PERSEO Registry:

PERcutaneouS coronary intErventions in patients treated with Oral anticoagulant therapy

Version: 3.0

Date: 25/10/2017

Principal Investigator	Alessandro Sciahbasi, Sandro Pertini Hospital, ASL RM2, Rome
Co-Principal Investigator	Andrea Rubboli, Ospedale Maggiore, Bologna
Steering Commettee	Battistina Castiglioni, Alessio La Manna, Ugo Limbruno, Alfredo Marchese, Ciro Mauro, Giuseppe Musumeci, Stefano Rigattieri, Giuseppe Tarantini, Fabio Tarantino, Ferdinando Varbella
Clinical Events Commettee	Salvatore De Rosa, Dionigi Fischetti, Guido Parodi

Signatures confirm that this protocol has been carefully read and fully understood, and that there is agreement to comply with the conduct and terms of the trial specified herein in compliance with Good Clinical Practice and all other regulatory requirements.

Role	**Name and Title**
Principal Investigator	**Alessandro Sciahbasi**
Signature **----------**	**Date** **----------**

Role	**Name and Title**
Co-Principal Investigator	**Andrea Rubboli**
Signature **----------**	**Date** **----------**

Table of Contents

Protocol Summary

Title	Percutaneous coronary interventions in patients treated with oral anticoagulant therapy
Acronym	PERSEO
Background	Percutaneous coronary interventions with stent (PCI-S) in patients requiring chronic oral anticoagulant therapy are associated with an increased risk of bleeding and ischemic complications. Limited data are available on the management of these patients, especially when oral anticoagulation is carried out with non-vitamin K antagonist (NOAC) which only recently have been introduced in clinical practice.
Objective	To evaluate in a “real world” setting the management and outcome of the different antithrombotic strategies used in patients with an indication for oral anticoagulant therapy, especially focusing on NOAC
Study Design	Prospective, multicenter, observational, controlled study
Sample size	At least 1080 patients treated with PCI-s and requiring oral anticoagulant therapy
Study sites	Approximately 30 or more Interventional Cardiology Centers across Italy
Co-Primary end-point	In the study there are two co-primary end-points: 1. Describe the current management of antithrombotic therapy after the introduction of NOAC in patients requiring oral anticoagulant therapy undergoing PCI-S. 2. A combined measure of efficacy and safety endpoints, the so-called Net Adverse Clinical Event (NACE) end-point including major bleeding events + major adverse cardiac and

	cerebral events (MACCE) at one year follow up in patients treated with NOAC (and various combinations of antiplatelet therapy) compared to the corresponding strategies of vitamin K antagonists.
Secondary end-points	a. The individual components of the primary endpoint b. Major bleedings according to the International Society on Thrombosis and Haemostasis (ISTH) classification
Inclusion criteria	All patients undergoing percutaneous coronary interventions with stent and an indication for chronic anticoagulant therapy.
Exclusion criteria	- Patients of age < 18 years old - Lack of written informed consent to participate in the study
Contact	Principal Investigator: Alessandro Sciahbasi, UOC Cardiologia, Ospedale Sandro Pertini ASL RM2 Tel.3472968314 E-mail: alessandro.sciahbasi@fastwebnet.it Co-Principal Investigator: Andrea Rubboli, UOC Cardiologia, Ospedale Maggiore di Bologna Tel: 335477354 E-Mail: andrearubboli@libero.it

1. INTRODUCTION

1.1 Background

Approximately 5 to 8% of patients undergoing percutaneous coronary interventions requires chronic anticoagulant therapy due to atrial fibrillation or other clinical entities (1-2). These patients pose particular problems when undergo percutaneous coronary intervention with stent implantation (PCI-S), because of the different antithrombotic and oral anticoagulant (OAC) strategies required after the procedure when dual antiplatelet therapy is recommended. Indeed dual antiplatelet therapy with clopidogrel and aspirin is superior to oral anticoagulation in term of stent thrombosis reduction (3) but OAC is superior to antiplatelet therapy for ischemic stroke reduction in patients requiring chronic OAC therapy for atrial fibrillation (4). Consequently, this scenario requires careful consideration balancing bleeding, stroke and acute coronary syndrome risks (5).

Recent guidelines on atrial fibrillation (6) suggest combined OAC and antiplatelet therapy to be modulated during follow up to prevent both thromboembolism and recurrent coronary events and/or stent thrombosis. In particular, a short period (1 month) of triple therapy (OAC, aspirin, clopidogrel) is recommended, followed by a period of dual therapy (OAC plus a single antiplatelet). However, in case of an acute coronary syndrome with stent implantation in atrial fibrillation patients at risk of stroke, a combination of triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 6 months to prevent recurrent coronary and cerebral ischemic events. For the first time these guidelines do not exclude the possible use of the new oral anticoagulants (NOAC) over warfarin and when NOAC are used, the consensus recommendation is that the lowest dose effective for stroke prevention in atrial fibrillation should be considered.

NOAC have been compared to warfarin for stroke prevention in the setting of atrial fibrillation and all these drugs showed a similar or improved efficacy over warfarin in term

of ischemic events as well as bleeding complications reduction (7-10). In particular, an important safety issue is the reduction of intracranial bleeding compared to warfarin. Currently, four different NOAC have been approved for the treatment of patients with atrial fibrillation: apixaban, edoxaban, rivaroxaban and dabigatran. The first three drugs are anti Xa inhibitors whereas the last one is a direct thrombin inhibitor.

A previous meta-analysis including all randomized phase II and III studies of NOAC in acute coronary syndromes showed that the combination of low dose NOAC and dual antiplatelet therapy is associated with a significant reduction in cardiovascular events at the price, however, of an increased risk of bleeding (11). Unfortunately, these studies did not include patients requiring chronic anticoagulant therapy.

Data regarding the combination of NOAC and antiplatelet therapy after PCI-S in patients requiring chronic anticoagulant therapy are currently scarce. Only recently, the randomized PIONEER study (12) showed the safety of the use of Rivaroxaban over warfarin in this setting of patients. In particular, the use of Rivaroxaban 15 mg combined with a single antiplatelet agent (mostly clopidogrel) was associated with a lower rate of clinically significant bleeding compared to standard therapy with a vitamin K antagonist plus dual antiplatelet therapy for 1, 6, or 12 months. However, the sample size of this study was not large enough to test accurately the efficacy in term of ischemic events prevention. Moreover, real world data on the use of the NOAC in combination with antiplatelet therapy after PCI-s in patients requiring chronic anticoagulant therapy are currently lacking.

Few years ago, in a previous observational Italian Registry (13), we presented the real world treatment of patients who underwent PCI-S and concomitant oral anticoagulant therapy with vitamin K antagonists. The study enrolled more than 400 patients and showed that there were no significant difference in term of ischemic events with triple therapy (vitamin K antagonist and dual antiplatelet therapy) or dual therapy (vitamin K antagonist and single antiplatelet agent) but all major bleeding episodes except one were detected in

the group of patients treated with triple (warfarin, aspirin and clopidogrel) therapy. However, in this Registry data on the association of antiplatelet and NAOC therapy were lacking because at that time these drugs were not available yet.

2. Study Objectives

The primary objectives of the study are:

1. To describe the contemporary antithrombotic management during and post PCI-S in patients treated with oral anticoagulant therapy
2. To evaluate, in this context, the efficacy and safety of the different NAOC compared to warfarin regimens.

3. Study design

Prospective, multicenter, observational, controlled study designed on patients requiring chronic anticoagulant treatment with either vitamin K antagonists or NOAC undergoing PCI-S for concomitant coronary disease.

4. Patient selection and follow up

4.1 Inclusion criteria

Patients with chronic disease requiring oral anticoagulant therapy (atrial fibrillation, prosthetic valves, previous pulmonary embolism, venous thrombosis) undergoing either elective, urgent or emergency percutaneous coronary interventions with stent implantation for acute or chronic coronary disease.

4.2 Exclusion criteria

Patients are not eligible if any of the following applies:

- Patients of age < 18 years old
- Lack of written informed consent to participate in the study

4.3 Informed Consent

The Principal Investigator, Sub-investigator, or designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and to answer questions of the subjects. All subjects or legally authorized subjects' representatives must sign the Ethics Committee (EC) approved informed consent prior to inclusion in the study. The signed informed consent will be kept in the subject's medical records and a copy will be given to the subject or the legally authorized representative.

4.4 Procedure and treatment regimen

According to the observational design of the study, anticoagulant therapy (vitamin antagonists or new oral anticoagulant drugs), other pharmacological therapy as well as procedural device utilized, before, during the procedure and at follow-up will be left to the physician decision.

4.5 Follow up

After the index event each subject will be followed with office follow-up visit at 30 ± 7 days and 12 ± 1 months. All follow-up visits are preferably scheduled as a visit to outpatient clinic. If patients are unable or unwilling to visit the outpatient clinic, the scheduled visit can be replaced by a telephone call.

Medication prescriptions are recorded at each follow-up visit. In case of an ischemic or bleeding event, the patient will be asked to provide documentation of the event as well as the troponin and hemoglobin values (when available).

4.6 Data collection

Patients are informed that data are collected at scheduled follow-up as well as at

unscheduled visits. The pre-procedural data to be collected include medical history, cardiac medications pre-PCI-S indication for PCI-S (elective, non-STEMI, or STEMI) and the reason for chronic anticoagulant therapy. The procedural details of the index PCI-S include location of treated lesions, number of stents, stent length, stent diameter, type of stents used and complications, the anticoagulant employed and its dose. The post-procedural medication is evaluated as well as clinical events (MACE and bleeding) that have occurred. INR is recorded if the patient is on chronic OAC with warfarin.

At each visit, the following information is collected:

- Medication prescription
- Major adverse cardiac and cerebral events
- Vital status
- Potential acute coronary syndrome
- Potential stroke of any etiology (ischemic, haemorrhagic and indeterminate)
- Stent thrombosis
- Any clinically overt bleeding events
- Coronary revascularization (PCI-S or coronary artery bypass grafting)

5. Endpoints

5.1 Primary end-point

In the study there are two co-primary end-points:

1. Describe the current management of antithrombotic therapy after the introduction of NOAC in patients requiring oral anticoagulant therapy undergoing PCI-S.

2. A combined measure of efficacy and safety endpoints, the so-called Net Adverse Clinical Event (NACE) end-point including major bleeding events + major

adverse cardiac and cerebral events (MACCE) at one year follow up comparing patients treated with warfarin or NOAC.

Major bleedings are defined according to the Bleeding Academic Research Consortium (BARC) (14) including BARC 2, 3 and 5 events.

Major adverse cardiac and cerebral events include target vessel revascularization, myocardial infarction, stent thrombosis, stroke or transient ischemic attack and death.

Stent thrombosis is defined according to the Academic Research Consortium (ARC) definition (15) including definite, probable and possible stent thrombosis.

5.2 Secondary end-points

The secondary end-points include:

a. The individual components of the primary endpoint
b. Major bleedings according to the International Society on Thrombosis and Haemostasis (ISTH) classification (16)

5.3 Subgroups analysis

A full subgroup analysis of the primary end-point and of the secondary end-points will be performed comparing:

c. The different NOAC used
d. The different anticoagulant strategies (i.e. uninterrupted therapy anticoagulant therapy versus bridging or interrupted anticoagulant therapy) during the PCI-S.
e. Transradial versus transfemoral access for PCI-S
f. Patients with prosthetic heart valves
g. Drug eluting stents versus bare metal stents.

6. Sample size calculation

The sample size was estimated on the basis of the primary end-point (the rate of NACE at 1 year follow up) according to a previous observational study performed in Italy (13) with a rate of NACE of 27% in the warfarin group and according to the results of the PIONEER trial that showed a 10% reduction of NACE with rivaroxaban (12).

Consequently assuming a 25% incidence of NACE in the warfarin group, in order to detect a difference of 7% with a power of 80% and an alpha error of 0.05 the number required was calculated to be at least 540 patients per group (totally 1080 patients).

7. Data Management

7.1 Data recording

The Case Report Forms (CRFs) in this study are implemented electronically using a dedicated electronic system. All data entered into the eCRF must be traceable to source documents available at the clinical site. In exceptional cases where data are recorded directly in the eCRF (i.e. no other source documentation exists), this must be explicitly documented (e.g. in a note to file). In such a case, eCRF should be printed out, signed, dated and filed with source document.

7.2 Record retention

The Investigator/Site will maintain all records pertaining to this study for at least five years following study completion or as otherwise instructed by the Coordinating Investigator (or designees) or per local regulations if longer.

8. Adjudication of events

The events are adjudicated by the clinical event committee (CEC) comprised of qualified physicians. The CEC is responsible for adjudicating all potential endpoint events, including death, bleeding, myocardial infarction, stent thrombosis, stroke, and coronary revascularization

9. Editorial Policy

At the conclusion of the study, a multicenter abstract reporting the primary results will be prepared by the Coordinating Investigator (in collaboration with the Executive Steering Committee) and presented at an annual scientific meeting. The first 15 top enroller Centers will have the local principal Investigator included in the list of authors (or a different collaborator indicated by the principal investigator). After the publication of the main paper, the local principal Investigators of each center that enrolled at least 15 patients and not included in the main study will be included in the secondary papers that will be published. Moreover, after the publication of the main paper all the co-authors aiming to perform further analysis for possible sub-studies will have access to the database (after the presentation of a specific protocol that should be approved by the Steering Committee). Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the Coordinating Investigator after review by the Executive Steering Committee.

10. References

1. Rubboli A, Colletta M, Herzfeld J, Sangiorgio P, Di Pasquale G. Periprocedural and medium-term antithrombotic strategies in patients with an indication for long-term anticoagulation undergoing coronary angiography and intervention. Coron Artery Dis 2007; 18: 193-9.
2. Wang TY, Robinson LA, Ou FS, Roe MT, Ohman EM, Gibler WB, Smith SC Jr, Peterson ED, Becker RC. Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: physician practice in the CRUSADE registry. Am Heart J 2008; 155: 361-8
3. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med 1998; 339: 1665-71
4. ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. Lancet 2006; 367: 1903-12
5. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the

European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014; 35: 2541-2619

6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893–2962
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-51
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365: 883-91
9. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-92
10. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369: 2093-104

11. Oldgren J, Wallentin L, Alexander JH, James S, Jönelid B, Steg G, Sundström J. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013; 34: 1670-80
12. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GYH, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016, ahead of print. DOI: 10.1056/NEJMoa1611594.
13. Rubboli A, Saia F, Sciahbasi A, Bacchi-Reggiani ML, Steffanon L, Briguori C, Calabrò P, Palmieri C, Rizzi A, Imperadore F, Sangiorgi GM, Valgimigli M, Carosio G, Steffenino G, Galvani M, Di Pasquale G, La Vecchia L, Maggioni AP, Bolognese L. Outcome of patients on oral anticoagulation undergoing coronary artery stenting: data from discharge to 12 months in the Warfarin and Coronary Stenting (WAR-STENT) Registry. J Invasive Cardiol. 2014; 26: 563-9.
14. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123: 2736-47
15. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007; 115: 2344-51
16. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on

Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non surgical patients. J Thromb Heamost 2005; 3: 692-694

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site:

Address:

Principal investigator:

_____ _____

Place/Date Signature