The MONET registry

Study Title: **M**aintenance **O**f a**N**tiplat**E**let **T**herapy in patients with coronary stenting undergoing surgery

Sponsor: *Fondazione GISE Onlus*

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Principal Investigator

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.

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Confidentiality Statement: This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, regulatory authorities, and members of the Research Ethics Committee

Contents

1. ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AE	Adverse event
AR	Adverse reaction
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CCU	Coronary Care Unit
CK-MB	Creatine Kinase-MB
CRO	Contract Research Organisation
CT	Computerised Tomography
e-CRF	electronic Case Report Form
DAPT	Dual antiplatelet therapy
DES	Drug Eluting Stent
EAC	Event adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	estimated Glomerular Filtration Rate
ICH	International Conference of Harmonisation
MI	Myocardial infarction
NSTE	Non ST Elevation
PCI	Percutaneous Coronary Intervention
SAE	Serious Adverse Event
ST	Stent Thrombosis
STE	ST Elevation
Tn	Troponin
ULN	Upper Limit of Normal Range

2. BACKGROUND AND RATIONALE

Every year more than 1 million PCIs are performed in United States and similar numbers in Europe[1,2]. In more than 85% of cases a coronary stent is implanted[3], with the ensuing need for prolonged antiplatelet therapy in order to prevent stent thrombosis (ST). The international Practice Guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor antagonist for at least one month after bare metal stent (BMS) implantation and for 6 months after drug eluting stent (DES)[4,5]. In patients with acute coronary syndrome (ACS), DAPT should be prolonged up to 12 months.

Premature discontinuation of antiplatelet therapy is associated with a significant increase in the risk of ST[6-9], an infrequent but lifethreatening event which occurs most of the times as acute myocardial infarction (MI), with a mortality rate of 10-40%. The single most important predictor of ST is the cessation of antiplatelet therapy[,10-12]. Previous studies demonstrated that premature discontinuation of antiplatelet therapy (permanent or transitory) after stent implantation occurs in 10-50% of patients[7,13], most frequently due to surgical interventions[13].

It has been estimated that 4-8% of patients submitted to stent implantation undergo surgery within the first year[3]. The perioperative management of antiplatelet therapy represents a relevant issue, not only as it is epidemologically relevant, but also because it may have significant clinical consequences[17]. A patient who experiences a perioperative MI has an inhospital mortality of 15-25%[18-20].

Perioperative management of antiplatelet therapies raises important challenges and safety concerns. On one hand, withholding therapy to reduce the risk of bleeding complications is associated with a heightened risk of ischemic events, including life-threatening stent thrombosis (ST), myocardial infarction (MI) and stroke [8-10]. Surgery leads to inflammatory, hypercoagulable and hypoxic states which are associated with plaque instability and perioperative

arterial thrombosis[3,14]. Thus, the perioperative risk of ST and other cardiac ischemic events is high, particularly if antiplatelet therapy is discontinued[15,16]. On the other hand, maintaining antithrombotic therapy may increase the risk of bleeding and the need for transfusions, which are both known determinants of poor prognosis [3-10].

Defining the trade-off between ischemia and bleeding requires not only an understanding of the thrombotic risk of the individual patient, typically defined by the cardiologist, but also a clear understanding of the hemorrhagic risk specific to each surgical procedure, which requires the expertise of the surgeon. Although guidelines provide recommendations with respect to the perioperative management of antiplatelet and anticoagulant drugs, these have been developed primarily by cardiologists who may be less informed of the inherent bleeding risk of specific surgical procedures [11, 12]. Therefore, the surgical point of view is essential when it comes to issuing recommendations on how to manage antithrombotic therapies in the perioperative period. However, characterization of the perioperative bleeding risk of each surgical procedure is an area not addressed by current guidelines [11, 12].

On this background, the Italian Society of Interventional Cardiology (GISE) has previously promoted the creation of a task force integrating the expert opinions from a multidisciplinary collaboration between cardiologists, anesthesiologists, hematologists and surgeons, providing recommendations on the antithrombotic treatment regimen to be used in patients treated with coronary stents undergoing surgical and endoscopic procedures [13]. In particular, this led to the creation of a consensus document, called Surgery after Stenting (SAS), which provided practical recommendations for standardizing the approach to antithrombotic therapy management with respect to various types of surgery based on the predicted individual risk of thrombotic complications against the anticipated risk of surgical bleeding complications. A national registry surveyed the applicability of the recommendations in real-world clinical practice and supported

the relative merit of a risk stratification approach for both ischemia and bleeding in patients with coronary stents undergoing cardiac and NCS [21]. However, the landscape of devices, antithrombotic drugs, and surgical techniques has changed over the past years. In particular, the advent of the newer generation of DES has been associated with a remarkable risk reduction of ST, potentially allowing for a safe shorter DAPT duration, particularly in low ischemic risk patients [12, 22, 23]. On the other hand, data have shown potential for a protective effect of prolonged DAPT duration in high-risk settings [12, 22, 23]. The POISE-2 trial, investigating the effects of perioperative aspirin use, showed that this had no significant effect on the combined risk of death or nonfatal MI in patients undergoing non-cardiac surgery [24]. Nevertheless, it is important to note that only one patient out of four in this study had a history of coronary artery disease and only 4% of randomized patients had previously received coronary stents. Moreover, patients with implantation of DES within 1 year and BMS <6 weeks were excluded. Due to this limitation, the results of the POISE-2 trial should not be applied to patients with previous coronary stent implantation. Thus, while being an important study, it should not be considered when managing perioperative antiplatelet therapy in patients with coronary stents undergoing surgery.

The SAS 2 Consensus Document derives from a multidisciplinary collaboration and provides practical recommendations on the perioperative management of antithrombotic therapy in patients treated with coronary stents. These recommendations are summarized in the present document and can be accessed through a workable web application, which can be downloaded at https://itunes.apple.com/us/app/stent-surgery/id551350096?mt=8. The Writing Committee was composed of cardiologists, surgeons, anesthesiologists, and hematologists. Overall, the recommendations summarized in this document were finally endorsed by 23 scientific societies, including interventional cardiology (n=1), anesthesiology (n=1), hematology (n=1), and a number of surgical specialties (n=20).

Cardiologists defined the thrombotic risk based on a series of clinical features and procedural characteristics. In particular, the definition of thrombotic risk (low, intermediate or high) was derived after careful revision of the literature which led to the formulation of a tables which summarized the information obtained. All Cardiology members of the Writing Committee provided their feedback until a consensus was reached. Surgeons classified all interventions according to the inherent hemorrhagic risk (low, intermediate, or high) of each specific surgery. In particular, bleeding risk was not solely based on the amount of blood loss, but mostly according to the anticipated difficulty in achieving adequate local hemostasis. The bleeding risk was defined in a total of about 250 surgical procedures. Finally, the most appropriate antithrombotic treatment regimen in the perioperative phase was defined for each procedure taking into consideration both the thrombotic and bleeding risk profiles. Ultimately, a consensus agreement was reached which involved not only cardiologists and surgeons, but also anesthesiologists and hematologists. Importantly, the recommended antithrombotic treatment regimen was not standard to a given thrombotic/bleeding risk profile, but was specific to each individual surgical specialty.

In general, if surgery cannot be delayed, it should be performed after the first month and ideally after at least 3 months from PCI [25, 32, 46, 49]. The vast majority of procedures may be performed while on aspirin, with the possible exception of surgeries at extremely high risk of bleeding (e.g., neurosurgery). When a wash-out of P2Y12 inhibiting therapy is required, this should be performed judiciously according to the timing of surgery: 5 days for clopidogrel and ticagrelor and 7 days for prasugrel. Recent data from a large observational study in CABG patients demonstrated that discontinuation 3 days before surgery, as opposed to 5 days, did not increase the incidence of major bleeding complications with ticagrelor (OR 0.93 (95% CI 0.53-1.64), p=0.80), but increased the risk with clopidogrel (OR 1.71 (95% CI 1.04 – 2.79), p=0.033 [71]. On the basis of these findings, in selected cases, surgery might be performed after 3 days of

ticagrelor discontinuation.

In selected cases, according to the SAS 2 recommendations, a bridging of antiplatelet therapy should be considered. A bridge therapy indicates a strategy of temporary transition with an intravenous antiplatelet agent in patients on oral antiplatelet therapy typically consisting of aspirin and a P2Y12 inhibitor. This strategy is usually reserved for patients deemed at high thrombotic risk (who thus cannot safely interrupt oral antiplatelet therapy) undergoing non-deferrable surgery at high risk of bleeding, which requires a predictable interruption of platelet inhibition at the time of the intervention [3-6].

The only intravenous antiplatelet agents available for clinical use, and thus of potential utility for antiplatelet bridging, include cangrelor and glycoprotein IIb/IIIa inhibitors (GPI). Cangrelor is an intravenous analog of adenosine triphospate with a potent, selective and specific affinity for P2Y12 receptors [63]. Given that cangrelor is not renally cleared, there is no need for dose adjustment in patients with impaired renal function. Reversible binding to P2Y12 receptors of this agent along with its very short half-life (3-6 minutes) allows for resumption of platelet function within 60 minutes of infusion cessation [64]. Cangrelor was recently approved for the reduction of thrombotic cardiovascular events in patients with CAD undergoing PCI who have not received an oral P2Y12 inhibitor prior to the PCI [65]. Cangrelor has also been specifically tested against placebo as a bridging agent among thienopyridine-treated patients undergoing coronary artery bypass grafting surgery (CABG) in the Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery (BRIDGE) trial [66]. In conclusion, in line with the BRIDGE trial approach, if intended as a bridging agent, cangrelor can be commenced any time between the next expected dose of the P2Y12 inhibitor and within 72 hours from P2Y12 inhibitor discontinuation, and stopped up to 1 hour before the start of surgery.

Alternatively, small molecule GPI's (eptifibatide or tirofiban) may be considered for bridging therapy [67]. Compared with cangrelor however, these agents have a slower offset of

action and they do not target the P2Y12 receptor. In addition, since they are renally cleared, dose adjustments are required among patients with impaired renal function. There are no randomized trials on bridging with small molecule GPIs and data derive from observational studies. Infusion should be commenced three days prior to surgical intervention, whereas clopidogrel and ticagrelor should be discontinued five days prior to surgery and seven days with prasugrel. GPI infusion should be interrupted at least four hours prior to surgery (eight hours in patients with creatinine clearance <30 ml/min).

P2Y12 inhibitors resumed within 24-48 hours after the intervention after confirmation of successful hemostasis, and with a loading dose. In patients with an increased bleeding risk in the post-operative period, clopidogrel should be preferred over prasugrel or ticagrelor. If gastrointestinal function has not yet recovered (e.g., abdominal surgery), intravenous infusion of antiplatelet agents (cangrelor or GPI) should be restarted after the surgical procedure, after careful evaluation of the bleeding risk. After complete intestinal recanalization, therapy with P2Y12 inhibitors should be resumed with a loading dose, after which the infusion of intravenous antiplatelet agents can be stopped. Because thrombotic complications occur most frequently soon after surgery, close post-operative clinical and electrocardiographic monitoring is strongly encouraged.

Notably, the impact of the application of the SAS 2 document on perioperative antiplatelet therapy in clinical practice has not been evaluated.

3. OBJECTIVES

3.1 Primary Objective

- To assess outcomes associated with the application of the Consensus Document "Stent and Surgery-2" on perioperative antiplatelet therapy in patients with coronary stenting undergoing surgery.

3.2 Secondary Objectives

- To assess ischemic and hemorrhagic events in relation to the application of the Consensus Document. Length of any antiplatelet discontinuation and delay in performing surgical procedures will also be evaluated.

4. STUDY DESIGN

4.1 Summary of Study Design

The SAS registry will include any patient with previous coronary stenting undergoing any type of surgery or operative endoscopic/endovascular procedure at the participating Centers. Centers will be divided into two groups: Centers that routinely follow the recommendations of the SAS 2 Document and Centers that do not. The relevant clinical, procedural and outcome data (within index admission and at 30 days) will be entered in a specifically designed electronic case record form (eCRF).

4.2 Primary endpoint

- Rate of discontinuation of P2Y12 inhibitors and/or aspirin (without bridging) in the first 3 months after PCI with low risk characteristics and 6 months after PCI with high risk characteristics or any antiplatelet therapy discontinuation without bridging therapy

4.3 Secondary endpoints

Patients undergoing non cardiac surgery:

- The composite of death, myocardial infarction, probable/definite stent thrombosis according the Academic Research Consortium definition44 and bleeding events of Bleeding Academic Research Consortium (BARC) grade □3 at 30 days
- The composite of death, myocardial infarction and probable/definite stent at 30 days
- The incidence of bleeding events of Bleeding Academic Research Consortium (BARC) grade ≥ 3 at 30 days
- The type and the length of discontinuation of any antiplatelet therapy in patients undergoing non cardiac surgery according to time from PCI to surgery
- Rate of non cardiac surgical procedures within 12 months from PCI divided into quartiles (0-3, 3-6, 6-9, 9-12 months)
- Delay in performing non cardiac surgical procedure

Patients undergoing cardiac surgery:

- The composite of death, myocardial infarction, probable/definite stent thrombosis according the Academic Research Consortium definition44 and bleeding events of Bleeding Academic Research Consortium (BARC) grade □4 at 30 days
- The composite of death, myocardial infarction and probable/definite stent at 30 days
- The incidence of bleeding events of Bleeding Academic Research Consortium (BARC) grade ≥ 4 at 30 days
- The type and the length of discontinuation of any antiplatelet therapy in patients undergoing cardiac surgery according to time from PCI to surgery
- Rate of cardiac surgical procedures within 12 months from PCI divided into quartiles (0-3, 3-6, 6-9, 9-12 months)
- Delay in performing cardiac surgical procedure

4.4 Participants

4.4.1 Inclusion Criteria

Eligible will be male and female patients > 18 years of age.

Eligible will be patients with previous coronary stenting undergoing any kind of surgical or operative endoscopic procedure at the participating Centers, irrespective of the distance in time between stenting and surgery.

Both candidates to elective and urgent/emergent surgical procedures will be included in the MONET registry.

4.4.2 Exclusion criteria

Unwillingness/inability to sign the Informed Consent Form (ICF). Patients with an active bleeding requiring discontinuation of one or both antiplatelet agents will be also excluded. There are no other exclusion criteria.

4.4.3 Enrolment time

The enrolment period is 12 months after authorization of respective Ethics Committee.

4.5 Study Procedures

4.5.1 Informed Consent

Patients will be asked to sign an ICF for participation in the Registry.

4.5.2 Screening

Screening for inclusion into the registry will be made at the time of preoperative evaluation: this will be made by the consultant cardiologist in cooperation with the anaesthesiologist and/or surgeon/endoscopist in charge of the operation.

4.5.3 In-hospital assessments

The MONET registry does not imply any assessments additional to routine treatment. The following clinical and laboratory variables will be captured by the eCRF:

Clinical characteristics

- Age, gender, body weight.
- Selected coronary risk factors, such as diabetic status, smoking, hypertension, dyslipidemia.

- Cardiovascular status: prior MI, PCI (date of latest stenting), CABG, heart failure, atrial fibrillation, latest left ventricular ejection fraction.

Laboratory tests

- Baseline serum creatinine (eGFR will be automatically calculated by the eCRF using the Cockroft-Gault formula) and peak serum creatinine during hospital stay.
- Baseline haemoglobin/haematocrit and nadir values during hospital stay.
- CKMB and troponin values should be checked at 6-hour intervals for 24 hours after any suspect ischemic symptoms and/or ischemic ECG changes in the perioperative period, unless otherwise recommended by local practice. The peak value of CKMB will be recorded in the eCRF.

Electrocardiogram

A standard 12-lead ECG will be taken preoperatively, in the case of ischemic symptoms and at discharge.

Concomitant Medications

The following medications will be captured by the eCRF:

- Aspirin
- $P2Y_{12}$ inhibitors (further subdivided as ticlopidine, clopidogrel, prasugrel, ticagrelor)
- Betablockers
- Statins
- ACEI, ARBS
- Oral anticoagulants (warfarin, acenocumarol, apixaban, dabigatran, edoxaban, rivaroxaban)

- Low-molecular weight heparin
- Tirofiban or eptifibatide
- Cangrelor

The dates and times of perioperative discontinuation and reinstitution (if any) will also be captured.

Drug therapy at discharge and at the 30-day contact will be captured by the eCRF.

Index PCI and surgical procedure details

Details of PCI and surgical procedures will obtained from interrogation of the medical records and hospital charts.

The delay from stenting to surgery and the type of stent (BMS, first or second generation DES), stent number, length and diameter will be recorded. Surgeries will risk-stratified according to the American College of Cardiology/American Heart Association classification [11]. Moreover, the American Society of Anaesthesiologists (ASA) physical status will be assessed for each patient [21].

For each patient, surgical hemorrhagic and thrombotic risk (according to the SAS 2 Consensus Document definitions) will be identified at the time of data analysis according to clinical and angiographic characteristics that will be captured in the eCRF.

Outcome Events

The following outcome events will be captured by the eCRF:

- Death

- Myocardial infarction, recurrent ischemia, heart failure, ventricular tachycardia, ventricular fibrillation.
- Major bleeding
- Transfusions
- Reoperation due to bleeding

See point 8 for definitions

4.5.4 Follow-up

A follow-up contact visit is planned at 30 days (± 7 days) after the surgical procedure using hospital records, outpatient visits, or telephone contact. A standard questionnaire will be used to collect information on the medications the patients were taking and the occurrence of any adverse events. Each site will have a designated individual who entered raw data into an electronic case report form, allowing immediate and continuous monitoring of its completeness and accuracy. Unscheduled visits can also take place whenever necessary.

Relevant information to be inquired and collected in the e-CRF will include:

- check of items describing the primary and secondary study endpoints, with special reference to new hospitalizations;
- ongoing medications
- compliance with medication prescribed at discharge
- adverse events

4.6 Source Data

When required for the adjudication of endpoint clinical events, original documents, data, and records from which participants' CRF data are obtained will be electronically uploaded in the

eCRF (see point 9). These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiological images.

5. TREATMENT OF PARTICIPANTS

The Registry will record actual perioperative management strategies in patients with previous stent implantation undergoing surgical and operative endoscopic/endovascular procedures. A guidance for the perioperative management of antiplatelet therapy is provided by the Consensus Document SAS 2 issued by GISE. The document is enclosed as an Appendix to the present protocol. The recommendations can be accessed by the Investigators through a workable web application, which can be downloaded at https://itunes.apple.com/us/app/stent-surgery/id551350096?mt=8.

6. DEFINITIONS OF THE ENDPOINT COMPONENTS

6.1 Antiplatelet therapy discontinuation

Antiplatelet discontinuation is defined as P2Y12 inhibitors and/or aspirin withdrawal for >5 days at the time of surgical procedure without bridging therapy with antiplatelet agents in the first 3 months after PCI with low risk characteristics and 6 months after PCI with high risk characteristics or any any antiplatelet therapy discontinuation without bridging therapy at any time after PCI. A detailed description on the perioperative management of oral antiplatelet therapy will be obtained for both aspirin and $P2Y_{12}$ inhibitors (ticlopidine, clopidogrel, prasugrel, and ticagrelor). This includes the time delay from drug interruption to surgery as well as the time from surgery to reintroduction of therapy. The use of any bridging strategy will also be recorded. According to the SAS 2 Consensus Document, in selected patients at high risk for both bleeding and ischemic events, when withdrawal of oral antiplatelet therapy is required, bridging with cangrelor or with a short-acting intravenous glycoprotein IIb/IIIa inhibitor (GPI) (tirofiban or eptifibatide) can be considered.

6.2 Death

All-cause mortality will be considered for the primary analysis. All-cause mortality includes all deaths, regardless of whether the cause of death is determined.

For the secondary analysis, death will be classified in two primary categories, cardiovascular or non-cardiovascular.

- Cardiovascular death is defined as death due to atherosclerotic coronary heart disease, cerebrovascular accident or (complication of) peripheral embolization, and includes deaths due to acute MI, stroke, sudden death, non-sudden death, unwitnessed death, and procedure-related deaths.

- Non cardiovascular death includes deaths due to all other causes.

All deaths will be assumed cardiovascular in nature unless a non-cardiovascular cause can be clearly shown, with the exception of death without any additional information, which will be classified as unknown cause of death.

6.3 Myocardial Infarction

All definite MIs will be counted as events whether they occurred spontaneously or as the direct consequences of a procedure or operation.

The definition of perioperative MI includes cardiac marker evidence of MI with either troponin or CK-MB elevation greater than the ULN with a typical rise and fall[44] and 1 or more of the following defining features[45]:

- ischemic symptoms (such as chest, epigastric, arm, wrist, or jaw discomfort or shortness of breath),
- development of pathologic Q waves in 2 contiguous leads during ECG,
- ischemic changes detected with ECG (new or presumed-new ST-segment elevation or depression or T-wave inversion in at least 2 contiguous leads during ECG),
- coronary artery intervention (such as percutaneous coronary intervention or coronary artery bypass graft surgery),
- or evidence of MI on cardiac imaging (a new or presumed-new cardiac wall–motion abnormality on echocardiographic imaging or a new or presumed-new fixed defect on radionuclide imaging).
- a patient's autopsy findings demonstrated acute MI.

According to the 3rd Universal Definition of MI[44],

- following PCI, CK-MB elevation must be >5 x ULN.
- Following CABG, the definition for an MI requires that cardiac markers are >10 x ULN.

Outcome adjudicators evaluated all potential MIs, and their decisions will be used in the statistical analyses. The event adjudication committee should also consider the clinical features (eg, renal insufficiency), possible alternative diagnoses (eg, pericarditis), pattern of marker release (eg, absence of a rise and fall), and known sensitivity/specificity of the various cardiac markers in the adjudication of infarction, particularly when there is discordance in the results of multiple markers.

6.3 Stent thrombosis

Probable/definite stent thrombosis will be defined according the Academic Research Consortium definition[42]. With regard to the primary endpoint of the study, the adjudication will follow a hierarchical order with death first, MI second and stent thrombosis third, mostly in the case of recurrent ischemia without enzyme elevation.

6.4 Bleeding Classification

All bleeding events will be considered in patients undergoing cardiac and non cardiac surgery. Bleeding events will be classified according to BARC classification.

Bleeding Academic Research Consortium Definition for Bleeding (Ref 43)

- Type 0: no bleeding
- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

- Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- Type 3

  Type 3a: overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed); any transfusion with overt bleeding

  Type 3b: overt bleeding plus hemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents

  Type 3c: intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture; intraocular bleed compromising vision
- Type 4: CABG-related bleeding, including perioperative intracranial bleeding within 48 h, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of >5 U whole blood or packed red blood cells within a 48-h period, chest tube output >2L within a 24-h period
- Type 5: fatal bleeding

  Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

  Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

6.5 Rate of non cardiac surgical procedures within 12 months from PCI

The rate of cardiac and non cardiac surgical procedures performed within 12 months from PCI will be assessed. Time from PCI to surgery will be divided into 4 quartiles: from 0 to 3 months, from 3 to 6 months, from 6 to 9, and from 9 to 12 months.

6.6 Delay in performing non cardiac surgical procedure

The delay in performing cardiac and non cardiac surgical procedures will be defined as the time from the time of surgical indication to the time of surgical procedure.

7. STATISTICS

7.1 The Number of Participants

Consecutive patients will be enrolled over one year of time at the participating Centers.

Cases and controls patients will be divided into those who will use Consensus Document "Stent and Surgery-2" (group 1) vs those who traditionally will be managed by local practice (group 2). On the basis of previous data reported SAS, a sample size of 1623 patients would be required to have a case-control matching 1:2, assuming a study power of 80% and 5% significance. Of those, 324 case-patients (20% of group 1) vs 162 control-patients (ratio 1:2) would be required for enrollment within one-year after implanted stents. Two preplanned interim analyses will be performed by an independent statistician when 800 and 1500 of patients will be enrolled.

7.2 Description of Statistical Methods

Continuous numeric variables will report as means with SD and compared using the Student's t- or Wilcoxon rank-sum test. Categorical variables will be presented as counts and percentages and will be compared using the chi-square or Fisher's exact test. To examine the effect of significant factors on two different groups (Group 1 vs Group 2) the hazard ratio of the interaction term will be calculated. To identify the independent predictors for in hospital NACE, 30day MACE and 30-day BARC bleedings, first univariate and then multivariate logistic regression models will apply. The BARC bleedings will be considered according to type of surgery. Specifically, BARC bleedings grade $\geq$3 will be considered in patients undergoing cardiac surgery, and BARC bleedings grade $\geq$4 will be taken into account for non-cardiac surgery. Covariates for multivariable models will be selected on the basis of a backward stepwise algorithm in a Cox proportional hazards model. Additionally, to minimise group differences on confounding covariates between patients who will be managed with consensus document (group 1) and those who will be received local practice (group 2), a 1:2 propensity score matching would be used. Propensity scores will be calculated with logistic regression, with multiple imputation and backwards elimination with a significance level to stay of 0.05. To ensure that the comparison between two groups (group 1 vs group 2) would not be bias, the proportion of patients who will not received consensus document within center that traditionally used it, will be excluded. The results will be presented as ORs with 95% confidence intervals (CI) and p values. For all

analyses, a two-sided P <0.05 will be required for statistical significance. All data will be analyzed using the Statistical Package of Social Sciences version 20 (IBM SPSS, Chicago, IL).

8. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

An expert academic Clinical Research Organization especially expert in cardiovascular clinical trials (Advice Pharma, Italy) will be in charge of data management, control and quality assurance. Patients data will be collected using and electronic CRF using a centralized system for collecting data via the Web that can be operated via a simple web browser and an internet connection.

8.1 Main platform characteristics of the eCRF system

- Compliance with FDA 21 CFR part 11 requirements and guidelines concerning security and data protection;
- Full web: requirements are browser and Internet connections;
- Compatible with Windows / SQL Server and Linux / MySQL and with main browsers (Internet Explorer, Mozilla Firefox, Google Chrome, Safari and Opera);
- Access control and advanced user management;
- Advanced user profiling management and customization;
- Audit Trail: tracking all user operations (e.g. visited pages); user data audit, patients and centres audit, CRF data audit;
- CRF source verified data locking at visit / page / single variable levels;
- On-line control of data plausibility and consistency;
- Automatic query generation;
- Electronic upload of selected source data for evaluation by the Event Adjudication Committee;
- Production of blank and annotated CRF;
- SAS clinical data base
- Exporting data to SAS and Excel format;
- Graphic reports and descriptive statistics.

8.2 Security of data

- Secure data transmission using 256-bit SSL (HTTPS) protocol and relative Certificate from Thawte Certification Authority.
- Access with personal password with complexity requirements, password expiration are customizable, but at least quarterly;
- Expiry of the session after 15 minutes of inactivity;
- Hosting of data in web-farm monitored and controlled 7x24;
- Redundant hardware;
- Daily backups and redundant.

8.3 Help desk and investigator training

- Help Desk technical support to investigators (5 days/7 - office hours - availability outside office hours);
- Participation in meetings and training meetings for investigators on the characteristics and use of the e-CRF (if required);
- Participation in periodic teleconference (if required);
- Database data production for individual centres as CD / DVD

9. ETHICS

9.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki.

9.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with the ICH Guidelines for Good Clinical Practice and all relevant local regulations (DL 211/2003; DL 200/2007)

9.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Ethics Committee (EC) and competent authorities (CA) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

9.4 Participant Confidentiality

The trial staff will ensure that the participants' confidentiality is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Italian Law on the protection of personal data and with guidelines dated July 24th 2008.

10. DATA HANDLING AND RECORD KEEPING

Data will be entered by the Investigators in the electronic CRF provided by the CRO. The Principal Investigator or Co-Investigator must ensure the accuracy and completeness of the recorded data.

The entire process of the clinical data treatment (from the collection to the final statistical analysis) will be conducted following the internal standard operative procedures in accordance with the European regulations and international standards. The participants will be identified by a study specific participants number and/or code in any database.

Security of the data will be ensured according to explanations given at point 9 of the present protocol.

11. STUDY COMMITTEES

11.1 Steering Committee

The Steering Committee is listed in the "MONET_Annex 1 – Steering Committee".

The Steering Committee will be responsible for:

- preparation of the protocol and preparation of the first draft of the CRF (the latter in co-operation with Advice Pharma)
- selection of the study centers conducting the investigator meetings (one at the beginning and one at the end of the study)
- writing newsletters for the investigators
- establishing a troubleshooting call-line for the investigators
- negotiating the statistical analysis with the chief statistician
- preparing the manuscript and taking care of the main study publication and its offsprings
- appointing experts in charge of any substudies.

11.2 Event-adjudication Committee

The following experts, designated by the Steering Committee and not involved in enrolment for the present study, will constitute the Event-Adjudication Committee.

The Event-Adjudication Committee is listed in the "MONET_Annex 2 - Event-Adjudication Committee".

The Event-adjudication Committee will screen and adjudicate all critical adverse events based on the review of CRF, original source documents and films.

12. PUBLICATION POLICY

The final manuscript of the study will be prepared by the Principal Investigators, reviewed and approved by the Steering Committee, presented in a final meeting to all of the Investigators (pre-view by e-mail and Cyber-Session allowed) and published under the authorship of "The MONET Registry Investigators". Dr Roberta Rossini will act as the corresponding author. Any sponsor must agree not to interfere on the interpretation and presentation of data. The data will remain property of the Steering Committee.

Any substudies derived from subgroup analyses of the study will have to be decided in coordination with the Steering Committee of the study.

13. STUDY COORDINATING CENTER AND DATA RESPONSIBILITY

The study will be promoted by the Fondazione GISE Onlus.

The Coordinating Center will act as the study sponsor and will therefore be responsible – among the other sponsor reponsibilites - for handling, managing and storing the data according to current regulations. (DL 196/2003: “Codice in materia di protezione dei dati personali, 30 giugno 2003”). Some of the sponsor responsibilities will be delegated to the CRO Advice Pharma.

14. FINANCING

The study will be co-financed by liberal contributions and research grants from the pharmaceutical industry.

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APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	**Screening**	**Index admission**	**Discharge**	**1 month**
Informed consent	X			
Demographics	X			
Medical history	X			X
Concomitant medications	X	X	X	X
Physical examination	X	X		
ECG	X	X	X	
Laboratory tests: blood cell count	X	X	X	
Eligibility assessment	X			
Compliance with medications				X
Assessment 1			Report of MACCE and bleeding during index admission	
Assessment 2 and following				Report of MACCE and bleeding
Adverse event assessments		X	X	X