Management of Antithrombotic Therapy in Patients with atrial fibrillation or Developing Atrial Fibrillation During Hospitalization for PCI (MATADOR-PCI)

Protocollo N° K20

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Co-Chairmen: Andrea Di Lenarda, Andrea Rubboli, Michele M Gulizia

Study promoted by Fondazione per il Tuo cuore Onlus
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature page for Study Chairman and Co-Chairmen</td>
<td>3</td>
</tr>
<tr>
<td>Signature page for Principal investigator</td>
<td>4</td>
</tr>
<tr>
<td>1.0 PROTOCOL SYNOPSIS</td>
<td>5</td>
</tr>
<tr>
<td>2.0 LIST OF ABBREVIATIONS</td>
<td>6</td>
</tr>
<tr>
<td>3.0 INTRODUCTION</td>
<td>7</td>
</tr>
<tr>
<td>4.0 STUDY DESIGN &amp; OBJECTIVES</td>
<td>8</td>
</tr>
<tr>
<td>4.1 Study overview</td>
<td>8</td>
</tr>
<tr>
<td>4.2 Inclusion and exclusion criteria</td>
<td>9</td>
</tr>
<tr>
<td>4.3 Study objectives and endpoints</td>
<td>9</td>
</tr>
<tr>
<td>4.4 Sample size and statistical analysis</td>
<td>10</td>
</tr>
<tr>
<td>5.0 DATA COLLECTION AND MONITORING</td>
<td>11</td>
</tr>
<tr>
<td>6.0 STUDY ORGANIZATION</td>
<td>12</td>
</tr>
<tr>
<td>7.0 SAFETY</td>
<td>13</td>
</tr>
<tr>
<td>8.0 PUBLICATION POLICY</td>
<td>13</td>
</tr>
<tr>
<td>9.0 ETHICAL ISSUES</td>
<td>14</td>
</tr>
<tr>
<td>10.0 REFERENCES</td>
<td>15</td>
</tr>
</tbody>
</table>
Signature page for Study Chairman and Co-Chairmen

Protocol:
MATADOR-PCI

Approved by:

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Signature Page for Principal Investigator

Protocol:
MATADOR-PCI

I have read this protocol and I agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the current regulations.

Site

Principal Investigator ______________ Signature ______________ Date ______________
# 1.0 PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th>Title</th>
<th>MATADOR-PCI (Management of Antithrombotic TherApY in Patients with atrial fibrillation or DevelOping AtRial Fibrillation During Hospitalization for PCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research description</td>
<td>Prospective, multicenter, observational, nationwide survey</td>
</tr>
<tr>
<td>Promoter</td>
<td>Fondazione per il Tuo cuore – HCF Onlus</td>
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<tr>
<td>Participants</td>
<td>All consecutive patients with a confirmed diagnosis of acute coronary syndrome (ACS) treated with a percutaneous coronary intervention (PCI) and stent implantation who present atrial fibrillation (AF) at admission or during hospital stay, before or after stent implantation</td>
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<tr>
<td>Enrollment</td>
<td>About 12 months in each center</td>
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<tr>
<td>Follow-up</td>
<td>Clinical Follow-up at 6 months. All serious adverse events will be recorded; major outcomes (including cardiac and all-cause deaths and hospitalizations for major bleeding, non-fatal stroke, systemic embolism, transient ischaemic attack, MI recurrence) will be assessed and reported by Investigators.</td>
</tr>
<tr>
<td>Study objectives</td>
<td>The main objective is to obtain a complete national data set in order to improve our knowledge on antithrombotic strategies employed during hospitalization in ACS patients treated with PCI and with AF (at hospital admission or during the hospital stay, before or after stent implantation).</td>
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<td>Estimated number of patients</td>
<td>The estimated number of patients is 500, enrolled in about 100 Italian CCUs in 1 year. This number is based on previous registries endorsed by ANMCO</td>
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</tbody>
</table>
2.0 LIST OF ABBREVIATIONS

ACS: Acute coronary syndrome
AF: Atrial fibrillation
ADR: Adverse Drug Reactions
ANMCO: Associazione Nazionale Medici Cardiologi Ospedalieri
CABG: coronary artery bypass grafting
CCU: cardiology intensive care units
CRF: Case report form
DAPT: dual antiplatelet therapy
MATADOR PCI: Management of Antithrombotic Therapy in Patients with atrial fibrillation or Developing AtRial Fibrillation During Hospitalization for PCI
MI: Myocardial infarction
NOAC: non-VKA oral anticoagulants
NSTE-ACS: Non-ST-elevation acute coronary syndrome
PCI: percutaneous coronary intervention
SADR: Serious Adverse Drug Reaction
STEMI: ST-elevation myocardial infarction
VKA: vitamin K antagonists
3.0 INTRODUCTION

Atrial fibrillation (AF), one of the most common cardiovascular conditions worldwide, confers a substantial risk of mortality and morbidity mainly from stroke and peripheral thrombo-embolism (1-3). Stroke prevention is central to the management of AF patients, with the current guidelines recommending oral anticoagulation (OAC) using well-controlled adjusted dose vitamin K antagonists (VKAs, e.g. warfarin) or non-VKA oral anticoagulants (NOACs, previously referred to as new or novel OACs) for patients with AF and ≥1 stroke risk factor(s). In everyday clinical practice, over 80% of all patients with AF have an indication for OAC, and vascular disease coexists in ~30% of them (1-3).

Acute coronary syndromes (ACS), including unstable angina/non-ST segment elevation myocardial infarction (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI), constitute another cardiovascular syndrome with associated risks of mortality and morbidity from myocardial infarction (MI), heart failure, and life-threatening ventricular arrhythmias. ACS are a potent risk factor for AF, with new onset AF occurring in up to 1 in every 5 patients hospitalized with an ACS (4-9). A particular challenge in terms of management and antithrombotic treatment are patients who develop AF during an ACS episode, especially since such patients are at high risk for short-term clinical events (4-9). As with the use of several antithrombotic drugs, clinicians need to balance the risks of ischaemic stroke and thrombo-embolism, recurrent cardiac ischaemia or MI and/or stent thrombosis, and bleeding (10-13).

Despite its relatively frequent occurrence and the many etiologic factors involved in its pathogenetic condition, the frequency and prognostic significance of AF complicating ACS remain unclear. Several studies have shown increased hospital and long-term death rates associated with AF (4-9). On the other hand, many studies have shown no
independent effect of this rhythm disturbance on in-hospital or death after discharge after controlling for other variables of prognostic importance, including hemodynamic dysfunction and arrhythmic abnormalities. Nevertheless, prior investigations examining the magnitude of death associated with AF complicating ACS have been limited by small sample sizes, short duration of follow-up periods, and/or inclusion of less generalizable patient populations (4-9). Surprisingly, very few studies have been carried out in the post-thrombolytic era and from a more generalizable cardiology-wide perspective. In addition, there are limited data available, particularly from a representative population-based perspective describing recent pharmacological and non-pharmacological management and clinical event rates associated with AF complicating ACS in the era of novel treatment strategies (in both AF and ACS) and high coronary reperfusion rates.

In addition, when these patients have to undergo percutaneous coronary intervention (PCI) the peri-procedural, in-hospital and post-discharge pharmacologic management appears even more complex in terms of treatment strategies decisions (10-32).

This registry will assess the current in-hospital management and clinical events at 6 months of consecutive patients admitted in Italian cardiology intensive care units (CCUs) for an ACS treated invasively with PCI and stent implantation who present AF at admission or during hospital stay, before or after stent implantation.

4.0 STUDY DESIGN & OBJECTIVES

4.1 Study overview

The MATADOR-PCI (Management of Antithrombotic Therapy in Patients with atrial fibrillation or Developing Atrial Fibrillation During Hospitalization for PCI) is a prospective, multicenter, observational survey of consecutive patients with a confirmed
diagnosis of ACS treated with a PCI with a stent placement who present AF at admission or during hospital stay, before or after stent implantation. Patients will be enrolled in about 100 Italian CCUs during a period of about 12 months.

4.2 Inclusion and exclusion criteria

All consecutive ACS patients treated with PCI with stent implantation who present AF at admission or during hospital stay, before or after stent implantation, will be included.

Patients admitted with a diagnosis of ACS at the time of enrolment but not confirmed during hospitalization, ACS treated medically or with PCI but without stent implantation, and those not giving informed consent will be excluded from the survey.

4.3 Study objectives and endpoints

- The primary objective is to obtain a complete data set in order to improve our knowledge on clinical epidemiology, management, and specifically the antithrombotic strategies (IV or oral antiplatelet and/or anticoagulation therapies and their combination) commonly employed during hospitalization and at discharge in ACS patients with AF undergoing PCI with stent implantation;

- Secondary objectives are: a) To evaluate the use and persistence at 6 months of pharmacological therapies prescribed at discharge in these patients; b) their major clinical outcome (including cardiac and all-cause deaths and major bleeding, non-fatal stroke, systemic embolism, transient ischaemic attack, MI recurrence) during index hospital admission and at 6 months and c) to compare the management and outcomes of ACS patients developing AF before or after stent implantation.
4.4 Sample size and statistical analysis

All Italian Hospitals with a CCU and a cath lab performing PCI (n~250) will be invited to participate in this study. The expectation is that about 100 centers well representing the country in terms of geographical distribution and well balanced in terms of complexity (PCI volume, cardiac surgery, etc.) will accept to participate. Considering the number of ACS patients treated with PCI and with AF at the time of hospital admission (about 4%) or developing AF during the index hospitalization (approximately 4%) enrolled in previous snapshots performed in Italy and endorsed by ANMCO in the last 15 years (from BLITZ-1 to EYESHOT) (33,34), it is estimated to hospitalize in 1 year in 100 CCUs about 10,000 ACS patients, 6,500 treated with PCI, enrolling approximately 500 patients with AF (8% of ACS patients undergoing PCI).

Considering the explorative and observational nature of the study, no formal sample size calculation has been performed. However, the current study is aiming at a sample of about 500 patients from about 100 centers to allow for a representative national cohort describing reliably characteristics, outcomes and use of resources of the population (main objective).

All patients enrolled will be included in the analysis. Since this is an observational study, descriptive summaries will be presented for all the patients, and for subgroups of patients. Statistical tests may be carried out for exploratory purposes, as appropriate. No comparisons between drugs will be performed; only descriptions of different pharmacological strategies (eg. dual antiplatelet therapy vs oral anticoagulation therapy + single oral antiplatelet therapy vs triple Rx) and major outcomes occurrence will be conducted.

Categorical variables will be presented as number and percentages. Continuous variables will be presented as means with standard deviation or median and inter-quartile ranges (IQR), when not normally distributed.
5.0 DATA COLLECTION AND MONITORING

A web-based case report form (eCRF) will be used for data entry and transferred via the web to a central database located in the Coordinating Centre (ANMCO Research Center, Firenze), where they will be checked for missing data, inconsistencies, and outliers. Patient name will not be recorded on the eCRF. Patients will be identified in the eCRF by numerical codes, initials and date of birth.

In each participating centre, a data collection officer will be responsible for screening of eligible consecutive patients. Patients will be followed throughout their hospitalization and will be asked to sign an informed consent for the collection and centralization of their individual data. Local Ethical Committees will be asked to evaluate and approve the study according to national rules.

Data will be collected on description of demographics, cardiovascular and non-cardiovascular medical history, previous interventional procedures, the timing of AF onset, type of AF, type of ACS, in-hospital management, pharmacological treatment, timing of PCI, severity and extension of coronary artery disease, number and type of stent, laboratory values, ECG characteristics, hemodynamic parameters, in-hospital major clinical events and their management.

A clinical follow-up visit will be performed 6 months after the index admission for ACS. All serious adverse events will be recorded and clinical records will be required. Major outcomes (including cardiac and all-cause deaths and hospitalizations for major bleeding, non-fatal stroke, systemic embolism, transient ischaemic attack, MI recurrence) will be assessed and reported by investigators.

In the case the clinical visit is not possible, a telephone interview can replace the clinical visit collecting information at least on survival status and hospitalization.
Major bleeding will be defined according to the Bleeding Academic Research Consortium (BARC) criteria (35).

The study will be monitored to ensure overall quality of data.

The Steering Committee of the study delegates the monitoring aspects to the monitoring group of the Coordinating Centre (ANMCO Research Centre). All centers participating in the study will be monitored according to monitoring procedures set out by HCF for observational studies.

A centralized Web monitoring of eCRF entries will be conducted with periodical emission of queries to the participating centers.

On site monitoring could be conducted following a risk-based approach.

The investigator must maintain source documents for each patient in the study, including documentation of AF, notes containing demographic and medical information, copies of laboratory and clinical tests and documentation of serious adverse events. The investigator must also keep the original informed consent form signed by the patient. In the case of on-site monitoring visit, the investigator must give the monitor access to all relevant source documents to confirm their consistency with eCRF entries.

6.0 STUDY ORGANIZATION

6.1 Study sponsor

ANMCO - Heart Care Foundation ONLUS is the promoter of this survey, therefore is the database owner implying permissions to perform all activities in the database

6.2 Steering Committee

The Steering Committee has the full responsibility for planning, conduct, analysis, and publication of study protocol and results.
7.0 SAFETY

In agreement with the current rules regarding pharmaco-vigilance (Good pharmaco-Vigilance Practice, GVP), regarding non-interventional studies, the responsible of the study has the duty to promptly communicate to the competent Authorities all adverse reactions occurring during this observational study according with the rules of spontaneous reporting (post-marketing). In any case, the sponsor of the study should be informed by the Investigator of those adverse reactions.

8.0 PUBLICATION POLICY

The study will be published anyhow, independently of the final results, on the behalf of the study group. An appropriate Appendix will include the names of the members of the study committees, of the coordinating center and of representatives from each individual study site. Manuscripts and abstracts will be prepared through cooperation between the Steering Committee and the ANMCO Research Centre. Ancillary analyses can be proposed by the member of the Steering Committee and by each Investigator. The Steering Committee has the commitment to evaluate these proposal, to approve them if scientifically sound and prioritize the analysis of the database. The Steering Committee must receive a copy of any presentation, manuscript, or abstract prior to any outside submission. A period of 5 working days for presentational materials and abstracts and 15 working days for a journal submission will be required for the Steering Committee review. Authorship of the ancillary analyses will be determined according to the current medical community rules. The author must have (a) contributed substantially to the conception and design of the study, the acquisition of data, or their analysis and interpretation and (b) drafted or provided a critical revision of the article.
9.0. ETHICAL ISSUES

The survey is an observational study that does not dictate the manner in which patients are evaluated or treated. Physicians may decide to evaluate and manage patients in any way they deem appropriate according to the local standard of care.

The study will be conducted according to the protocol, the principles contained in the Helsinki declaration (last revision October 2013), the ICH-GCP, the legislation regulating the protection of personal data and other relevant legislation.

The protocol will be submitted to local Ethical Committees according to current national regulations.

Each patient shall sign an informed consent to the study. Data will be transferred to the central server. The main database will be secured according to current standards to ensure both ethical and integrity requirements of the data. In order to maintain strict security, each investigator/study personnel will have a unique login and password to enter patient’s information.
10.0 REFERENCES


15. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous


