Design and rationale of the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT) Study

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TRIAL DESIGN

Design and Rationale of the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT) Study.

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ABBREVIATIONS:

ASA= Acetylsalicylic Acid

BARC= Bleeding Academic Research Consortium

BMS= Bare Metal Stent

CAD= Coronary Artery Disease

CEC= Clinical Event Committee

CI= Confidence Interval

CrCl= Creatinine Clearance

DAPT= Dual Antiplatelet Therapy

DES= Drug Eluting Stent

DMC= Data Monitoring Committee

eCRF= Electronic Case Report Form

ExC= Executive Committee

E-ZES= Zotarolimus-Eluting Endeavor Sprint Stent

HBR= High Bleeding Risk

INR= International Normalized Ratio

MACE= Major Adverse Cardiovascular Events

MACCE= Major Adverse Cardiac and Cerebral Events

MCB= Major or Clinically relevant non-major Bleeding

MI= Myocardial Infarction

NACE= Net Adverse Clinical Endpoint

OAC= Oral AntiCoagulant

PCI= Percutaneous Coronary Intervention

RCT= Randomized Controlled Trial

RR= Relative Risk

ST= Stent Thrombosis

TIA= Transient Ischemic Attack

TLR= Target Lesion Revascularisation

TVR= Target Vessel Revascularisation

Abstract

Background: The optimal duration of antiplatelet therapy in high bleeding risk (HBR) patients with coronary artery disease treated with newer generation drug eluting bioresorbable polymer coated stents remains unclear.

Design: MASTER DAPT (clinicaltrial.gov NCT03023020) is an investigator-initiated, open label, multicenter, randomized controlled trial comparing an abbreviated versus a standard duration of antiplatelet therapy after bioresorbable polymer coated Ultimaster sirolimus-eluting stent implantation in approximately 4,300 HBR patients recruited from ≥100 interventional cardiology centers globally. After a mandatory 30 day DAPT run-in phase, patients are randomized to; a) a single antiplatelet regimen until study completion or up to 6 months in patients with clinically indicated oral anticoagulation (OAC) (experimental 1 month DAPT group), or b) continue DAPT for at least 6 months in patients without, or 3 in patients with concomitant indication to OAC, followed by a single antiplatelet regimen (standard antiplatelet regimen). With a final sample size of 4,300 patients, this study is powered to assess the non-inferiority of the abbreviated antiplatelet regimen with respect to the net adverse clinical and major adverse cardiac and cerebral events composite endpoints and if satisfied for the superiority of abbreviated as compared to standard antiplatelet therapy duration in terms of major or clinically relevant non major bleeding. Study endpoints will be adjudicated by a blinded Clinical Events Committee.

Conclusions: The MASTER DAPT study is the first randomized controlled trial aiming at ascertaining the optimal duration of antiplatelet therapy in high bleeding risk patient treated with sirolimus-eluting bioresorbable polymer coated stent implantation.

Keywords: antiplatelet therapy, high bleeding risk, percutaneous coronary intervention, Ultimaster, randomized clinical trial.

Introduction

High bleeding risk patients (HBR) represent up to 45% of the patients with coronary artery disease (CAD) undergoing stent implantation, depending on the setting and bleeding risk definition (1).

The European and American Guidelines endorse by consensus the assessment of bleeding risk to inform the decision-making on duration of antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI) and suggest a shorter than average antiplatelet therapy duration in patients fulfilling at least one HBR criterion (2,3). However, only few studies have so far focused on HBR patients receiving stent implantation (4-9), no dedicated randomized controlled trial (RCT) has assessed the optimal antiplatelet therapy regimen in HBR patients undergoing PCI whereas pivotal antiplatelet therapy duration studies have excluded patients with one or more HBR criteria (2,3,10). Therefore, the optimal antiplatelet therapy duration in HBR patients receiving coronary stenting remains uncertain.

High bleeding risk and type of coronary stent

The Zotarolimus-Eluting Endeavor sprint stent in Uncertain DES candidates (ZEUS), which compared any commercially available thin-strut bare metal stent (BMS) or Zotarolimus-eluting Endeavor Sprint stent (E-ZES) at the time of PCI, was the first randomized controlled study that included, among others, patients with HBR features (4-6). It included a total of 1,606 participants and a total of 828 patients fulfilled one or more HBR criteria, of whom 425 (51.3%) aged >80 years, 311 (37.6%) had clinical indication to oral anticoagulant, 113 (13.6%) reported previous or recent bleeding requiring hospitalization or medical attention, 95 (11.5%) presented bleeding diathesis, 68 (8.2%) had known anemia and 25 (3.0%) were in the need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs. In this selected high-risk patient population, the study protocol mandated 30 day DAPT irrespective of the stent type. HBR patients derived benefits

in terms of reductions of major adverse cardiac events (MACE), MI, target vessel revascularization (TVR) and ST when treated with E-ZES as compared to BMS. More recently, the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial was designed to evaluate the efficacy and safety of the polymer-free Biolimus A9-coated stent as compared with a BMS in HBR patients, with a 1-month regimen of dual antiplatelet therapy in both groups (7,8). Definition of HBR differed from that used in the ZEUS trial and also included patients who were otherwise considered by the investigator to be candidates for implantation of a bare-metal stent instead of a drug-eluting stent, owing to the perceived need to terminate dual antiplatelet therapy at 1 month. In a total of 2,466 patients, a polymer-free Biolimus A9-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy, owing to lower TVR and MI rates (8,11).

Finally, 1200 patients aged 75 years or older have been included in the short duration of dual antiplatelet therapy with Synergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization (SENIOR) trial which compared everolimus-eluting Synergy stent with BMS followed by 1 or 6 month DAPT duration in stable or unstable CAD patients, irrespective of the stent type (9). At 12 months, the primary endpoint—a composite of all-cause mortality, MI and ischemia-driven target lesion revascularization (TLR)—occurred in 16.4% of patients treated with the BMS and 11.6% among those treated with Synergy, a 29% relative reduction in risk (RR 0.71; 95% CI 0.52-0.94). There was no statistically significant difference in the risk of death, stroke, or MI at 12 months, nor was there any difference in the risk of bleeding, but TLR was higher with BMS as compared to Synergy (9).

Therefore current evidence(4,6,8,9) suggests that BMS should no longer be considered the device of choice in HBR patients undergoing PCI even if a relatively short BMS-like DAPT duration is anticipated. Accordingly, the European Society of Cardiology DAPT focused update recommended

the use of DES (drug eluting stent) over BMS irrespective of the planned DAPT duration with a class I level of evidence A (2).

High Bleeding risk and DAPT duration

There is no dedicated RCT assessing the optimal DAPT duration in patients at high bleeding risk. Moreover, many, if not all, available DAPT studies formally excluded these patients from inclusion.

In a post-hoc analysis of the Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study (PRODIGY), it was observed that patients at HBR according to the CRUSADE score, treated with a 24-month DAPT experienced a three fold higher risk of major bleeding and a five-fold risk of red blood cell transfusion as compared with a 6-month therapy, without clear evidence of benefit (12,13). The number of patients needed to treat for harm in the HBR group was as low as 17 and 15 for major bleeding and red blood cell transfusion respectively, which was lower than corresponding figures in the unselected patient cohort, suggesting that long-term DAPT has a narrow therapeutic window and high potential for harm in this selected high bleeding risk patient population. More recently, it was observed that among patients deemed at high bleeding risk based on PRECISE-DAPT, prolonged (i.e. 12 months or longer) DAPT regimen was associated with no ischemic benefit but a remarkable bleeding burden as compared to 3 or 6 month DAPT, leading to a number needed to treat for harm of 38 (14). Conversely, longer treatment duration in patients without high bleeding risk was associated to a marginal or even no increase of bleeding and a significant reduction of the composite ischemic endpoint, with a significant interaction terms between HBR status according to the PRECISE-DAPT score and anticipated treatment benefits and risks (14).

Ultimaster Stent

The Ultimaster coronary stent system consists of a cobalt-chromium (Co-Cr) bare metal stent platform featuring thin struts (80 μm) (15-17). The Ultimaster platform is coated with sirolimus (3.9

μg/mm stent length) in a matrix with bioresorbable, Poly (DL-lactide-co-caprolactone) polymer. A thin biocompatible, bioresorbable gradient coating is intended to reduce polymer cracking and delamination on the hinges of the stent. Within three to four months the polymer is metabolized, through the hydrolysis of DL-lactide and caprolactone into carbon dioxide and water. Due to an abluminal (outside surface) coating, the dose of drug was reduced as compared to stents coated both endo- and abluminally. Furthermore, coating only the abluminal surface leaves the luminal side of the stent free from drug and polymer, as such enhancing endothelial coverage(18).
The Ultimaster stent is the only sirolimus-eluting stent having received CE mark labeling for 1-month DAPT duration in HBR population. More precisely, the instruction for use indicates that dual antiplatelet therapy after implantation of Ultimaster stent can be discontinued earlier in case of clinical need (i.e. high bleeding risk) but not before one month.

METHODS

Study Design and population

The MAnagement of high bleeding risk patients post bioresorbable polymer coated STEnt implantation with an abbReviated versus standard DAPT regimen (MASTER DAPT, clinicaltrial.gov NCT03023020) is an investigator-initiated, open label, multicenter, randomized trial comparing an abbreviated (experimental arm) versus a standard (control group) duration of antiplatelet therapy after bioresorbable polymer coated Ultimaster sirolimus-eluting stent implantation in approximately 4,300 HBR patients recruited from ≥100 interventional cardiology centers across the globe. After a mandatory 30 day DAPT run-in phase, patients are randomized to; a) a single antiplatelet regimen until study completion or up to 6 months in patients with clinically indicated oral anticoagulation (OAC) (experimental 1 month DAPT group), or b) continue DAPT for at least 6 months in patients without, or 3 in patients with concomitant indication to OAC, followed by a single antiplatelet

regimen (standard antiplatelet regimen). Eligible patients are aged 18 or more, with at least one high bleeding risk criteria (**Table I**) and with all intended coronary lesions successfully treated with Ultimaster stent without flow limiting angiographic complications which require prolonged prescription of DAPT at operator's discretion. In addition, all staged PCIs (if any) must be completed and no further PCI should be planned.

Detailed inclusion and exclusion criteria are shown in **Table II**.

Screening Phase

Patients are screened for inclusion from immediately after the index procedure —defined as either a single procedure or the last installment in planned staged procedure —and up to one-month randomization visit, occurring between 30 and 44 days thereafter. Consenting patients are entered into the electronic case report form and further re-assessed for eligibility at the time of randomization (**Figure 1**). Patients experiencing spontaneous MI, symptomatic restenosis, stent thrombosis, stroke or any revascularization requiring prolonged DAPT after index PCI will be excluded. Similarly, patients with ongoing bleeding or prior bleeding since after PCI requiring permanent DAPT discontinuation are deemed ineligible. Adherence to only one type of DAPT (i.e. avoiding switching among P2Y12 inhibitors) is required for at least 7 days prior to randomization. In addition, in patients with clinically indicated oral anticoagulation, adherence to one type of oral anticoagulant (i.e. avoiding switching among oral anticoagulants) and to DAPT in form of aspirin and clopidogrel is protocol mandated for ≥7 days prior to randomization.

Randomization and treatment protocol

At randomization, occurring 30 to 44 days after index PCI, patients are centrally allocated in a 1:1 ratio to an abbreviated or standard antiplatelet regimen using secuTrial data capturing system available at https://secutrial.insel.ch/apps/WebObjects/ST21-productive-DataCapture.woa/wa/. The randomization sequence is computer generated and stratified per site, by a history of acute myocardial infarction within 12 months prior to index PCI and use of OAC.

Abbreviated antiplatelet regimen

In the experimental arm, the DAPT regimen is immediately discontinued after randomization followed by a single antiplatelet regimen (either aspirin or P2Y12 inhibitor at discretion of the treating physician) until study completion or up to 6 months in patients with clinically indicated oral anticoagulation, which is continued until at least 11 months post randomization (**Figure 2**).

Standard antiplatelet regimen

In the standard antiplatelet regimen arm, patients without clinically indicated oral anticoagulation continue aspirin until 11 months post randomization plus a P2Y12i inhibitor (i.e. ticagrelor, prasugrel or clopidogrel) for at least 5 and up to 11 months post randomization, at discretion of the treating physician (**Figure 3**).

In patients with clinically indicated oral anticoagulation, aspirin and clopidogrel are continued for at least two and up to 11 months post randomization, at discretion of the treating physician. Thereafter, a single antiplatelet agent (aspirin or clopidogrel) is continued up to 11 months post randomization. OAC is continued until 11 months thereafter (Figure 3).

In both study groups, switching among anti-thrombotics (i.e. from one P2Y12 inhibitor to an other or among OACs) is discouraged, unless dictated by a clinical and documented reason.

All antiplatelet or anticoagulant treatment options are to be dosed according to the corresponding authorization for use and locally approved regimens. Daily doses of allowed anti-platelet regimens include 75-162 mg for aspirin, 75 mg for clopidogrel, 90 mg for ticagrelor BID, 10 mg for prasugrel or 5 mg in patients weighting less than 60 kg or who are over 75 years old. In Japan, prasugrel is approved and prescribed at a dose of 3.75 mg.

Daily doses of allowed oral anticoagulants include apixaban 5 mg BID or apixaban 2.5 mg BID, if at least two among age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (or 133 mol/L); dabigatran 150 mg BID or 110 mg BID; edoxaban 60 mg or 30 mg if creatinine clearance (CrCl) is 30–50 mL/min or body weight ≤60 kg or there is concomitant use of verapamil or quinidine or dronedarone; rivaroxaban 20 mg or 15 mg OD if CrCl 30–49 mL/min.

Finally, the dose intensity of vitamin K antagonist is monitored with a target international normalized ratio (INR) in the lower part of the recommended target range, in keeping with guidelines recommendations (2).

Follow-up visits

Scheduled follow-up visits occur at 60 (±14), 150 (±14), 335 (±14) days and 420 (±14) days post randomization. All follow-up visits are preferably scheduled on-site. If the patients are unable or unwilling to visit the outpatient clinic, the scheduled visit can be replaced by telephone call except for the randomization and the 1-year visits. At each visit, self-reported adherence to study and non-study medications is collected together with the assessment of any cardiac or cerebrovascular ischemic or bleeding occurrences or any serious adverse event.

Study endpoints

This study has 3 co-primary endpoints, including (1) net adverse clinical endpoints (NACE) defined as the composite of all-cause death, myocardial infarction, stroke and BARC 3 or 5 bleeding

events; (2) major adverse cardiac and cerebral events (MACCE) defined as a composite of all-cause death, myocardial infarction and stroke and (3) major or clinically relevant non major bleeding (MCB) defined as a composite of type 2,3, and 5 BARC bleeding events.

The secondary endpoints include the individual components of the three co-primary endpoints; the composite of cardiovascular death, myocardial infarction and stroke; the composite of cardiovascular death, myocardial infarction definite or probable stent thrombosis, any revascularization, transient ischemic attack, and bleeding events adjudicated according not only the validated BARC classification(19) but also the TIMI as well as GUSTO classifications.

The main analyses evaluate the occurrence of the primary endpoints between randomization and 11 months thereafter. Secondary analyses include the occurrence of primary endpoints between randomization and 15 months and other secondary endpoints at any time frames throughout study duration. All primary and secondary endpoints are adjudicated by an independent clinical event committee (CEC) who will be blinded to randomized treatment allocation.

Statistical considerations

Main analysis of the primary endpoints is conducted on the full analysis set of all randomized patients according to the intention to treat principle based on CEC adjudicated endpoints.

Rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to 335 days (11 months) after randomization by Kaplan-Meier methods. Rate differences are defined as the rate in the abbreviated antiplatelet minus that in the standard antiplatelet arms.

The study is designed to test the following hypotheses: (1) an abbreviated antiplatelet regimen is non inferior to standard antiplatelet in terms of NACE; (2) an abbreviated antiplatelet regimen is

non inferior to standard antiplatelet in terms of MACCE and (3) an abbreviated antiplatelet regimen is superior to standard antiplatelet in terms of MCB. These hypotheses are tested in a hierarchical order, preserving type 1 error rate.

Based on conservative assessments of the previous evidence (4,6-8,12,13), the event rates of NACE MACCE and MCB in the standard antiplatelet group are assumed to be respectively 12%, 8% and 6.5% at one year.

Non-inferiority of the abbreviated antiplatelet regimen in terms of NACE is declared if the 95% confidence interval (CI) of the rate differences excludes 3.6%. Non-inferiority of the abbreviated DAPT regimen in terms of MACCE is declared if the 95% CI of the rate differences excludes 2.4%.

With 2 x 2050 evaluable patients, this study has >90% power to detect non-inferiority of abbreviated antiplatelet for NACE, >80% power to detect non-inferiority of abbreviated antiplatelet on MACE and >90% to detect superiority of the abbreviated antiplatelet arm on MCB assuming a 35% relative risk reduction with nominal 5% type I error preserved by the sequential hierarchical testing. To compensate for 5% attrition rate, 2 x 2150 patients are being randomized.

Predefined subgroup analyses

Prespecified subgroup analyses of the 3 primary and major secondary endpoints entail stratification on the need for OAC at the time of randomization, history of acute MI within 12 months prior to randomization, acute coronary syndrome as indication to index PCI, PRECISE-DAPT or DAPT scores, gender, age, diabetes mellitus and the fulfillment of each inclusion criterion.

Study organization, timelines and conclusions.

This study is an investigator-driven clinical trial sponsored by European Cardiovascular Research Institute (ECRI -9) and supported by an unrestricted research grant from TERUMO. The Executive Committee (ExC) is responsible for scientific content and oversight of the study and oversees publication. The Steering Committee is comprised of the Executive Committee and national/regional lead investigators. The Operational Committee is responsible for executing and implementing study procedures under the supervision of ExC. The Data Monitoring Committee (DMC) is an independent, multi-disciplinary board composed of 3 members who are not directly involved in the conduct of the trial and is responsible for ensuring the safety of the patients participating in the clinical study. The DMC members will review the study on a periodic basis. An independent, multi-disciplinary and blinded Clinical Event Committee (CEC) is responsible for the adjudication of all investigator-reported as well as electronically triggered potential endpoints events from the eCRF. Independent study monitoring and site management are performed by CERC (Cardiovascular European Research Center, Massy, France), Cardialysis (Rotterdam, The Netherlands) and CV Quest (Tokyo, Japan). Data management, central data review and statistical analyses will be conducted by an independent academic Clinical Trial Unit located in Bern, Switzerland. The first study patient was randomized in April 2016 and enrolment is projected to reach completion by early 2019. At 20th April 2018, 894 patients were randomized and their distribution according to each HBR criterion is shown in Figure 4.

MASTER DAPT is the first dedicated randomized clinical trial aiming at investigating the optimal duration of antiplatelet therapy in patients with high bleeding risk features after bioresorbable polymer coated stent implantation.

Disclosures:

Dr Valgimigli reports grants from The Medicines Company and Terumo during the conduct of the study; personal fees from AstraZeneca, grants and personal fees from Terumo, personal fees from

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Figure Legends

Figure 1. Study design and Key Features. Patient selection starts immediately after index PCI and patients can be consented at any time between the index PCI and the one-month randomization visit. After index PCI, Dual Antiplatelet Therapy (DAPT) is mandatory for 1 month. During the randomization visit, eligibility is reassessed and if met, the patient is randomized to an abbreviated or a standard antiplatelet regimen.

Figure 2. Treatment in the Experimental Arm. In patients randomized to an abbreviated antiplatelet regimen without oral anticoagulant (OAC), a single anti-platelet agent (SAPT-either ASA or P2Y12i) is continued until 11 months post randomization. In patients requiring OAC, a SAPT (either ASA or clopidogrel) is continued until 5 months post randomization and OAC is prescribed until at least 11-month post randomization.

Figure 3. Treatment in the Control Arm. In patients randomized to a standard antiplatelet regimen without oral anticoagulant (OAC), aspirin is continued until at least 11 months post randomization. The P2Y12 inhibitor being taken at the time of randomization is continued for at least 5 months post randomization and up to 11 months post randomization. In patients requiring OAC, aspirin and clopidogrel are continued for at 2 months after randomization and up to 11 months post randomization. Thereafter, a single anti-platelet (SAPT- either aspirin or clopidogrel) is continued up to 11 months post randomization. OAC is continued until at least 11 months post randomization.

Figure 4 Distribution of high bleeding risk criteria among randomized patients

High bleeding risk criteria are not mutually exclusive and many patients fulfill more than one

Table I. High Bleeding Risk Criteria.

Post-PCI patients are at HBR if at least one of the following criteria applies:
1. Clinical indication for treatment with oral anticoagulant (OAC) for at least 12 months
2. Recent (< 12 months) non access site bleeding episode(s), which required medical attention (i.e. actionable bleeding)
3. Previous bleeding episode(s) which required hospitalization if the underlying cause has not been definitively treated (i.e. surgical removal of the bleeding source)
4. Age equal or greater 75 years
5. Systemic conditions associated with an increased bleeding risk (e.g hematological disorders, including a history of current thrombocytopenia defined as a platelet count <100.00/ mm^3 (<100 x 10^9/L) or any known coagulation disorder associated with increased bleeding risk
6. Documented anemia defined as repeated hemoglobin levels <11 g/dl or transfusion within 4 weeks before inclusion
7. Need for chronic treatment with steroids or non steroidal anti-inflammatory drugs
8. Diagnosed malignancy (other than skin) considered at high bleeding risk including gastro-intestinal, genito-urethral/renal and pulmonary
9. Stroke at any time or TIA in the previous 6 months
10. PRECISE-DAPT score ≥ 25

Table II. Inclusion and exclusion criteria.

Inclusion Criteria
Inclusion Criteria after index PCI 1. Age ≥18y 2. At least one HBR criteria (listed above) 3. All coronary lesions are successfully treated with Ultimaster stent 4. Free of any flow-limiting angiographic complications which required prolonged DAPT duration based on operator's decision 5. All stages of PCI are complete (if any) and no further PCI is planned
Inclusion Criteria at one-month randomization visit (30-44 days after qualifying index PCI) 1. At least one HBR criteria (listed above) or on the basis of post-PCI actionable non access-site related bleeding episode 2. Uneventful 30 days clinical course (i.e. new episode of acute coronary syndrome, symptomatic restenosis, stent thrombosis, stroke, any revascularization requiring prolonged DAPT) 3. If not on OAC: a) Patient is on DAPT regimen of aspirin and a P2Y12 inhibitor; b) Patient with one type of P2Y12 inhibitor for at least 7 days 4. If on OAC: a) Patient is on the same type of OAC for at least 7 days; b) Patient is on clopidogrel for at least 7 days
Exclusion Criteria
Patients are not eligible if any of the following applies: 1. Treated with stent other than Ultimaster stent within 6 months prior to index PCI 2. Treated for in-stent restenosis or stent thrombosis at index PCI or within 6 months before 3. Treated with a bioresorbable scaffold at any time prior to index procedure 4. Incapable of providing written informed consent 5. Under judicial protection, tutorship or curatorship 6. Unable to understand and follow study-related instructions or unable to comply with study protocol 7. Active bleeding requiring medical attention (BARC≥2) on randomization visit 8. Life expectancy less than one year 9. Known hypersensitivity or allergy for aspirin, clopidogrel, ticagrelor, prasugrel, cobalt chromium or sirolimus 10. Any planned and anticipated PCI 11. Participation in another trial 12. Pregnant or breast feeding women

Figure 1

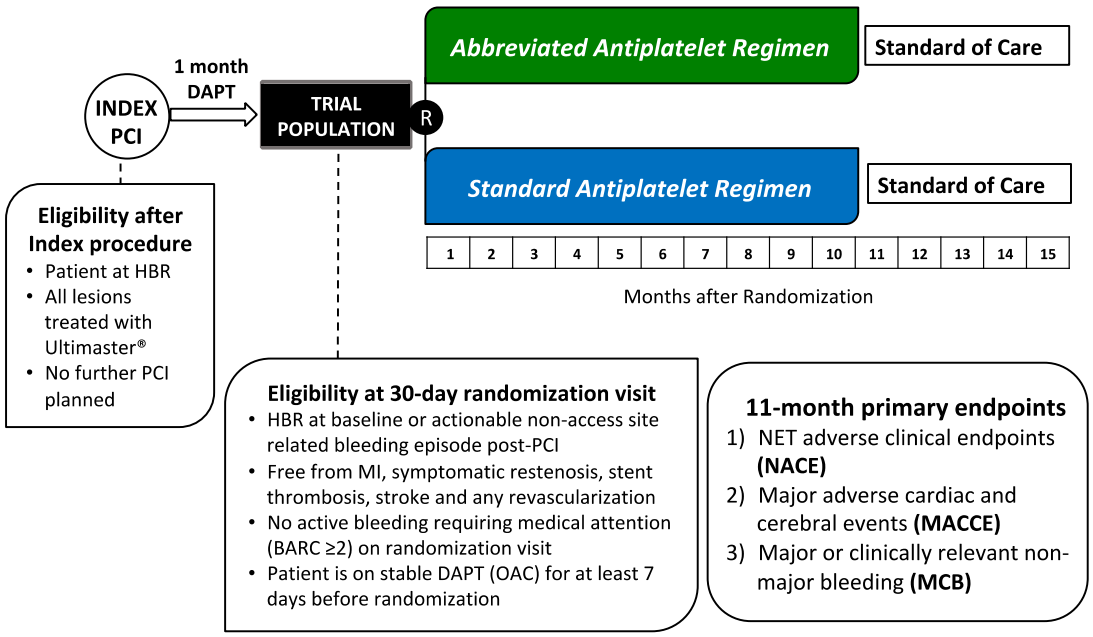

INDEX PCI
1 month DAPT
TRIAL POPULATION
R
Abbreviated Antiplatelet Regimen
Standard of Care
Standard Antiplatelet Regimen
Standard of Care
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Months after Randomization
Eligibility after Index procedure
• Patient at HBR
• All lesions treated with Ultimaster®
• No further PCI planned
Eligibility at 30-day randomization visit
• HBR at baseline or actionable non-access site related bleeding episode post-PCI
• Free from MI, symptomatic restenosis, stent thrombosis, stroke and any revascularization
• No active bleeding requiring medical attention (BARC ≥2) on randomization visit
• Patient is on stable DAPT (OAC) for at least 7 days before randomization
11-month primary endpoints
1) NET adverse clinical endpoints (NACE)
2) Major adverse cardiac and cerebral events (MACCE)
3) Major or clinically relevant non-major bleeding (MCB)

Figure 2

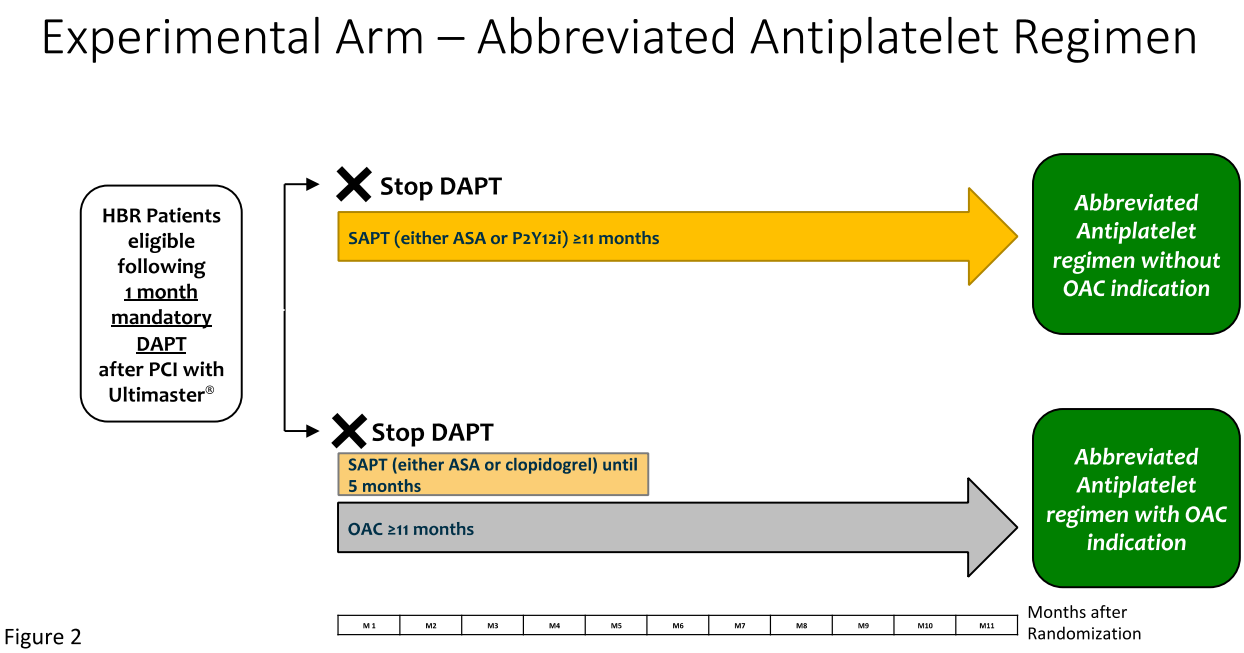


Figure 2

Figure 3

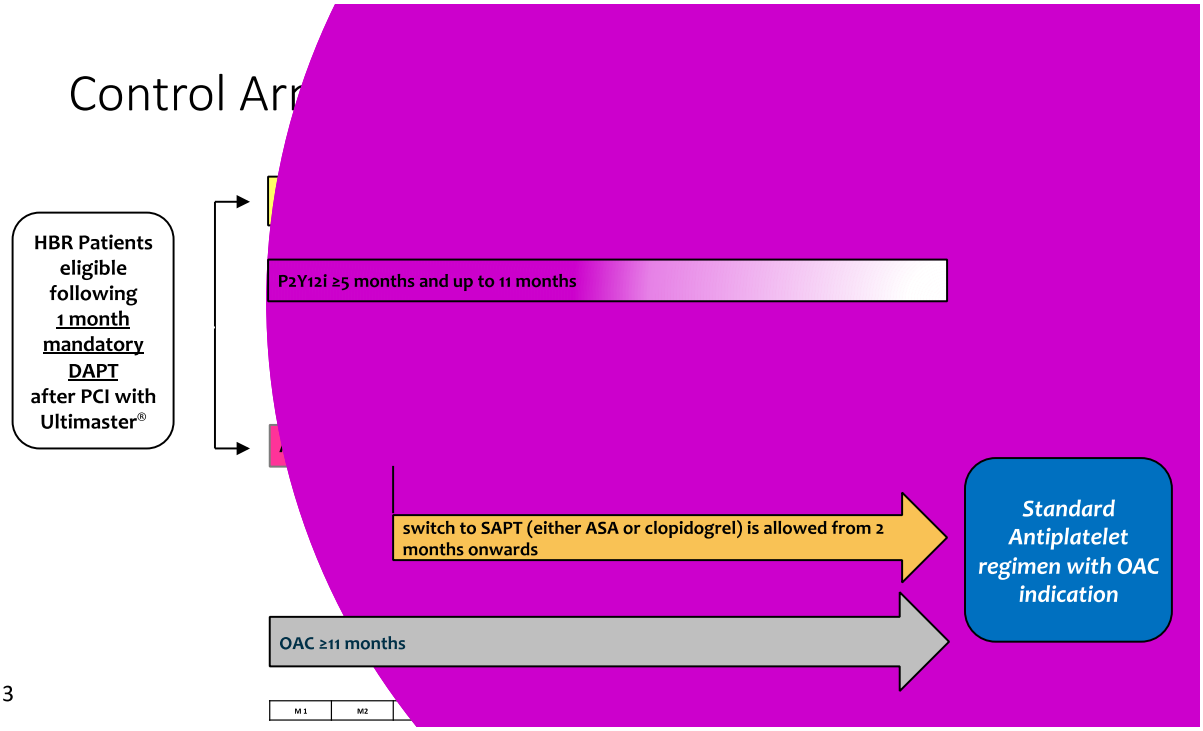
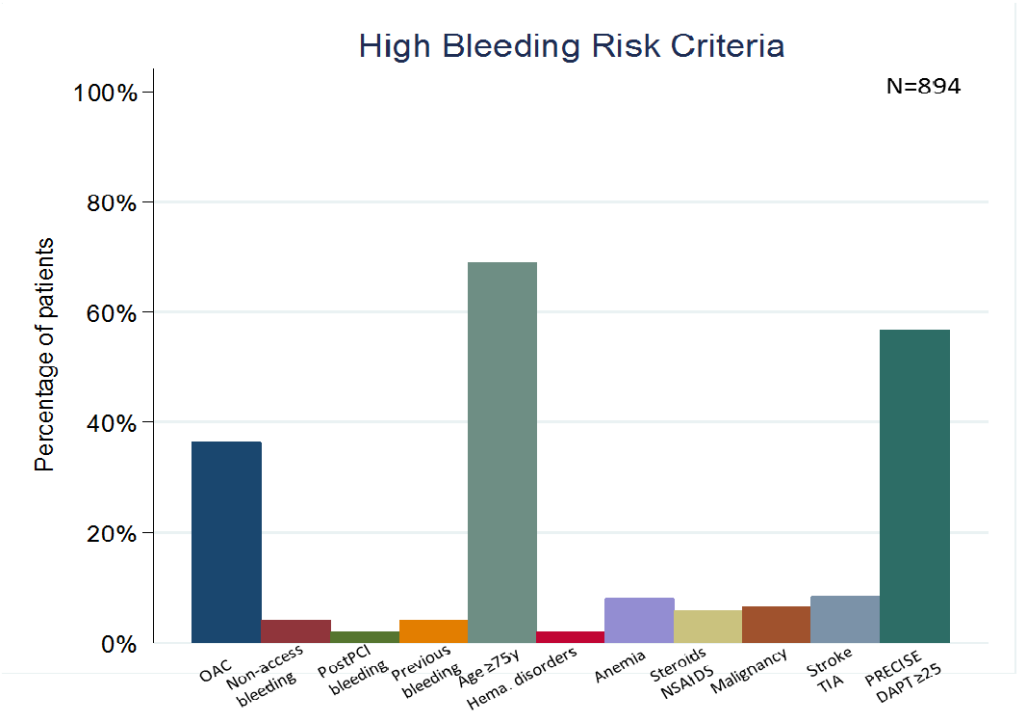


Figure 3

Figure 4


High Bleeding Risk Criteria
N=894
Percentage of patients
100%
80%
60%
40%
20%
0%
OAC
Non-access bleeding
PostPCI bleeding
Previous bleeding
Age ≥75y
Hema. disorders
Anemia
Steroids NSAIDS
Malignancy
Stroke TIA
PRECISE DAPT ≥25