjusted to achieve the recruitment objectives.

STATISTICAL CONSIDERATIONS

All variables will be analysed descriptively with the appropriate statistical methods:

- for categorical variables, by means of frequency tables;

- for continuous variables, with sample statistics (i.e. average, median, standard deviation, minimum and maximum value, 25th and 75th Quartile).

All statistical tests will be 2-tailed, and set at a significance level of 0.05, unless otherwise specified.
Primary and secondary efficacy and safety analyses will be performed on the intention-to-treat (ITT) population, which will include all subjects enrolled in the study.
Subjects completing an uneventful follow-up, or dropping-out without experiencing events, will be censored, participating to the risk estimate with the available observation period.

PRIMARY ANALYSIS

For the primary analysis, only the first safety and efficacy events occurring will be counted.
The magnitude of the risk estimate will be assessed by Cox regression for proportional risks, using as covariates: age at the start of follow-up, gender, type and compliance to treatment, and any additional risk factor found to be significantly associated with the end-points at the univariate analysis. Putative additional risk factors entered in the univariate analysis will be: obesity, varicose veins, cancer, standing or prolonged immobilization, recent surgery, severe infections, previous VTE, thrombophilia, chronic heart failure NYHA III-IV, and use of contraceptives.
All variables included in the model will be tested for the assumption of risks proportionality with the usual graphic method. The subset of variables significantly associated with the occurrence of safety and efficacy endpoints will be chosen by the Wald method, employing a "forward stepwise" approach. Both unadjusted and adjusted cumulative proportions of event-free subjects during follow-up will be described by the Kaplan-Meier method.

SECONDARY ANALYSIS

For the secondary analysis a cumulative time-to-event approach will be used. Differences between various types of treatment will be tested by the log-rank test.

FINAL REPORT AND PUBLICATION OF RESULTS

The results of the study will be reported in an integrated statistical and clinical final report, compliant with the GCP-ICH guidelines. The contents of the report will be approved jointly by the Clinical Coordinator of the study and the Promoter.

The same joint approval will apply to the contents of the first publication and of the first public presentation of the results of the study, which the Promoter commits itself to carry out in any case. Any secondary publications and / or presentations will be subject to prior notification, by the Coordinator to the Promoter or vice-versa, with the faculty of comment from the recipient.

ETHICAL ASPECTS

The protocol was submitted to the Ethics Committee of the Coordinating Centre and by the ECs of the various participating Clinical Centres. Consent to participate in the study and processing of sensitive personal data from participating subjects will be collected.

The latest revision (2013) of the Helsinki Declaration and the Oviedo declaration will form the basis for the ethical conduct of the study.

According to the Decree of the Ministry of Health 17.12.2004, considering that both the Promoter and the data owner are represented by a non-profit association, and that the objective of the project is to achieve improvements in clinical practice, the MAC project can be labelled as “no-profit”.

The study protocol was designed, and will be conducted, to ensure adherence to the principles and procedures of Good Clinical Practice, and to comply with the Italian law, as described in the following documents, and accepted by the Investigators of the study:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice (http://www.ich.org/products/guidelines.html)
2. EU Regulation n. 536/2014 on the clinical trial of medicinal products for human use.
3. D.L. n. 211, del 24.6.2003.
4. D.L. n. 200, del 6.11.2007.
5. Determina AIFA 20.09.2012.
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Flow Chart

MAC Project Flow Chart	**Base Line**	**FU1**	**FU2**	**FU3**	**FU4 to FU7**	**FU addictional**
Time point (months)	0	3	6	12	every 12 months (up to 5th year)	in case of recurrence
Date	x	x	x	x	x	x
Eligibility	x					
Demographic data	x					
Visit						
Vital signs	x	x	x	x	x	x
VTE and other related diseases						
VTE anamnesis and current status: diagnosis and therapy	x					
VTE recurrence: diagnosis and therapy		x	x	x	x	x
General anamnesis	x					
Concurrent therapies	x	x	x	x	x	x
Laboratory data (if relevant)	x	x	x	x	x	x
Other related VTE clinical events	x	x	x	x	x	x
More information on concomitant diseases	x					
Villalta Score		x	x	x	x	x
Hospitalizations		x	x	x	x	x
Related VTE therapies	x					
Anti-aggregating therapy (history and current)	x	x	x	x	x	x
Anti-coagulant therapy (history and current)	x	x	x	x	x	x
ACTS score	x	x	x	x	x	x
ADR reporting	x	x	x	x	x	x
Termination of treatment (if applicable)	x	x	x	x	x	x

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