Dual Antiplatelet Therapy after Coronary Stenting in High Bleeding Risk Patients

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This supplement contains the following items:

MASTER DAPT

MAnagement of high bleeding risk patients post bioresorbable polymer coated **STE**nt implantation with an abb**R**eviated versus prolonged **DAPT** regimen – MASTER DAPT

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Date	**Ver 1.0, November 2, 2016**
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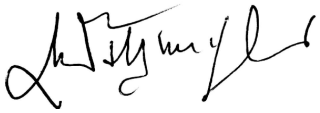
Protocol approval page

MASTER DAPT

Protocol version: 1.0, dated on November 2, 2016

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:



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Nov 2, 2016

Date_____

Protocol Signature Page

MASTER DAPT Protocol Version 1.0 dated on November 2, 2016

I have read the Protocol mentioned above and agree to adhere to its requirements.
I will provide copies of the Protocol and access to all information furnished by Sponsor and Coordinating Principal Investigators to the study personnel under my supervision and involved in carrying out the study. I will discuss this material with them to ensure that they are fully informed about the conduct of the study.
The contents of this Protocol may not be used in any other clinical study and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation, for example submission to an Ethics Committee; however, I will give prompt notice to the Sponsor of any such disclosure.

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1. Protocol Summary

Background	High bleeding risk population represents a significant proportion of coronary artery disease (CAD) patients undergoing coronary stent implantation. Decisions regarding the duration of dual antiplatelet therapy (DAPT) after stent implantation are difficult, especially after implantation of newer generation drug eluting stents (DES) due to conflicting results from recent trials. The current ESC guidelines of myocardial revascularization indicate that in patients at high bleeding risk (HBR), shorter DAPT duration (<6 months) might be considered after DES implantation (Class of recommendation: IIb). Similarly, the more recent American guidelines on DAPT duration, stated that in patients treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 or 6 months may be reasonable (Class of recommendation IIb). Both the European and American guidelines acknowledge that limited data is currently available to sustain this practice and call for dedicated DAPT studies in HBR patients. Therefore, further randomized trials are needed to appraise the optimal DAPT duration in HBR patients treated with contemporary DES.
Objectives	The objective is to compare, within current guidelines (GL) and instructions for use (IFU), an abbreviated versus a prolonged DAPT duration after bioresorbable polymer coated Ultimaster sirolimus-eluting stent implantation in patients presenting HBR features.
Study Design	An Investigator-initiated, multi-center, randomized clinical trial in HBR patients after PCI with Ultimaster bioresorbable polymer coated sirolimus-eluting stent implantation.
Index PCI	The index procedure is either single procedure or the last instalment in planned staged procedure.
Inclusion criteria	**Inclusion criteria after index PCI** After index PCI, patients aged 18 years or more are eligible for inclusion into the study if the following criteria are met. **1)** At least one among the HBR criteria (as defined below) is met. **2)** All lesions are successfully treated with Ultimaster stent in the context of routine clinical care, i.e. post-procedural angiographic diameter stenosis <20% by visual estimation **3)** Free from any flow-limiting angiographic complications (i.e. significant untreated dissection or major side-branch occlusion), which require prolonged DAPT duration based on operator's opinion. **4)** All stages of PCI are complete (if any) and no further PCI is planned. **Inclusion criteria at one-month randomization visit** At randomization visit (one month after index PCI), the following criteria must be met: **1)** Fulfilment of at least one HBR criterion (as defined below), or on the basis of post-PCI actionable (i.e. requiring medical attention) non-access site related bleeding episode **2)** Uneventful 30-day clinical course, i.e. free from spontaneous MI, symptomatic restenosis, stent thrombosis, stroke and any revascularization (coronary and non-coronary) requiring prolonged DAPT

	3) If not on OAC, a. Patient is on a DAPT regimen of aspirin and a P2Y12 inhibitor b. Patient with one type of P2Y12 inhibitor for at least 7 days (i.e. no switching between oral P2Y12 inhibitors has occurred in the previous 7 days) **4)** If on OAC a. Patient is on the same type of OAC (e.g. Vitamin K antagonist or NOAC) for at least 7 days b. Patient is on clopidogrel for at least 7 days *Definition of HBR* Post-PCI patients are at HBR if at least one of the following criteria applies: • Clinical indication for treatment with oral anticoagulants (OAC) for at least 12 months • Recent (<12 months) non-access site bleeding episode(s), which required medical attention (i.e. actionable bleeding). • Previous bleeding episode(s) which required hospitalization if the underlying cause has not been definitively treated (i.e. surgical removal of the bleeding source) • Age equal or greater than 75 years • Systemic conditions associated with an increased bleeding risk (e.g. haematological disorders, including a history of or current thrombocytopaenia defined as a platelet count <100,000/mm^3 (<100 x 10^9/L), or any known coagulation disorder associated with increased bleeding risk. • Documented anaemia defined as repeated haemoglobin levels <11 g/dl or transfusion within 4 weeks before inclusion. • Need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs • Diagnosed malignancy (other than skin) considered at high bleeding risk including gastro-intestinal, genito-urethral/renal and pulmonary. • Stroke at any time or TIA in the previous 6 months • PRECISE DAPT score of 25 or greater
Exclusion criteria	Patients are not eligible if any of the following applies **1)** Treated with stents other than Ultimaster stent within 6 months prior to index procedure **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)** Cannot provide 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

Informed consent	Eligible patients can be consented at any time between index PCI and a randomization visit at one month
Randomization	Randomization is performed at a randomization visit at one month that occurs between 30 and 44 days after index PCI. Patients are randomized to abbreviated or prolonged dual antiplatelet regimen. Randomization is stratified per site, by history of acute myocardial infarction (≤12 months prior to randomization), and planned use of OAC.
Abbreviated DAPT regimen	**Patients not on OAC** DAPT is discontinued and a single anti-platelet agent (SAPT) is continued until at least 11 months post randomization (i.e.12 months after index PCI). **Patients on OAC** DAPT is discontinued and either aspirin or clopidogrel is continued until 5 months post randomization (i.e. 6 months after index PCI). OAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).
Prolonged DAPT regimen	**Patients not on OAC** Aspirin is continued until at least 11 months post randomization (i.e.12 months after index PCI). The P2Y12 inhibitor being taken at the time of randomization is continued for at least 5 months and up to 11 months post randomization (i.e.12 months after index PCI). **Patients on OAC** Aspirin and clopidogrel are continued for at least 2 months (i.e. 3 months after index PCI) and up to 11 months post randomization (i.e. 12 months after index PCI). Thereafter, SAPT (either aspirin or clopidogrel) is continued up to 11 months post randomization (i.e.12 months after index PCI). OAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).
Treatment and Follow-up	Patients are treated according to the randomized regimen until 11 months after randomization. Clinical follow-up is performed 2, 5, 11 and 14 months after randomization.
Primary endpoints	This study has 3 primary endpoints: **1)** Net adverse clinical endpoints (NACE) defined as a composite of all-cause death, myocardial infarction, stroke and bleeding events defined as BARC 3 or 5 **2)** Major adverse cardiac and cerebral events (MACCE) defined as a composite of all-cause death, myocardial infarction and stroke **3)** Major or clinically relevant non-major bleeding (MCB) defined as a composite of type 2, 3 and 5 BARC bleeding events The main analyses evaluate the occurrence of the primary endpoints between randomization and 11 months thereafter. In secondary analyses, the occurrence of primary endpoints between randomization and 15 months after index PCI is evaluated.
Major Secondary endpoints	The secondary endpoints of the study are the following: **1)** The individual components of each composite primary endpoints **2)** The composite of cardiovascular death, MI, and stroke **3)** The composite of cardiovascular death, MI, and any revascularization **4)** Death from cardiovascular causes **5)** The composite of definite or probable stent thrombosis **6)** Myocardial infarction **7)** Any target vessel revascularization **8)** Urgent target vessel revascularization

	9) Urgent non-target vessel revascularization **10)** Clinically indicated non-target vessel revascularization **11)** Bleeding events according to the BARC, TIMI and GUSTO classification **12)** Transfusion rates both in patients with and/or without clinically detected over bleeding
Statistical Hypotheses	The study was designed to test the following hypotheses **1)** The abbreviated DAPT regimen is non-inferior to the prolonged DAPT regimen in terms of NACE within 12 months. **2)** The abbreviated DAPT regimen is non-inferior to the prolonged DAPT regimen in terms of MACCE within 12 months. **3)** The abbreviated DAPT regimen is superior to the prolonged regimen in terms of MCB within 12 months. These hypotheses are tested in a hierarchical order, in order to preserve type I error rate. Rates of primary endpoints are estimated as the cumulative incidence between randomization and 11 months (335 days) thereafter by the Kaplan-Meier methods. Rate differences are defined as the rate under abbreviated APT minus that under prolonged DAPT.
Sample size	The study includes 2 x 2150 (i.e. 4,300) patients. Sample size calculations have been made for a formal sample size of 2 x 2040 evaluable patients. This allows for attrition rate of 5%. The assumed event rates under prolonged DAPT are 12% for NACE, 8% for MACCE and 6.5% for MCB. All tests are carried out with a one-side type I error rate of 0.025. With this sample size, the study has: • >90% power to establish non-inferiority in NACE with a non-inferiority margin of 3.6% • >80% power to establish non-inferiority in MACCE with a non-inferiority margin of 2.4% • >90% power to establish superiority in MCB if abbreviated DAPT reduces the MCB rate from 6.5% to 4.2%, which corresponds to a 35% relative risk reduction.
Study sites	Approximately 100 or more Interventional Cardiology Centers across the globe excluding the USA.
Time-lines	Approximately 6 months for setting up the study organization, an expected enrolment period of approximately 18 months For each patient, the expected duration of participation is 14 months.

Contact	**Sponsor:** European Cardiovascular Research Institute (ECRI) ECRI-9 B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands **Coordinating Principal Investigators:** Marco Valgimigli Inselspital Universitätsspital Bern, Bern, Switzerland Pieter Smits Maasstad Ziekenhuis, Rotterdam, The Netherlands **Data Management, Central Data Review and Statistical Analysis:** Clinical Trials Unit (CTU) Universität Bern, CTU Bern Finkenhubelweg 11, 3012 Bern, Switzerland **Site Management and Monitoring (all countries except for Belgium and the Netherlands):** Cardiovascular European Research Center (CERC) 7 rue du Théatre, 91300 Massy, France **Site Management and Monitoring (for Belgium and the Netherlands), Safety Report and Clinical event committee:** Cardialysis B.V. PO Box 2125, 3000 CC Rotterdam, The Netherlands

2. Introduction

High bleeding risk patients undergoing PCI
High bleeding risk (HBR) population represents a large proportion of coronary artery disease (CAD) patients undergoing coronary stent implantation. In the BERN PCI registry, including all PCI patients receiving PCI at the University Hospital of BERN in Switzerland, 40% or more and 30% or more of patients fulfill HBR criteria as defined by the LEADERS FREE and ZEUS study, respectively (data on file).

The HBR patients undergoing PCI also frequently present risk factors of stent thrombosis and future athero-thrombotic events. Managing these patients in terms of decision on the most appropriate course of dual antiplatelet therapy (DAPT) after stent implantation remains a clinical challenge, especially after implantation of newer generation drug eluting stents (DES). Moreover, no single randomized controlled study has so far investigated the optimal duration of DAPT after stenting in HBR patients (who have largely been excluded from almost all studies investigating different DAPT durations after stenting or ACS). This largely contributes to the existing uncertainties with respect to optimal medical management of this selected yet largely prevalent population after stent implantation.

DAPT usage of HBR-PCI population in the current guidelines and in current practice
Current European or American Guidelines discuss DAPT duration in HBR populations after implantation of drug-eluting stent and both emphasize that evidence is missing or largely incomplete. As a result, current recommendations derive from inference of evidence generated in the context of DAPT studies, which did not or only partially include HBR patients or are based on consensus opinions.

The European guidelines of myocardial revascularization issued in 2014 indicated that DAPT is in general indicated for at least 6 months after DES implantation (Class I, level B) while in patients at HBR, shorter DAPT duration (<6 months) may be considered after DES implantation (Class IIb, level A).[1] The class IIb recommendation means that usefulness or efficacy is less well established by evidence or opinion. The Level of evidence A was supported by two randomized controlled studies, which recruited low risk and largely elective CAD patients (i.e. HBR patients were largely excluded) and in both studies the 3 month DAPT duration (experimental arm) was associated to Endeavor Sprint zotarolimus-eluting stent implantation[2-5]. The Endeavor Sprint zotarolimus-eluting stent is a rapidly (i.e. within 30 days) eluting stent which is currently no longer available on the market due to a higher need for target vessel reintervention compared to other DES and it has been replaced by the more effective Resolute Zotarolimus-eluting stent, which, in contrast to its predecessor, requires 180 days or more to completely elute the drug.

In the European guidelines of management of non-ST elevation ACS, 3-6 months of DAPT after DES in non-ST ACS is a IIb Class A recommendation in patients deemed at high bleeding risk [6]. Similarly, the more recent American guidelines on DAPT duration stated that in patients treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding

complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 or 6 months may be reasonable (Class of recommendation IIb).[7] Both the European and American guidelines acknowledge that limited data is currently available to sustain this practice and call for dedicated DAPT studies in HBR patients.

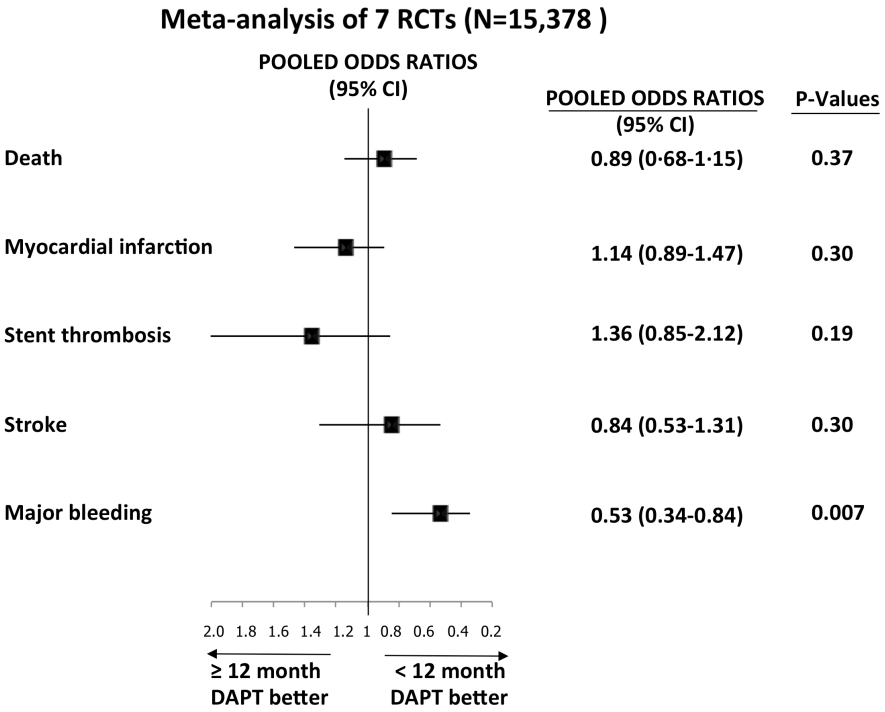
These guideline recommendations were largely based on studies using first-generation or Endeavor zotarolimus-eluting stents (RESET, OPIMIZE, EXCELLENT, PRODIGY and ISAR-SAFE) and not specifically recruiting HBR patients.[2-5] The data transferability from these trials to the newer generation drug-eluting stents is questionable, since newer generation DES have thinner struts with biocompatible polymer, biodegradable polymer or polymer-free elution mechanism, which may enable earlier vessel healing and earlier cessation of antiplatelet therapy.

In summary, clinicians are currently required to tailor DAPT regimen within guideline recommendations in patients at HBR after DES implantation, as captured in a recent survey performed under the auspices of the European Association of Percutaneous Intervention (EAPCI) on DAPT duration prescription[8]. A total of 1,134 physicians across the globe responded to the survey. The belief that first generation DES are more thrombogenic than newer generation devices and as such require long-term DAPT was highly prevalent among responders (93.5%). However, 54.8% of participants thought that there is still insufficient data to conclude that vulnerability to short DAPT duration is stent-specific within the class of newer generation DES. The majority agreed that 6-month DAPT is a safe pharmacological strategy after implantation of newer generation DES, but expressed a need for more clinical data, particularly if a duration shorter than 6-month DAPT is to be recommended, for example after implantation of new generation non-polymeric DES. The majority also stated that there is insufficient data to draw conclusions on the optimal DAPT duration regimen in HBR patients.

Evidence regarding DAPT duration in the first year after coronary stenting in unselected patients or patients not being at HBR

Including the recent ISAR-SAFE, seven studies, recruiting 15,378 patients have so far compared shorter than 12-month DAPT duration, (ranging from 3 to 6 months), to 12 month (5 studies) or 24 month (2 studies) DAPT duration[9, 10]. The mean age was comparable across these seven studies, ranging from 62 to 68 years, and the prevalence of diabetes mellitus ranged from 25% up to 39%. The prevalence of ST-segment elevation myocardial infarction at presentation varied widely amongst the included studies. Importantly, in all trials DAPT consisted of aspirin and clopidogrel. Loss at follow-up was variable across studies: SECURITY[11] and the ISAR-SAFE trials had the highest loss at follow-up, while in the EXCELLENT[12], RESET[4], PRODIGY [13] and ITALIC[14] trials loss at follow-up was minimal. ISAR-SAFE is the only study among those included based on a double-blind design. No detectable heterogeneity for the explored endpoints, as assessed by the Q chi^2 test was found, and I^2 was consistently equal to 0. Compared to at least 12 month DAPT duration, patients receiving shorter than 12 month DAPT therapy, had similar risk of death from all cause (OR 0.89; 95% CI, 0.68 to 1.15; P=0.37, fixed-effects) (**Figure**), myocardial infarction (OR 1.14; 95% CI, 0.89 to 1.47; P=0.30, fixed-effects) (**Figure**), definite or probable stent thrombosis (OR 1.36; 95% CI, 0.85 to 2.16; P=0.19, fixed-effects) (**Figure**), stroke (OR 0.84; 95% CI,

0.53 to 1.31; P=0.30, fixed-effects) (**Figure**), and lower risk of major bleeding (OR 0.53; 95% CI, 0.34 to 0.84; P=0.007, fixed-effects) (**Figure**).



Stent thrombogenicity: First and newer generation DES versus BMS

The threat of early (i.e. within the first 30 days) stent thrombosis (ST) has always been a major complication of percutaneous coronary intervention since the early days of stent intervention with bare metal stent (BMS). ST occurring after thirty days was considered to be rare in the BMS era. Drug-eluting stent (DES) were initially considered as more thrombogenic devices. This was due to their intrinsic capability to minimize late loss and as such potentially compromise stent coverage. Inflammation was also noted in experimental animal models. In the pivotal studies designed for stent approval, dual antiplatelet therapy (DAPT) was recommended for 2[15] or 3[16] months after sirolimus-eluting stent or 6[17] months after paclitaxel-eluting stent. No safety issues were noted early on, up to at least 1 year, as compared to the uncoated stents[15-17].

Following several anecdotal observations that first generation DES were associated to the occurrence of very late stent thrombosis, an entity which was at that time hardly known to exist after BMS, the community reacted by endorsing a long-term, or even an indefinite, DAPT regimen after DES implantation. First generation DES are associated with a two- to five fold higher risk of very late (i.e. after the first year) stent thrombosis as compared to BMS[18, 19]. This observation corroborated the perception of increased thrombogenicity of DES as compared to BMS and fueled *the longer the better* notion for DAPT duration in DES treated patients

First generation DESs have been entirely replaced by newer generation devices. Emerging evidence of superior safety with respect to ST and target vessel myocardial infarction has

been generated for many of the newly introduced devices when compared to first generation DES[20-22]. Importantly, most of these second generation stents were approved in non-inferiority trials compared with first generation DES. Therefore, few studies have directly compared second generation DES with BMS.

A network meta-analysis of 49 randomized trials, including 50,844 patients suggested that cobalt-chromium everolimus eluting stent were associated with a significant reduction of definite stent thrombosis up to 2-year follow-up as compared to bare metal stents[23]. However, only two direct randomized trials comparing cobalt-chromium everolimus eluting vs. bare metal stents were included [24, 25], and greater than 1-year follow-up data was available for only one[25] of these two studies.

More recently, a pooled analysis of 4,896 largely acute coronary syndrome patients showed a cardiac mortality benefit associated with the use of cobalt-chromium everolimus eluting, as compared to bare metal stent[26]. This treatment effect was shown to be persistent after multivariable adjustment of confounders, including duration of dual antiplatelet therapy after stenting. When all cardiac fatalities temporarily associated (i.e. occurring within one week) to the occurrence of definite or probable stent thrombosis were censored, cardiac mortality was no longer different between the two stent groups, suggesting a mechanistic interpretation of these clinical findings[26]. In the randomized PRODIGY trial (N=2,013), both composite major cardiovascular events and definite/probable stent thrombosis through 2 years were significantly higher among patients receiving BMS compared with newer generation DES[27-29]. Within the DAPT Study, the EES cohort represented 4496 randomized patients. [30] While stent type was not randomly assigned, significant reductions in ST and MI beyond 12m were observed with continued thienopyridine therapy, albeit smaller in absolute magnitude compared with the overall cohort of patients treated with DES. To better characterize BMS outcomes, the DAPT trial compared major adverse events among 10,026 patients treated with DES or BMS[31]. Although not designed to address stent selection at the time of revascularization, the study demonstrated a higher rate of stent thrombosis through 33 months of follow-up for BMS compared with DES[31]. Moreover, compared with 12 months of DAPT, a 30-month DAPT regimen after BMS treatment was associated with a consistent reduction in stent thrombosis similar to that of patients treated with DES, although these findings did not achieve statistical significance due to the smaller BMS cohort sample size[31].

In summary, current evidence suggests an improved safety profile of many second generation DESs as compared to BMS under similar DAPT durations and strongly suggests that a short DAPT duration does not justify the selection of BMS instead of those second generation DES, which have been proven superior in patients undergoing 30-day DAPT duration (see paragraph below).

Given the fact that second generation DES have been largely approved in head to head studies versus first or other second generation DES based on relatively large non-inferiority margins, and none of them was powered for ST, current evidence for each second generation DES should be interpreted as stent specific. This implies that only second generation DES that have proven safety and efficacy in studies mandating a short DAPT duration regimen should be used as such in clinical practice.

Recent trials of stent and DAPT in HBR population

Although several studies provided some reassurance that a short course of DAPT might be safe in certain patients treated with a particular type of DES, the optimal duration of dual antiplatelet therapy in HBR population remains uncertain. The ZEUS trial provided for the

first time data showing that a BMS-like DAPT regimen (30-day or even shorter) in patients receiving Endeavor sprint Zotarolimus-eluting stent (E-ZES) did not pose safety concerns while achieving superior clinical efficacy in patients with high bleeding risk. Yet, E-ZES has been withdrawn from the market due to higher late loss and suboptimal results in terms of target vessel revascularization as compared to other more potent DES. This study had paradigm-shift potential, as it suggested that, unlike original beliefs, a short duration of DAPT after stent implantation is possible and safe in selected DES patients. In particular, in the ZEUS trial, 828 patients fulfilling at least one pre-specified high bleeding risk (HBR) criterion were randomized to receive BMS or E-ZES, which is a hydrophilic polymer-based second-generation device with a unique drug fast-release profile. In this selected high-risk patient population, the study protocol mandated 30 day DAPT irrespective of the stent type[9]. The ZEUS study was therefore the first randomized controlled trial comparing two different stent types (BMS versus a second generation DES) after mandating a similarly short course of DAPT[9].
HBR patients derived benefits in terms of reductions of MACE (22.6% vs. 29%; HR 0.75; 95% CI 0.57-0.98; P=0.033), MI (3.5% vs. 10.4%; HR 0.33; 95% CI 0.18-0.60; P<0.001), TVR (5.9% vs. 11.4%; HR 0.50; 95% CI 0.30-0.80; P=0.005) and definite or probable ST (2.6% vs. 6.2%; HR 0.42; 95% CI 0.21-0.85; P=0.016) when treated with E-ZES as compared to BMS, which is consistent with study results observed in the overall population[32]. The lower risk of MI or ST observed in patients treated with E-ZES as compared to BMS, despite a similarly short DAPT duration in both stent groups, is consistent with the growing evidence that lower in-stent intimal hyperplasia may carry not only greater efficacy (e.g. lower TVR) but also improved safety (e.g. lower stent thrombosis or stent-related MIs).

More recently, the LEADERS FREE trial has been published, where 2466 HBR patients were allocated in a double blind manner to a drug coated stent (DCS) or the corresponding uncoated stent (Gazelle)[33]. All patients received 1 month of dual antiplatelet therapy. At 390 days, the primary safety end point (a composite of cardiac death, myocardial infarction, or stent thrombosis) occurred in 112 patients (9.4%) in the drug-coated–stent group and in 154 patients (12.9%) in the bare-metal–stent group (0.71; 95% CI, 0.56 to 0.91; P = 0.005 for superiority) due to a significant reduction of MI (6.1% vs. 8.9%; HR: 0.68; 95% CI: 0.50 50 0.91; p=0.01)[33]. This study extended to DCS the results previously reported by the ZEUS study, by showing not only improved efficacy in terms of lower target lesion revascularisation but also a lower risk of myocardial infarction in patients who received DCS.

It remains unclear if the results obtained by E-ZES, a peculiar durable and hydrophilic polymer DES which elutes the drug from the stent platform in less than 30 days and by the DCS, which is a polymer-free rapidly (i.e. mainly within 30 days) eluting stent can be transferred to other less rapidly eluting DES such as those based on hydrophobic durable or bioresorable polymers. In addition, the ZEUS and LEADERS FREE studies compared a specific DES versus BMS under a similarly short DAPT duration (i.e. 30 days). As a result, no study has so far specifically investigated the optimal DAPT duration (i.e. 30 days or longer) in patients at high bleeding risk. However, these two studies provide compelling evidence suggesting that BMS is no longer a contemporary treatment option in HBR and the need for a shortened DAPT duration should not justify the implantation of BMS [9, 34].

The Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study (PRODIGY) is the only DAPT study, which included patients on an all-comer basis. The median CRUSADE score was 25 (IQR= 18-35; mean±SD; 26.5±12.8) whereas the median ACUITY and HAS-BLED scores were 15 (IQR; 10-21;mean±SD = 15.8±7.9) and 1 (IQR; 1-2; mean±SD = 1.3±0.7) respectively [35]. By applying previously validated cut-offs, 307 (15.8%) patients based on CRUSADE, 991 (50.9%) patients based on ACUITY and 55 patients (2.8%) based on HAS-BLED, fulfilled high or very HBR category. Most of the patients with a high CRUSADE score also satisfied HBR criteria according to both HAS-BLED and ACUITY, whereas the vast majority of patients at HBR according to ACUITY did not reach the same risk category for the other two scores. The CRUSADE score provided a reasonable sensitivity and the highest specificity, correctly classifying 67% of patients without events in the low risk category. At the C-Statistics analysis, the CRUSADE risk score better predicted the occurrence of major bleeding (AUC=0.71) compared to ACUITY (AUC=0.68) and HAS-BLED scores (AUC=0.63) both as a continuous and as a three-risk category variable ($p< 0.005$ for all the observations). Patients fulfilling the high CRUSADE score (HCS) showed almost a three-fold greater rate of major bleeding when treated with a 24-month as compared to 6-month DAPT (9.7 vs. 3.7%; ARD 6%; 95%CI 0.4, 12.3%; p=0.04); patients with low to intermediate CRUSADE score (LICS) did not experience a significant increase of major bleeding when treated with long vs. short DAPT duration (2.4 vs. 1.6%; ARD 0.8% CI −0.6, 2.2%; p=0.25). A quantitative interaction was noted between bleeding risk and duration of antiplatelet therapy with respect to major bleeding (P_{int}=0.05). The number of patients needed to treat for harm (NNTH) to experience a major bleeding with prolonged DAPT in the HCS group was 17. These findings remained consistent across bleeding scales**.** Patients with HCS experienced an almost five-fold increase of red blood cell transfusion in the 24-month as compared to the 6-month DAPT duration arms (8.3% vs. 1.8%; ARD 6.5%; 95%CI 1.6, 12.3%; p=0.02; NNTH: 15.4) whereas it did not differ in patients with LICS (1.7% vs. 1.2%; p=0.45; ARD 0.5%; 95%CI −0.6, 1.7%; p=0.45), with positive interaction testing (P_{int} =0.01).

Bleeding events in practice and their impact on short- and long-term outcomes

Haemorrhagic complications occur with a frequency of 1-10% during treatment for ACS and after PCI [36-38]. This variability in the measured incidence is due to several factors including differences in patient characteristics, concomitant therapies, and definitions across datasets. Regardless of the definition used, several studies have demonstrated that bleeding is associated with an increased risk for short- and long-term adverse outcomes including recurrent myocardial infarction (MI) [39], stroke[40], stent thrombosis (6), and death[36-38, 41]. The nature of this relationship, however, and its implications for clinical practice remain unclear. The exact mechanisms underlying this relationship are not known, but may include the cessation of evidence-based therapies in patients who suffer bleeding complications[42, 43], the direct effects of blood transfusion used to treat bleeding[44, 44], or greater prevalence of comorbidities in patients who bleed[45], as well as a deleterious role of anemia[46].

It is possible that bleeding may simply be a surrogate for high-risk patients, because those patients at increased risk for bleeding complications (such as the elderly) are also at increased risk of death after an ACS event, irrespective of whether they had experienced a bleeding complication. This interpretation about the possible lack of cause-effect relationship between bleeding and subsequent worse outcomes is at least partially supported by retrospective studies showing that the hazard posed by bleeding may extend well after the effects of the

bleeding event itself should have resolved (i.e. after 1 year)[47]. On the other hand, since the exact mechanisms through which bleeding is deleterious are not known, caution should be taken before assuming that the risk of bleeding is to be restricted to a limited interval after the event.

An interesting observation on this important matter comes from a sub-analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38)[41]. This study suggested that the impact of instrumented or traumatic serious bleeding on mortality was of short duration (i.e. less than one week) whereas serious spontaneous bleeding tended to have a longer impact on mortality, with a significantly elevated HR for approximately 1 month and a non-significant trend beyond that time[41]. Hence, the hazard of bleeding on outcomes may last for a variable period of time depending on the type (i.e. instrumented vs. spontaneous) and perhaps severity of the haemorrhagic event.

The most compelling evidence today about the cause-effect relationship between bleeding and impaired short- to medium term outcomes is provided by interventional studies demonstrating that bleeding reduction strategies are associated with improved survival in patients with ACS and those undergoing PCI. In the OASIS-5 trial that compared the synthetic indirect Factor Xa inhibitor fondaparinux with enoxaparin in 20,078 patients with non-ST-segment elevation ACS, fondaparinux was statistically noninferior to enoxaparin with respect to 9-day death, MI or refractory ischemia (fondaparinux 5.8% vs. enoxaparin in 5.7%) and was superior with respect to 9-day major bleeding (fondaparinux 2.2% vs. enoxaparin 4.1%, $p<0.001$)[48]. At 30 days, the number of deaths was significantly lower among patients assigned to fondaparinux (295 vs. 352, p=0.02); this persisted at 180 days (deaths in fondaparinux arm 574 vs. deaths in enoxaparin arm 638, p=0.05). Similarly, in the HORIZONS AMI trial comparing the direct thrombin inhibitor bivalirudin with unfractionated heparin plus glycoprotein IIb/IIIa inhibitor in 3602 patients with ST-segment elevation MI undergoing primary PCI, the strategy of bivalirudin was associated with a significant reduction in major bleeding at 30 days (4.9% vs. 8.3%, $p<0.001$) and mortality at 30 days (2.1% vs. 3.1%, p-0.047) and thereafter (3.5% vs. 4.8%, p=0.037)[49]. The WOEST study recruited 573 patients undergoing PCI with an indication to oral anticoagulation (largely driven by concomitant or previous atrial fibrillation). 284 patients were assigned to the double-therapy group, consisting of clopidogrel and warfarin and 289 to the triple-therapy group based on aspirin, clopidogrel and warfarin[50]. Bleeding episodes were seen in 54 (19.4%) patients receiving double therapy and in 126 (44.4%) receiving triple therapy (hazard ratio [HR] 0.36, 95% CI 0.26–0.50, $p<0{\cdot}0001$). In the double-therapy group, six (2.2%) patients had multiple bleeding events, compared with 34 (12.0%) in the triple-therapy group. 11 (3.9%) patients receiving double therapy required at least one blood transfusion, compared with 27 (9.5%) patients in the triple-therapy group (odds ratio from Kaplan-Meier curve 0.39, 95% CI 0.17–0.84, p=0.011). Interestingly, the combined secondary endpoint of death, MI, stroke, target-vessel revascularisation, and stent thrombosis as well as overall mortality rate were significantly lower in the double therapy regimen, again emphasizing the importance of preventing bleeding as key strategy to avoid ischemic recurrences and improve global survival[50].

More recently, the results of the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) were published.[51, 52] In this study, 8,404 ACS patients were randomly allocated to receive transradial versus transfemoral access site and in those undergoing PCI or with ST-elevation myocardial infarction (STEMI)

at presentation, a second randomization was performed to two different anti-thrombin agents (unfractionated heparin or bivalirudin). Interestingly, both transradial as compared to transfemoral, and bivalirudin, as compared to unfractionated heparin, resulted in a lower risk of major bleeding complications and this resulted in lower overall and cardiovascular mortality rates. Hence, current evidence demonstrates that bleeding is not only associated but also a driver of mortality rate in patients undergoing PCI. Efforts should be made in clinical practice to minimize that risk as long as these measures do not generate an unacceptable high ischemic risk.

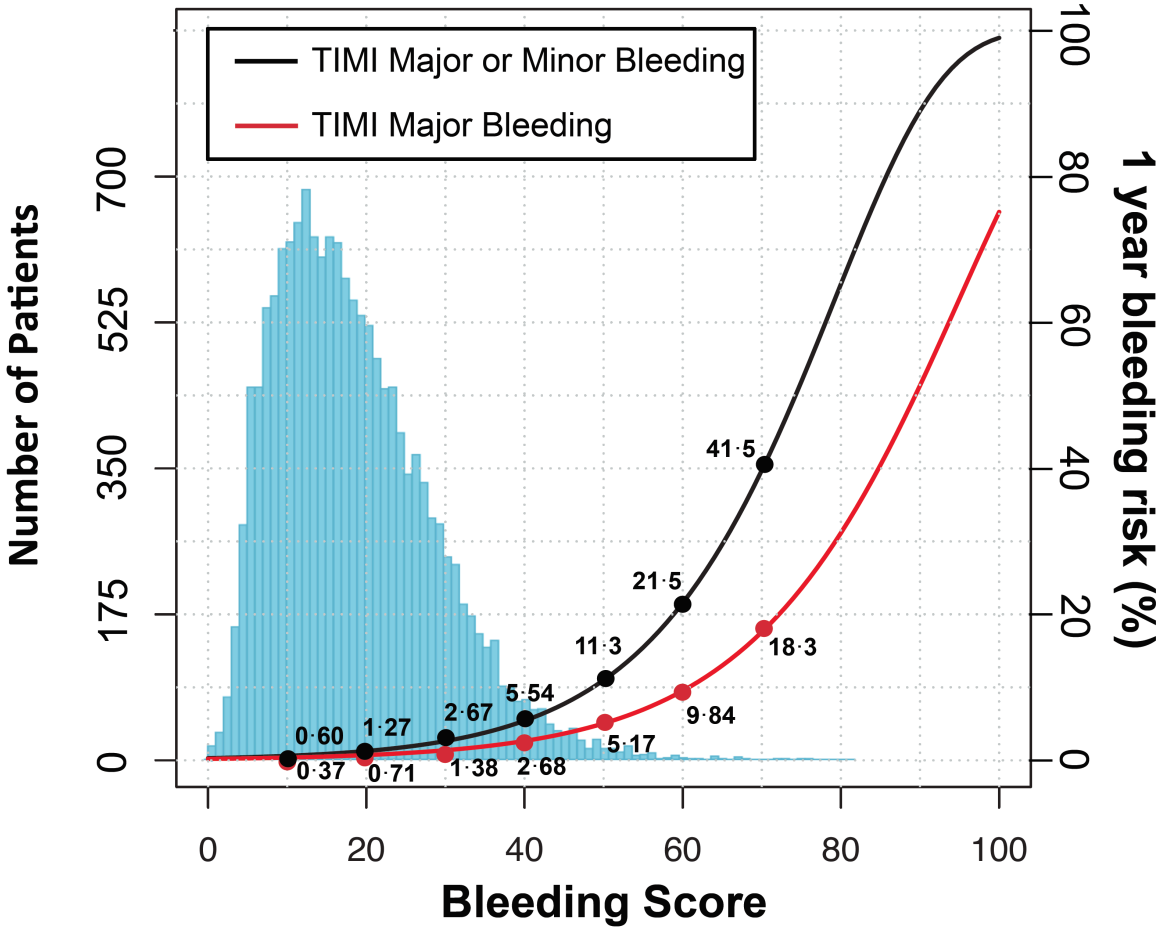
Tools to predict bleeding risk in practice

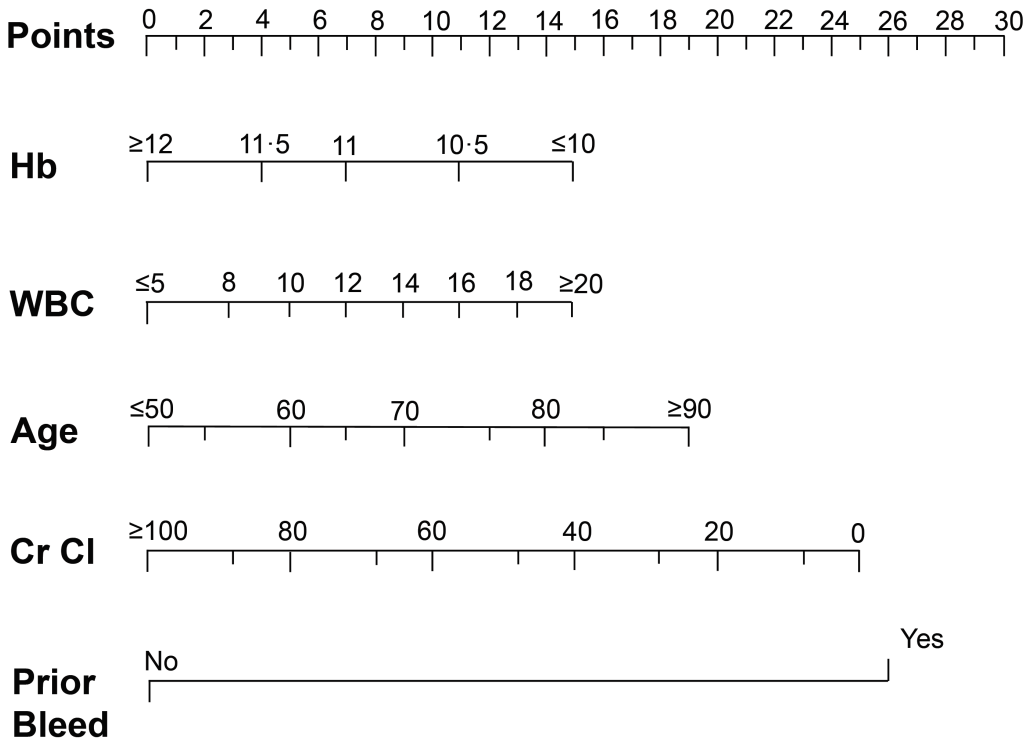
As discussed previously, despite being promising, the use of CRUSADE bleeding risk score in assessing which patient should be treated with prolonged or a shortened DAPT duration remains questionable. This is based on the concern that the CRUSDAE bleeding risk score was developed to predict in hospital bleeding events, which are largely driven by access site complications.[53]

In response to the clinical need to develop a risk model able to predict out of hospital bleeding events in patients on DAPT, the PRECISE-DAPT (**P**RODIGY–**R**ESET–**E**XCELLENT–**C**OMFORTABLE AMI– B**I**OSCIENCE–**S**ECURITY–ZEUS–OPTIMIZ**E**) bleeding risk was recently developed.

The study population included 14,963 patients with established coronary artery disease, treated with coronary stent implantation. Dual antiplatelet therapy at discharge was implemented virtually in all patients (98.3%) with median treatment duration of 360 days (IQR 95-365).

From the final multivariable model, a five-item bleeding risk score (age, creatinine clearance, haemoglobin and WBC at baseline, and prior spontaneous bleeding – PRECISE-DAPT score) was generated by assigning points to each factor based on the magnitude of association of each predictor with bleeding. A nomogram to calculate the score and the risk of bleeding at 12 months is presented below:


TIMI Major or Minor Bleeding
TIMI Major Bleeding
Number of Patients
0
175
350
525
700
1 year bleeding risk (%)
0
20
40
60
80
100
0·37
0·60
0·71
1·27
1·38
2·67
2·68
5·54
5·17
11·3
9·84
21·5
18·3
41·5
0
20
40
60
80
100
Bleeding Score


Points
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Hb
≥12 11·5 11 10·5 ≤10
WBC
≤5 8 10 12 14 16 18 ≥20
Age
≤50 60 70 80 ≥90
Cr Cl
≥100 80 60 40 20 0
Prior Bleed
No
Yes

A web-calculator and mobile App are available at **www.precisedaptscore.com**. The PRECISE-DAPT score showed a c-index of 0.73 (95%CI 0.61-0.85) for out-of-hospital TIMI major or minor bleeding and 0.71 (95%CI 0.57-0.85) for TIMI major bleeding. The score's discrimination was also consistent irrespective of the clinical presentation at the time of PCI. On further sensitivity analysis, the score discriminated TIMI bleeding in patients receiving clopidogrel (c-index: 0.76, 95%CI 0.65-0.86) or ticagrelor (c-index: 0.71, 95%CI 0.44-0.98).
The PARIS bleeding risk score was also used as a benchmark comparator for the risk prediction offered by the PRECISE DAPT score. In the validation cohort, the PRECISE-DAPT score showed superior discrimination as compared to the PARIS score for both TIMI major or minor (0.68 vs. 0.65; p= 0.016) and for TIMI major bleeding (0.67 vs. 0.61; p= 0.003). A simplified score modelled without WBC was also derived and validated. This simplified four-item score showed reasonable discriminatory capability and may help provide objective bleeding risk assessment in cases where WBC might not be readily available. Importantly, The PRECISE DAPT score without WBC provided consistent superior discrimination compared to the PARIS score for both TIMI major or minor (0.68 vs. 0.65; p= 0.008) and TIMI major bleeding (0.66 vs. 0.61; p= 0.004). The nomogram to calculate the score and corresponding 12 month bleeding risk in the absence of WBC is presented above.

PRECISE BLEEDING RISK SCORE AND DAPT DURATION

A significant reduction in bleeding risk with a short (3-6 months) rather than a long (12-24 months) duration of treatment was observed exclusively in patients at high bleeding risk according to the PRECISE DAPT score (ARD -2.59, 95%CI -4.34 to -0.82; NNT: 38) but not in those with a lower bleeding risk profile (ARD -0.14, 95%CI -0.49 to +0.22) (P_{int}=0.007). The bleeding risk status-by-DAPT-duration-interaction on bleeding events remained significant after censoring events occurring beyond 12 months (P_{int}=0.047).
Hence, The PRECISE-DAPT score was able to identify patients at high bleeding risk, who may benefit from a shorter DAPT duration, and patients at lower bleeding risk, who may tolerate standard treatment duration.

These observations provide rationale for including patients at HBR based on the PRECISE DAPT score in the current study and testing in these selected HBR population whether further reducing DAPT duration will optimize risks versus benefits.

Ultimaster stent and 1 month DAPT CE Mark labeling

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 (IFU) 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. This labelling was based on the evidence, which is discussed below.

The Ultimaster coronary stent system consists of a cobalt-chromium (Co-Cr) bare metal stent platform featuring thin struts (80 µm) with a unique open-cell design for easy access to a side branch and conformability to the vessel wall. The stent is mounted on a rapid-exchange catheter with a high-pressure, semi-compliant balloon. 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. The drug coating components were chosen to optimize performance with minimal drug and polymer content and controlled drug release kinetics. 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. Furthermore, coating only the abluminal surface leaves the luminal side of the stent free from drug and polymer, as such enhancing endothelial coverage.

In *in vivo* study, the drug dose, 3.9 µg/mm-stent length, was justified by the dose range study in pigs. A 28-day implantation study and 90-day implantation study in porcine coronary artery demonstrated that the ULTIMASTER Terumo drug-eluting coronary stent suppresses neointima formation but does not inhibit healing process and does not induce any inflammation. Moreover, the results of *in vivo* elution profile study and *in vivo* degradation study for the polymer proved that the drug release profile is adjusted to best match the biological response: initial release will suppress injury and inflammation induced by catheters manipulation and stent implantation. The remaining drug is released along with polymer degradation within 3-4 months, after which time the Terumo drug-eluting stent becomes the bare metal stent: Kaname™ CoCr Stent.

Based on the results of the series of pre-clinical bench tests combined with chemical, animal, and biocompatibility studies conducted to date, it was concluded that the ULTIMASTER drug-eluting coronary stent system does not exhibit any toxic potential.

Clinical Studies

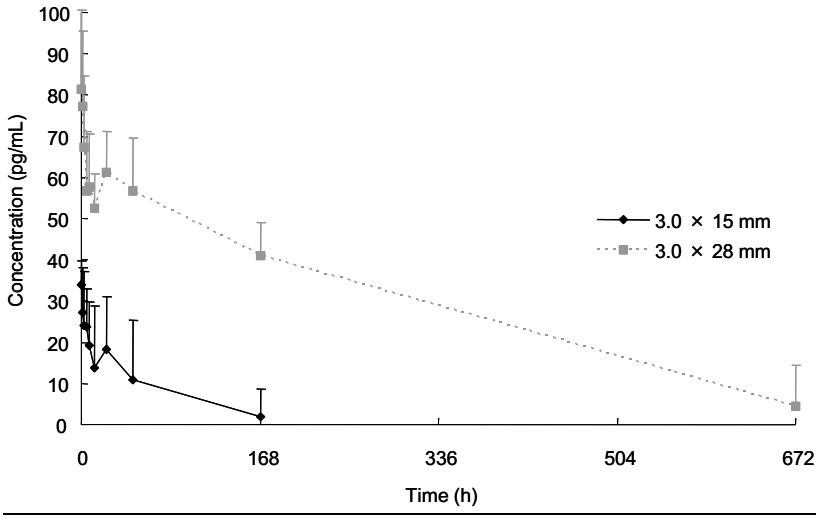
ULTIMASTER PK study

The "Pharmacokinetic study of the ULTIMASTER Terumo Drug Eluting Coronary Stent System" was performed to demonstrate the safety and pharmacokinetic profile of the ULTIMASTER DES when implanted in patients with de novo lesions in native coronary arteries.54 The potential influence on the coronary vasomotor response was also evaluated at 6 months follow-up.

Twenty patients with de novo stenosis of native coronary arteries were enrolled. Fifty-five (55)% were male and 45% female. Average age of patients was 61.75 ± 8.28 years and half had LVEF in the range of 40-50%. With regards to the angina status, almost all enrolled patients (90%) presented stable angina, predominantly CCS 2 (83.3 %), while 10% of patients had silent ischemia. Single vessel coronary artery disease (CAD) was detected in 60% and multivessel CAD in 40% of patients. As for their medical history 55% of patients had previous MI, 40% previous PCI and none of the patients had previous CABG before enrolment. Most of the patients had a lesion in the left anterior descending (60%), followed by the circumflex (25%) and the right coronary artery (15%).

After 28 days, 2 of the 10 subjects (20%) implanted with Ultimaster-3.0x28 mm and none of the 10 subjects (0%) implanted with Ultimaster-3.0x15 mm had a measurable concentration of sirolimus. In the figure below, sirolimus concentrations after implantation of 15mm-length (n=10) and 28mm-length (n=10) Ultimaster stent is shown as Mean ±S.D.[54] In case the

individual value was below the lower limit of quantification (LLOQ: 20.0 pg/mL), the value was treated as 0 pg/mL in the analysis.



The median maximum concentration (Cmax) in patients implanted with Ulttimaster-3028 was 87.2 pg/mL and ranged from 60.0 pg/mL and to 105 pg/mL. The median systemic exposure in patients_implanted with DS-3028, as measured by the area-under-the-time-concentration curve (AUC0-t) over the observation period, was 8.31 ng h /mL and ranged from 6.47 ng h /mL to 28.0 ng h /mL.

The maximum sirolimus concentration after implantation of a single Cypher stent (dosage: 150 µg/3.0mm-diameter and 18mm-lenghth) was 570±120 pg/mL [27]. In comparison, the Cmax of sirolimus in patients implanted with Ultimaster (dosage: 112 µg/3.0mm-diameter and 28mm-length) in this study was 87.2 pg/mL and thus 6.5-fold lower. The sirolimus AUC0-t after implantation of a Cypher stent was 55.1±15.5 ng h /mL, while the sirolimus AUC0-t after implantation of a single longest Ultimaster was only 8.31 ng h /mL (6.6-fold lower).

Due to the abluminal coating of Ultimaster, the systemic exposure of sirolimus released from the Ultimaster is quite low and a more specific distribution of sirolimus to the vessel is achieved.

CENTURY Study

The CENTURY study (Clinical Evaluation of New Terumo drug elUting coRonary stent system in the treatment of patients with coronarY artery disease, protocol number: T118E4) was performed in 8 hospitals in Europe to evaluate the safety and effectiveness of ULTIMASTER DES for the treatment of up to two de novo lesions or restenotic post-PTCA (non-stented) lesions located in up to two epicardial native coronary arteries (maximum one lesion per vessel) suitable for treatment with stents from 2.5 to 4.0 mm in diameter. Primary endpoint was in-stent late loss at 6 months follow-up, and the results were compared with the historical outcomes of the KARE study. The CENTURY Study was also intended to evaluate treated vessels and lesions by intravascular imaging such as intravascular ultrasound (IVUS) and Optical frequency domain imaging (OFDI) to further assess any local impact that the new stent could have on the vessel wall.

Among the 105 patients enrolled in the CENTURY study,[55] the large majority of patients were male (76.2%). The mean age of patients was 60.64±8.42. The incidence of cardiovascular risk factors was: diabetes (23.8%, out of which 24.0% were Insulin dependent), arterial hypertension (81.6%), dyslipidemia (85.6%), smoking (current/previous: 71.4%) or family history of coronary artery disease (58.8%). 20% of patients had previously undergone a PCI or CABG, and about half of patients (49%) had a history of MI. At admission, 20.0% of patients had silent ischemia, 77.1% and 2.9% stable angina and unstable angina respectively. Almost all patients (95.2%) were on Aspirin at admission and 78.1 % received clopidogrel.

In total 113 lesions were treated. A total of 39 lesions (34.5%) were located in the Right Coronary Artery (RCA), 45 lesions (39,8%) in the Left Anterior Descending (LAD) and 29 lesions (25,7%) in the Left Circumflex (CFX). A single lesion was treated in 97 patients (92.4%) while in 8 patients (7.6%) 2 lesions in 2 separate coronary vessels were treated. 88.6% of the patients had one stent implanted, while 11.4% of patients received multiple stents. Most of the lesions (89.5%) were treated through the femoral access site and 31.9% of the lesions were post-dilated.

The Ultimaster stent proved superior to BMS control regarding in-stent late loss at 6 months of 0.04±0.35 mm versus 0.75±0.43 mm, respectively ($p<0.001$). Up to 3 years follow up, there was 1 (0.95%) non-cardiac death and 4 patients (3.8%) had myocardial infarction (MI) in the CENTURY study. Clinically driven target lesion revascularization (CD-TLR) and clinically driven target vessel revascularization (CD-TVR) were 2.9% and 4.8% respectively, while in the BMS control they were 7.1% and 9.2%, respectively. Total TLR and TVR were 4.8% and 7.6%, which are significantly lower ($P<0.03$) when compared with the 3-year TLR (13.8%) and TVR (16.0%) in the BMS control. The rate of non-TVR was 12.4% and 7.8% at 3-year follow-up. The overall target lesion failure (TLF) and target vessel failure (TVF) at 3 years in the CENTURY study were 5.7% and 7.6%, while in the BMS historical control they were 9.6% and 11.4%, respectively. Notably in patients treated with Ultimaster DES in the CENTURY study, there were no stent thromboses between 1 day and 3 years, with only 1 possible stent thrombosis in BMS control. Between 1 and 3 years, there were only 1 death, 2 MIs, 1 TLR, and 2 TVRs. At 3-year follow up,[56] 94.2% and 94.3% of patients were angina free, and 1.9% and 4.6% of patients were on DAPT treatment in Ultimatser and BMS group, respectively.

The CENTURY study demonstrated that Ultimaster DES was superior to its bare metal stent platform with respect to in-stent late loss as well as long-term efficacy, with similar safety. There were only a few new events between 1 and 3 years follow up, which were more likely related to disease progression than initial treatment. The clinical benefit of Ultimaster DES was reflected by no new stent thromboses between 1 day to 3 years, and the low rates of clinically indicated revascularizations of target lesion up to 3 years.

CENTURY II Study

The CENTURY II study was designed to further evaluate the safety and efficacy of ULTIMASTER in more complex patients population and in comparison to the Xience stent which is one of the most frequently used stents and considered as a reference. The study was powered to show non-inferiority of ULTIMASTER versus Xience stent for the clinical endpoint of Target Lesion Failure (TLF), a composite of cardiac death and myocardial

infarction not clearly attributable to a non-target vessel and clinically indicated target lesion revascularization.

The primary endpoint[57], freedom from TLF at 9 months, was 95.6% with Ultimaster and 95.1% with Xience DES (P non-inferiority < 0.0001). At 2-year follow up,[58] TLF rates were 5.81% with Ultimaster vs 6.0% with Xience (P=0.73). Target vessel failure was also comparable between the two groups (7.99% with Ultimaster vs 8.18% with Xience, P=0.77). Cardiac death rate at 2 years was 1.27% with Ultimaster and 2.0% with Xience (P=0.34), respectively, while the total death rate was 2.18% with Ultimaster and 3.82% with Xience (P=0.11). MI was 2.36% in the Ultimaster and 2.91% in the Xience group (P=0.57), and total CI-TLR rate was also similar between the two groups (4.4% with Ultimaster vs 4.3% with Xience, P=0.62). Patient oriented composite endpoint (a composite of any death, any myocardial infarction and any coronary artery revascularization) was 13.4% and 16.9% (P=0.11). At 2 years, bleeding rates were 9.8% in the Ultimaster and 11.5% in the Xience group (P=0.37), while 31.1% and 29.2% of patients were on dual antiplatelet treatment respectively. Any angina at 2 years was recorded in 5.5% of patients in the Ultimaster and 7.4% of patients in the Xience group (P=0.23). Stent thrombosis rate was 1.1% in both groups at 2 years with no stent thrombosis between 12 and 24 months.[58]

This large-scale global trial enrolling a patient population representing daily clinical practice demonstrated the safety and efficacy profile of the Ultimaster stent.

MASTER STUDY

The Master study was a prospective, randomized, controlled, single blind, multicenter trial to compare the safety and efficacy of the Ultimaster DES with bare metal stent (BMS) in STEMI patients. The hypothesis was that the Ultimaster DES outperforms BMS in STEMI, with superiority in efficacy and equivalence in safety. The primary endpoints were (1) safety at 1 month: composite of all-cause death, recurrent MI, unplanned infarct related artery revascularization, stroke, definite stent thrombosis or major bleeding; (2) efficacy at 6 months: in-stent late loss in a subset of patients, and (3) safety and efficacy at 12 months: target vessel failure (TVF), composite of cardiac death, target vessel related MI and clinically driven target vessel revascularisation. Five hundred patients were randomized in 3:1 ratio (375 in Ultimaster and 125 in BMS). Among them, 100 patients were randomized in the same ratio to angiographic follow up at 6 months (75 in the Ultimaster and 25 in the BMS arm).

The mean age (60.2 vs. 61.5 y) and gender (81.0% vs. 80.0% male) were similar between the two randomized groups (P≥0.23). Basic characteristics including diabetes (15.2% vs 12.8%), hypertension (53.3% vs 51.2%), current smoking (50.7% vs 48%) and family history of coronary artery disease (33.9% vs 32.8%) did not differ (P≥0.56) between the two groups. The pain to balloon time (294 mins vs 263 mins, P=0.20) and door to balloon time (74 mins vs 70 mins, P=0.76) were also similar. The most frequent culprit vessel was the RCA, followed by the LAD in both groups. Thrombus aspiration was performed in more than one third of patients. More than 70% of the patients had TIMI 0 or 1 flow before the procedure in both groups, and after procedure 96% of patients in the Ultimaster and 95% in the BMS arm had TIMI 3 flow.

The primary safety endpoint at 1 month was 3.5% in the Ultimaster group and 7.2% in the BMS group (P=0.13). The primary efficacy endpoint of in-stent late loss at 6 months was 0.09±0.44 mm in the Ultimaster and 0.79±0.68 mm in the BMS group (P=0.013). The primary safety and efficacy endpoint assessed by target vessel failure (TVF) at 12 months was 6.1% in Ultimaster versus 14.4% in the bare metal stent group (p=0.007) demonstrating the superiority of the Ultimaster versus bare metal stents in a STEMI setting. Stent thrombosis was 1.9% versus 4.8% (p=0.10).

The MASTER trial demonstrated that the Ultimaster DES was superior to BMS in patients presenting with STEMI.

DISCOVERY STUDY

The DISCOVERY 1TO3 study aimed to assess the vessel healing pattern of the Ultimaster DES using optical frequency domain imaging (OFDI). The hypothesis was that early strut coverage would allow guiding reduction of duration of dual antiplatelet therapy. In this prospective, single arm, multicentre, open label study, a total of 60 complex patients with multivessel disease, requiring staged procedure at 1 month and agreeing to undergo an invasive follow-up at 3 months, were treated with the Ultimaster stent. OFDI imaging was acquired at baseline, 1, 2- and 3 months and analysis was performed by independent Corelabs (CERC&CRC). The primary endpoint of the DISCOVERY1TO3 study was OFDI-assessed the percentage of stent strut coverage at 3 months post-procedure, with the hypothesis of less than 20% uncovered stent struts. Secondary endpoints were percentage of acquired malapposed struts, neointimal hyperplasia and thickness at 1, 2 or 3 months. DAPT was prescribed for a minimal 6 months.

Mean age of patients was 67.2±9.9 years, 73.3% were male, 30.0% had a previous PCI or CABG, 23.3% had diabetes mellitus, 63.3% had hypertension and 36.7% of patients presented with acute coronary syndrome (ACS). The mean number of vessels diseased was 2.2±0.5 and the mean number of lesions detected was 3.2±1.6 per patient. A total of 132 lesions were treated, with 1.4 ± 0.6 treated at baseline and 1.1 ± 0.4 treated at the 1 month staged procedure, amounting to a total implanted stent length of 22.7 ± 10.8 mm per lesion and 50.7 ± 21.3 mm per patient. OFDI assessment was performed on 98% of lesions with 99% visualization success.

Strut coverage at 1 (n=49) and 2 months (n=38) was 85.1±12.7% and 88.1±10.9%, respectively. The primary OFDI endpoint, strut coverage at 3 months of single implanted stents (n=71), was 95.2±5.2%. A similar coverage rate (95.4±4.9%) was observed in the combined single and overlapped stents. The mean neointimal hyperplasia thickness over covered struts was 0.05±0.02 mm, 0.06±0.03 mm, and 0.07±0.03 mm while mean NIH obstruction was 4.5±2.4%, 5.6±4.0% and 6.6±3.3% at 1, 2 and 3 months, respectively. The frequency of malapposed struts per lesion over time was 1.8±2.6%, 1.6±2.9% and 0.79±1.4%.

At 3-month follow-up there were no deaths, 3 non-Q-wave myocardial infarctions, one target lesion and one single target vessel-non-target lesion revascularizations. One patient experienced subacute stent thrombosis due to a large malapposition left untreated.

The DISCOVERY 1TO3 study demonstrated that even in patients with complex lesions, the majority of Ultimaster stent struts were covered at one month after stent implantation. This OFDI study provides clinical evidence to support shortening of DAPT after implantation of the Ultimaster stent.

Summary of Ultimaster stent studies

In summary, the low sirolimus concentration of Ultimaster stent was justified from the dose range preclinical study, which demonstrated a sufficient suppression of neointima and inflammation without hindering the vessel healing. In clinical studies, the Ultimaster stent was superior to BMS in patients with simple lesions and in those presenting with STEMI. In more complex population, the Ultimaster was shown to be non-inferior to the Xience stent. The OFDI study showed a high percentage of tissue coverage at one month, which supports the concept of short DAPT duration.

The aim of MASTER DAPT study

The aim of the study is therefore to compare, in patients at high risk of bleeding after treatment of coronary artery stenosis with a bioresorbable polymer coated Ultimaster sirolimus-eluting stent, the abbreviated antiplatelet therapy and the prolonged antiplatelet therapy within the existing guidelines[6, 7] and in agreement with existing IFU for the selected implantable coronary device, in terms of ischemic and bleeding events, in the setting of daily clinical practice.

3. Study Objectives

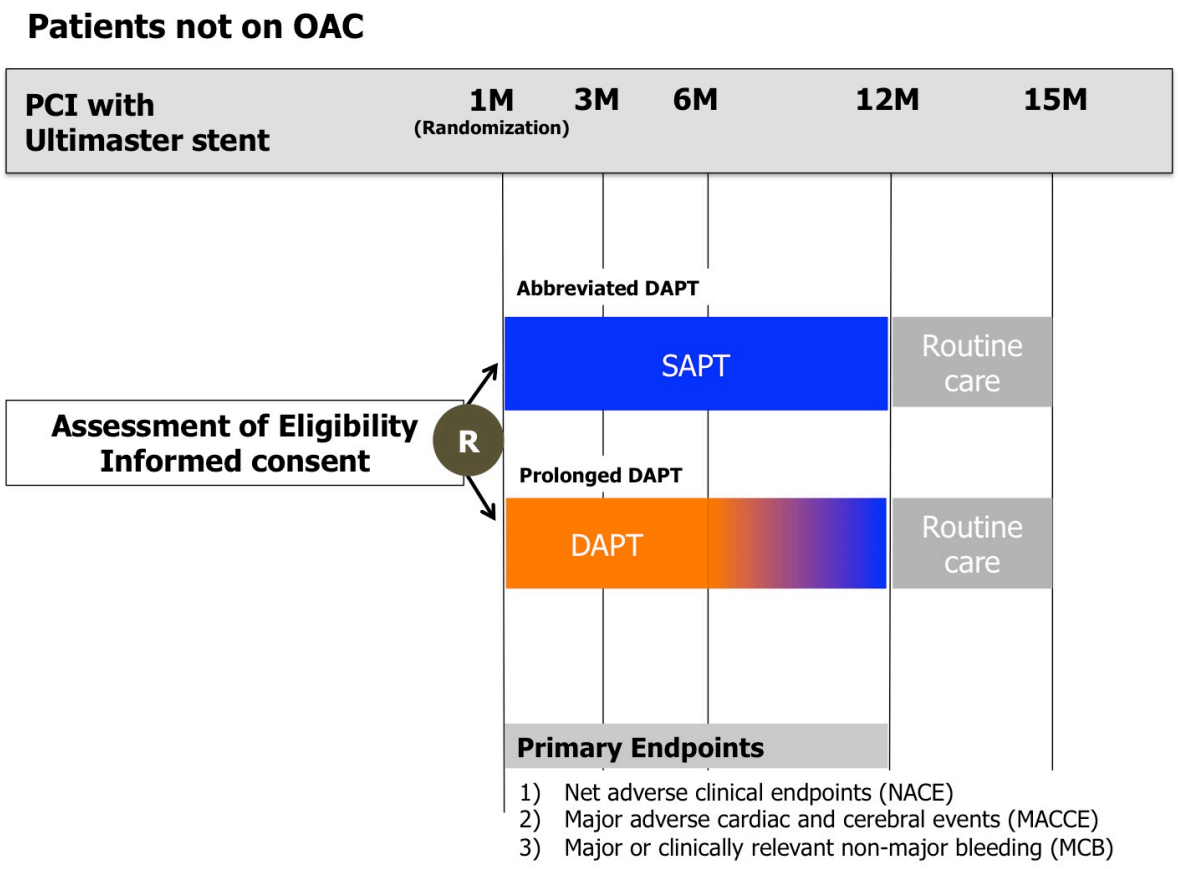
The objective is to compare, within current guidelines (GL) and instructions for use (IFU), an abbreviated DAPT regimen (of one month) versus a prolonged DAPT regimen (of 3 to 12 months) after implantation of a bioresorbable polymer coated Ultimaster sirolimus-eluting stent in patients with high bleeding risk (HBR) features.

More specifically, the objectives of the study are to test the following hypotheses

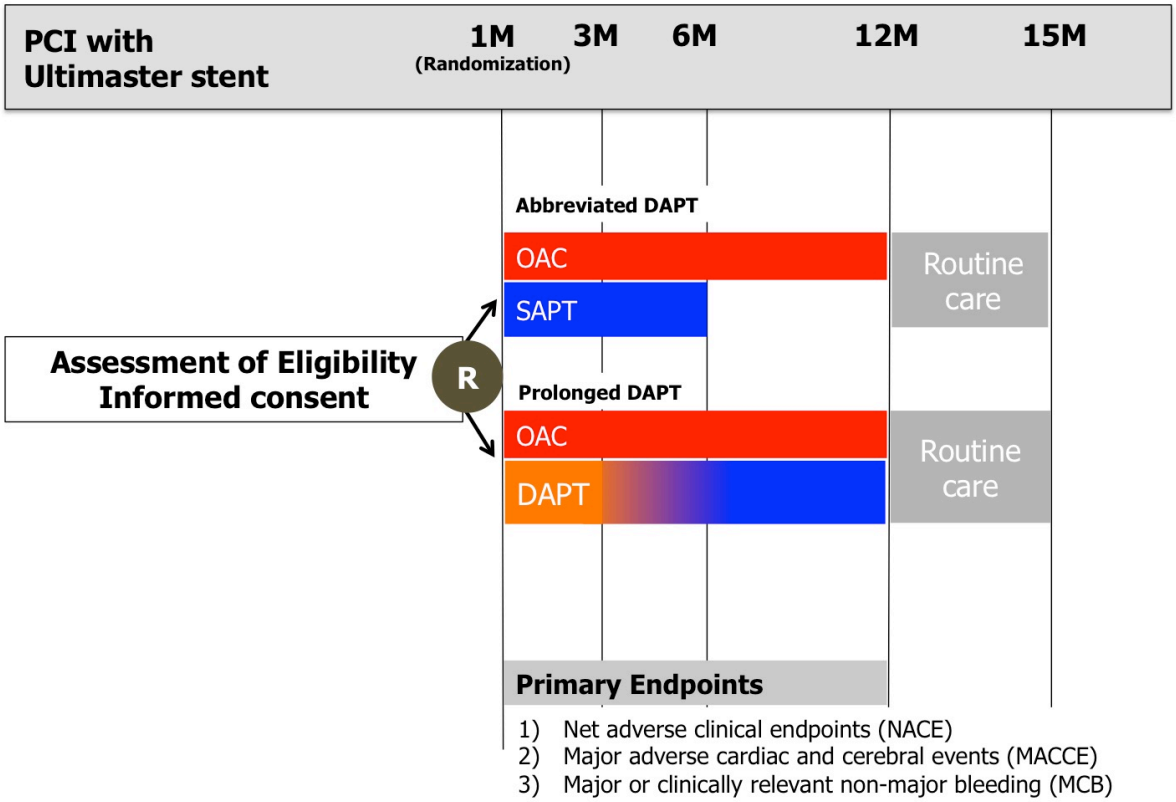
1) The abbreviated DAPT regimen is non-inferior to the prolonged DAPT regimen in terms of NACE
2) The abbreviated DAPT regimen is non-inferior to the prolonged DAPT regimen in terms of MACCE
3) The abbreviated DAPT is superior to the prolonged DAPT regimen in terms of MCB

4. Study design

This is an investigator-initiated, multi-center, randomized clinical trial in HBR patients who have had PCI with Ultimaster bioresorbable polymer coated sirolimus-eluting stent implantation.



Patients on OAC



5. Requirement for Participating sites

Primary participating sites are hospitals where a patient undergoes PCI (PCI site). Patients are identified and consented after PCI. The randomization visit at one month is scheduled at the PCI site. The PCI site is responsible for implementation of the randomized antiplatelet regimen and for collection of follow-up information. Patients referred for PCI from other sites can participate if the referring hospital has agreed to abide by the randomized duration of antiplatelet medication(s) and to provide the required follow-up information.

6. Patient selection, randomization and follow-up

6.1 Index PCI

The index procedure is either single procedure or the last instalment in planned staged procedure. Usage of imaging device during PCI procedure is left to the discretion of the operator. Staged procedure(s) are preferably planned with intervals of no more than 6 weeks.

6.2 Inclusion criteria

Patient selection takes place immediately after index PCI. For a consenting patient, a randomization visit at one month (30-44 days post index PCI) is scheduled. Definitive selection takes place at this visit after confirmation of inclusion and exclusion criteria.

6.2.1 Inclusion criteria after index PCI

Patients aged 18 years or more are eligible for inclusion into the study if the following criteria are met.

1) At HBR as defined below.
2) All lesions are successfully treated with Ultimaster stent in the context of routine clinical care, i.e. post-procedural angiographic diameter stenosis <20% by visual estimation
3) Free from any flow-limiting angiographic complications (i.e. significant untreated dissection or major side-branch occlusion), which require prolonged DAPT duration based on operator's opinion.
4) All stages of PCI are complete (if any) and no further PCI is planned.

6.2.2 Inclusion criteria at one-month randomization visit

Eligibility is definitively assessed at the randomization visit at one month. Patients are eligible if the following criteria are met:

1) Fulfilment of at least one HBR criterion (as defined below), or on the basis of post-PCI actionable (i.e. requiring medical attention) non-access site related bleeding episode
2) A 30-day clinical course without:
- New episode of acute coronary syndrome
- Symptomatic restenosis
- Stent thrombosis
- Stroke

- Any revascularization (coronary and non-coronary) requiring prolonged DAPT

3) If not on OAC,
- Patient is on a DAPT regimen of aspirin and a P2Y12 inhibitor
- Patient is with one type of P2Y12 inhibitor for at least 7 days (i.e. no switching between oral P2Y12 inhibitors has occurred in the previous 7 days)

4) If on OAC,
- Patient is on the same type of OAC (e.g. Vitamin K antagonist or NOAC) for at least 7 days
- Patient is on clopidogrel for at least 7 days

If a patient who has signed early informed consent cannot be randomized, the reason why is documented in the eCRF.

6.2.3 Definition of high bleeding risk

Patients are at high bleeding risk if at least one of the following criteria applies:
- Clinical indication for treatment with oral anticoagulants (OAC) for at least 12 months
- Recent (<12 months) non-access site bleeding episode(s), which required medical attention (i.e. actionable bleeding).
- Previous bleeding episode(s) which required hospitalization if the underlying cause has not been definitively treated (i.e. surgical removal of the bleeding source)
- Age equal or greater than 75 years
- Systemic conditions associated with an increased bleeding risk (e.g. haematological disorders, including a history of or current thrombocytopaenia defined as a platelet count <100,000/mm^3 (<100 x 10^9/L), or any known coagulation disorder associated with increased bleeding risk.
- Documented anaemia defined as repeated haemoglobin levels <11 g/dl or transfusion within 4 weeks before randomization.
- Need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs
- Diagnosed malignancy (other than skin) considered at high bleeding risk including gastro-intestinal, genito-urethral/renal and pulmonary.
- Stroke at any time or TIA in the previous 6 months
- PRECISE DAPT score of 25 or greater

6.3 Exclusion criteria

Patients are not eligible at any time if any of the following applies:
1. Treated with stents other than Ultimaster stent within 6 months prior to the index procedure
2. Treated for restenosis or stent thrombosis at index PCI or within the previous 6 months
3. Treated with a bioresorbable scaffold at any time prior to the 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 or to all three commercially available P2Y12 inhibitors including clopidogrel, prasugrel and ticagrelor, cobalt chromium or sirolimus
10. Any planned and anticipated PCI
11. Participation in another trial
12. Pregnant or breast feeding women

6.4 Informed consent

Eligible patients can be consented at any time between index PCI and the one-month randomization visit.

For patients who have signed informed consent, the randomization visit is scheduled between 30 and 44 days after index PCI. Patients who are considering participation in the study are also invited for a randomization visit at one month after having received oral explanation of the study and the written study information. A written informed consent is then obtained at the randomization visit.

The informed consent includes consent for the following:

- Randomization to abbreviated or prolonged DAPT
- Follow-up protocol
- Collection of clinical data
- Ascertainment of vital status via municipality registries
- Data collection in study database

Patients who provide informed consent are re-evaluated at the PCI site for randomization at 30-44 days following the index procedure. Patients are informed that they cannot participate in the trial if a new contraindication for randomization occurred before randomization visit.

Patients who are scheduled to have a regular follow-up at the PCI site can be consented. Patients who are not scheduled to have a regular follow-up at the PCI site are informed that the participation to the study implies scheduling of a study visit at the PCI site and upon agreement can be consented.

If a patient formally signed the informed consent at the index procedure or at any time before randomization visit, this is recorded in a separate (informed consent) section of the eCRF. Patients are assigned a study identification number.
.

Patients who explicitly refuse participation after the index procedure but before randomization are no longer contacted for the study.

6.5 Randomization

Randomization is performed at the one-month randomization visit, scheduled between 30 and 44 days post index PCI. Patients can only be randomized only if all inclusion criteria (section 6.2.2) are met and if no exclusion criteria apply. Patient can be only randomized in the presence of written informed consent.

The randomization procedure is programmed into the eCRF. After confirmation of selection criteria and presence of informed consent, the investigator triggers the randomization procedure, after which randomization to either abbreviated DAPT or prolonged DAPT is divulged. The randomization is stratified per site, by a history of acute myocardial infarction (within 12 months prior to the index procedure) and use of OAC.

If the subject is randomized to abbreviated DAPT, the Investigator takes the necessary measures so that the abbreviated DAPT regimen is implemented without any undue delay. If the subject is randomized to maintain the DAPT regimen, the existing DAPT regimen is continued.

6.6 Treatment regimen

Patients are treated according to the randomized regimen from the day of randomization until 11 months after randomization (12 months after the index procedure). After 11 months post randomization, antiplatelet therapy is at the discretion of treating physician.

6.6.1 abbreviated DAPT regimen

In patients not on OAC:

DAPT is discontinued and a single anti-platelet agent (SAPT) is continued until at least 11 months post randomization (i.e.12 months after index PCI).

In patients on OAC:

- DAPT is discontinued. Either aspirin or clopidogrel is continued until 5 months post randomization (i.e. 6 months after index PCI).
- OAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).

6.6.2 prolonged DAPT regimen

In patients not on OAC

- Aspirin is continued until at least 11 months post randomization (i.e.12 months after index PCI).
- The P2Y12 inhibitor being taken at the time of randomization is continued for at least 5 months and up to 11 months post randomization (i.e.12 months after index PCI).

In patients on OAC:

- Aspirin and clopidogrel are continued for at least 2 months (i.e. 3 months after index PCI) and up to 11 months post randomization (i.e. 12 months after index PCI). Thereafter, either aspirin or clopidogrel is continued up to 11 months post randomization (i.e.12 months after index PCI).

- OAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).

The rational for mandating clopidogrel as the only acceptable P2Y12 inhibitor in the OAC population in both study arms comes from the absence of safety and efficacy data regarding the combination of ticagrelor or prasugrel with aspirin and OAC (as patients requiring OAC were excluded from approval RCT) and a recommendation of Class III (i.e. not indicated) from European guidelines

6.6.3 Implementation of randomized study regimens

Study regimens are implemented by regular drug prescription as described above. The investigators provide the necessary prescription to the study participants. The followings are recommended according to the current guidelines and local practice.

- Aspirin is prescribed in standard dose of at least 75 mg/day and up to 162 mg/day.
- Clopidogrel is prescribed in standard dose of 75 mg once daily.
- Prasugrel is prescribed in standard dose of 10mg/day or 5mg/ day in patients weighing less than 60 kg or who are over 75 years old. In regions where other standard dose exists (i.e. Japan), prasugrel dosage is adjusted according to the locally approved dose.
- Ticagrelor is prescribed in standard dose of 180 mg/day (90mg bid).
- Vitamin K antagonist is dosed to keep INR within guidelines.
- NOACs (rivaroxaban, edoxaban, dabigatran and apixaban) are given in locally approved doses.
- Switching from Vitamin K antagonist to NOACs or vice-versa is not allowed unless there are clinical and well documented reasons for doing so. Similarly, switching from NOACs to VKA during the course of the study is not allowed, unless dictated by a clinical and documented reason (e.g. change in renal function during the course of the investigation), which will be captured in the eCRF.

Prescribed units of aspirin, clopidogrel, prasugrel, ticagrelor and OAC are recorded in the eCRF. Patients are queried on general drug adherence.

6.6.4 Treatment in the event of new onset atrial fibrillation or other new onset indication for OAC

If a patient develops any new indication for chronic oral coagulation, (i.e. new onset atrial fibrillation with CHADS-VASC2 score >1), treatment with oral anticoagulation must be started without any due delay. The choice of oral anticoagulant regimen (NOAC or VKA) is at the discretion of the treating physician. This rule also applies if a patient develops any other indication for oral anticoagulation.

In patients randomized to abbreviated DAPT:

- Treatment with a SAPT is as in patients on OAC at randomization (i.e. patients are treated with clopidogrel or aspirin for 6 months post index PCI). This implies that patients, who were on clopidogrel before the need for OAC arose, will continue with this treatment or switch to aspirin only, whereas patients on ticagrelor or prasugrel before the need for OAC arose will be immediately switched to clopidogrel only or aspirin only in combination to OAC.

In patients randomized to prolonged DAPT:

- Treatment with a DAPT is as in patients on OAC at randomization (i.e. patients are treated with clopidogrel and aspirin for at least 3 months post index PCI). This implies that patients, who were on clopidogrel before the need for OAC arose, will continue with this treatment, whereas patients on ticagrelor or prasugrel will be immediately switched to clopidogrel in combination to OAC.

These treatment switches are analyzed as an integral "per protocol" part of implementation of randomized treatment regimen.

6.6.5 Repeat PCI

In case of stent thrombosis and target lesion revascularization, the choice of stent type is at discretion of operator. In case of non-target lesion revascularization, the use of Ultimaster is recommended.

6.6.6 DAPT after specific clinical events

If any of the following events occurs, the following rules for the randomized treatment regimens apply.

- **Elective repeat PCI, antiplatelet treatment should be prescribed as local practice, we recommend:**
  - Abbreviated DAPT: If not on OAC, a P2Y12 or aspirin is added for one month to the pre-existing SAPT (i.e. a DAPT regimen is re-instituted for 1 month). If on OAC, DAPT with aspirin and clopidogrel are re-instituted for 1 month and thereafter clopidogrel or aspirin is continued for 5 months.
  - Prolonged DAPT: If not on OAC, treatment with aspirin and a P2Y12 inhibitor is continued or started for at least 6 months (i.e. a DAPT regimen is re-instituted for 6 months). If on OAC, aspirin and clopidogrel are re-instituted for at least 3 month.

- **Definite stent thrombosis**
  Further antithrombotic treatment is as per current guidelines and institutional recommendations.

- **Non-fatal myocardial infarction and no definite stent thrombosis, antiplatelet treatment should be prescribed as local practice, we recommend:**
  - Abbreviated DAPT: If not on OAC, a P2Y12 or aspirin is added for one month to the pre-existing SAPT (i.e. a DAPT regimen is re-instituted for 1 month). If on OAC, aspirin and clopidogrel are re-instituted for 1 month and thereafter clopidogrel or aspirin is continued for 5 months.
  - Prolonged DAPT: If not on OAC, treatment with a P2Y12 inhibitor is continued or started for at least 6 months (i.e. a DAPT regimen is re-instituted for 6 months). If on OAC, aspirin and clopidogrel are re-instituted for at least 3 months.

- **BARC 2 bleeding**
  The randomized treatment regimen is adhered to as much as possible.

- **BARC 3 to 5 bleeding**
  Further antithrombotic treatment is at the discretion of the treating physician.

- **Stroke**
  Further antithrombotic treatment is at the discretion of the treating physician.

- **Other contraindications for the randomized DAPT regimen**
  Further treatment is at the discretion of the treating physician.

- **Temporary discontinuation (e.g. Surgery, tooth extraction etc.)**
  The randomized trial regimen is resumed as soon as the indication of temporary discontinuation is resolved.

- **Dyspnea on ticagrelor**
  Ticagrelor is replaced preferably with prasugrel, or clopidogrel if prasugrel is not an option. When ticagrelor is switched to clopidogrel, loading dose of clopidogrel (3/600mg) is given. When ticagrelor is switched to prasugrel, the administration of prasugrel loading dose is at discretion of the physician.

If the randomized treatment regimen is changed or discontinued all together, the follow-up continues unchanged.

6.7 Follow-up

6.7.1 Scheduling of follow-up visit

In addition to the randomization visit at one month, there are scheduled follow-up visits at 90, 180 and 365 days and 450 days after the index procedure (appendix I). Medication prescriptions are implemented at each follow-up visit. Blood samplings are performed according to hospital standards (local laboratory).

6.7.2 Follow-up visits

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 except for the randomization visit at one month and for the follow-up occurring at 365 days. Under all circumstances it remains the responsibility of the investigator to make sure that adequate prescriptions for the randomized antithrombotic treatment is provided to the patient.

6.7.3 Data collection

Patients are informed that data are collected at scheduled follow-ups as well as at unscheduled visits.

The pre-procedural data to be collected include medical history, cardiac medications pre-PCI and indication for PCI (elective, non-STEMI, or STEMI).

The procedural details of the index PCI include location of treated lesions, number of stents, stent length, stent diameter, type of stents and complications etc.

The post-procedural medication is recorded as well as clinical events (MACCE and bleeding) that have occurred between index procedure and randomization.

INR is recorded if the patient is on chronic OAC.

At each visit, the following information is collected:

- 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 or coronary artery bypass grafting [CABG])
- Prescription of antiplatelet medication
- Compliance with randomized APT regimen

6.7.4 Assessment of DAPT being taken

At each follow-up the investigator collects information about adherence to the randomized DAPT regimen. In selected centres where an electronic drug monitoring system (e.g. MEMS caps, MWV Switzerland Ltd, Sion, Switzerland) is available, the adherence information is collected with the electronic monitoring system, when a patient agrees and is willing to use such a method.

6.7.5 Patient Withdrawal, Termination or Discontinuation of Trial

At any time during the study, the subject may withdraw their participation from the study. Every patient is encouraged to remain in the study until they have completed the protocol-required follow-up period. Patients who deviate from or discontinue the randomized APT regimen after randomization continue to be followed up as per standard of care.

Clinical follow-up is only discontinued if the patient explicitly forbids the continuation of follow-up. This decision should be an independent decision that is documented in the patient study files. Survival status should be collected within legal and ethical boundaries for all subjects randomized who withdrew participation from the study. If follow-up is discontinued prematurely, the reason for discontinuation is documented. In case of discontinuation, the already collected data remain in the database unless the patient explicitly requests complete deletion of the records, which should be documented by the site.

Decisions to discontinue the randomized study regimens or scheduled follow-up visit are considered modification of the informed consent.

Modifications of informed consent are recorded in the eCRF.

The eCRF distinguishes the following modifications in informed consent:

- Modification or Discontinuation of the randomized treatment regimen
- Discontinuation of scheduled follow-up visit

- Discontinuation of replacing telephone contacts
- Disallowance of gathering clinical information from referring hospitals or general practitioner
- Disallowance of collecting vital status from municipal registry

Informed consent is only considered as withdrawn if a request to implement all of the above has been made.

6.7.6 Lost to follow-up

A subject would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. If a subject is unable to return for a clinic visit or unable to be contacted by telephone, diligent attempts to contact the subject are made to obtain subject required information. All attempts are documented in the source documents. . Only after failing to contact the subject at the final follow-up visit, the subject is considered lost to follow-up after last contact. It must be a high priority to obtain at least survival data on all subjects lost to follow-up. Survival status will be collected within legal and ethical boundaries for all subjects randomized. Vital status will be searched in public sources at the end of the follow-up period. If vital status is known at the last study visit, the subject will not be considered lost to follow-up.

7. Endpoints

7.1 Primary Endpoints

This study has 3 primary endpoints

1) Net adverse clinical endpoints (NACE) defined as a composite of:
- All-cause death
- Myocardial infarction
- Stroke
- Bleeding events (BARC 3 and 5)

2) Major adverse cardiac and cerebral events (MACCE) defined as a composite of:
- All-cause death
- Myocardial infarction
- Stroke

3) Major or clinically relevant non-major bleeding (MCB) defined as a composite of Bleeding events according to BARC type 2, 3 and 5

7.2 Secondary Endpoints

The secondary endpoints of the study are the following:

1) The individual components of each primary endpoint
2) The composite of cardiovascular death, MI, and stroke
3) The composite of cardiovascular death, MI, and urgent revascularization
4) The composite of cardiovascular death, MI, and any unplanned revascularization
5) Death from cardiovascular causes

6) The composite of definite or probable stent thrombosis
7) Myocardial infarction
8) Any target lesion revascularisation
9) Urgent target lesion revascularization
10) Any target vessel revascularization
11) Urgent target vessel revascularization
12) Any non-target vessel revascularization
13) Any urgent non-target vessel revascularization
14) Bleeding events according to the BARC, TIMI and GUSTO classification
15) Transfusion rates both in patients with and/or without clinically detected over bleeding

8. Statistical methods and determination of sample size

8.1 General considerations

A general description of the statistical methods to be used to analyze the endpoints of the study drug is outlined below. A more detailed statistical analysis plan (SAP) is provided in a separate document. Statistical analysis is performed using STATA; the version used will be specified in the SAP. The SAP accommodates protocol amendments or unexpected issues in study execution or data that affect planned analyses, and provides more details on the analytic approaches, coding guidelines, censoring of time-to-event variables, and output tables and figures.

If not stated otherwise, all efficacy and the safety analyses are based on findings as confirmed by the Clinical Event Committee (CEC).

8.2 Analysis sets

Full analysis population (FAS) consists of all randomized subjects with Ultimaster stent. Subjects are categorized according to the group to which they were assigned by the randomization process.

Per-protocol (PP) population consists of randomized patients who met the following criteria.

- No violation of major inclusion criteria (HBR)
- Randomized treatment was implemented within 48 hours after randomization

In particular, the following patients are excluded from the PP population

- Not at HBR
- Randomized before 30 days or after 44 days post the index PCI
- Discontinuation of DAPT not implemented in patients randomized to abbreviated DAPT
- Permanent discontinuation of DAPT in patients randomized to prolonged DAPT occurring before 6 months in patients not on OAC or before 3 months in patients with OAC not justified by clinical events as detailed in section 6.6.5

8.3 Main analysis of the primary endpoints

The study was designed to test the following hypotheses

1) Abbreviated DAPT (one month) is non-inferior to a prolonged DAPT regimen in terms of NACE
2) Abbreviated DAPT (one month) is non-inferior to a prolonged DAPT regimen in terms of MACCE
3) Abbreviated DAPT (one month) is superior to a prolonged DAPT regimen in terms of MCB

These hypotheses are tested in a hierarchical order, in order to preserve type I error rate

Main analysis of the primary endpoints is performed in the FAS population under application of the Intention-to-treat principle that is, events are counted irrespective of their occurrence relative to termination of randomized APT regimen. Follow-up is censored at the last date of known outcome status or at 1 year, whichever comes first.

Rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to 335 days after randomization (~1 year post index PCI) by the Kaplan-Meier methods. Rate differences are defined as the rate under abbreviated DAPT minus that under standard DAPT.

1) Non-inferiority of the abbreviated DAPT regimen in terms of NACE is declared if the 95% confidence interval (CI) of the rate difference excludes 3.6%.
2) Non-inferiority of the abbreviated DAPT regimen in terms of MACCE is declared if the 95% CI of the rate difference excludes 2.4%.
3) Superiority of the abbreviated DAPT regimen in terms of MCB is declared if the 95% confidence interval of the rate difference excludes 0%, which is equivalent to $p<0.05$ for the log-rank test.

Use of 95% CI is equivalent to non-inferiority testing with a one-sided type I error (α) of 0.025.

8.4 Determination of sample size

The rates of the 3 primary endpoints between 1-12 months were primarily estimated from the Zotarolimus-eluting stent in uncertain DES candidates (ZEUS) trial and the Leaders Free trial.

NACE, MCB and MACCE rates under DAPT and MCB under 30-day DAPT were estimated as follows:

- NACE under prolonged DAPT : 12%
- MACCE under prolonged DAPT : 8%
- MCB under prolonged DAPT : 6.5%
- MCB under 30-day DAPT only : 5%

These estimates are in accordance with estimates from the LEADERS FREE trial. The Kaplan Meier curves for the primary safety endpoint (cardiac death, MI or stent thrombosis) indicated that one-third of the events occurred within 30 days and the remaining two-thirds between 30 days and one year. Bleeding according to BARC 2, 3 or 5 was observed in 14.5% of patients despite one month DAPT only. It is conceivable to expect that 50% of bleeding

events may have occurred within the first 30 days (based on data on file from the ZEUS trial). Hence, the LEADERS FREE indirectly (for NACE and MACE) or directly (for BARC 2,3, or 5 bleeding) supports current sample size calculation and the high event rates to be expected in this HBR population.

8.5 Statistical Power

Sample size calculations have been made for a sample size of 2 x 2040 evaluable patients. To compensate for attrition rate of 5%, 2 x 2150 patients are randomized. All tests are carried out for abbreviated DAPT vs. prolonged DAPT with a one-side type I error rate of 0.025. The assumed event rates under prolonged DAPT are 12% for NACE, 8% for MACCE and 6.5% for MCB.

With this sample size, the study has:

- >90% power to establish noninferiority in NACE with a noninferiority margin of 3.6%
- >80% power to establish noninferiority in MACCE with a noninferiority margin of 2.4%
- >90% power to establish superiority in MCB assuming a 35% relative risk reduction for MCB (from 6.5% to 4.2%).

8.5.1 Subgroup analysis by OAC usage

A full subgroup analysis of the 3 primary endpoints (NACE, MACCE and MCB) is performed for patients on OAC at the time of randomization vs. patients not on OAC at the time of randomization. Patients who develop an indication of OAC after randomization are analyzed as non-OAC users. Rate differences and hazard ratios for patients on OAC and not on OAC are presented for descriptive purposes.

8.5.2 Other subgroup analyses

The following subgroups are pre-specified:

- Patients with history of acute myocardial infarction (STEMI or non-STEMI) within 12 months prior to randomization vs. those without
- Patients with ACS as indication for index PCI vs. patients with elective PCI. (In a planned staged procedure, the indication is defined as the indication for the first PCI)
- High DAPT score (≥2) vs. Low DAPT score (<2)
- According to tertiles of the PRECISE DAPT score
- Female vs. male gender
- Creatinine clearance equal or greater than 60 ml/min or < 60 ml/min
- Age ≥75 years vs. age <75 years
- According to presence or absence of each single inclusion criteria
- According to presence or absence of diabetes mellitus

9. Safety reporting

The investigator monitors the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after randomization. In case of endpoint-related event (all cause death, myocardial Infarction, stent thrombosis, stroke, and bleeding events [BARC 2, 3 or 5]) the event sheet must be completed as soon as possible of the investigator's and study staff's awareness of the

event. All other Serious Adverse Events do not need to be reported, unless they are considered related to the duration of the DAPT treatment.

9.1 Serious Adverse Events (SAEs) Definitions

An AE is classified as "serious" if the event:

- Led to death;
- Led to serious deterioration in the health of a patient that:
    - Resulted in a life threatening illness or injury;
    - Resulted in a permanent impairment of a body structure or a body function;
    - Required in patients hospitalisation or prolongation of existing hospitalisation;
    - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

All SAEs related to endpoints or DAPT duration will be followed until the event has been resolved (with or without sequelae).

9.2 Reporting to EC / IRB

The investigator should report endpoint-related or DAPT-duration related serious adverse events to EC/IRB in accordance with the requirements of the applicable local regulations. Investigators are instructed to interview each patient carefully at each study visit to determine if serious adverse event may have occurred. When endpoint-related events (death, myocardial infarction, stent thrombosis, stroke, and bleeding events [BARC 2, 3 or 5]) occurs, then this shall be reported in the eCRF as soon as possible of the clinic study staff having become aware of this, including their judgement. At the time the event is reported in the eCRF, no event-supporting source documentation needs to be sent to the Safety Group, except at the request of the Safety Group (see below). The sponsor will forward any recommendation from DMC regarding a discontinuation of the study to EC/IRB.

9.3 Reporting to Authorization Holders

The investigator should report events considered related to the stent to the manufacturer of the stent as required by national/local regulations, if applicable. The investigator should report events considered related to the pharmaceutical products to the Marketing Authorisation Holders of the products as required by national/local regulations, if applicable.

10. Data Monitoring Committee

Endpoint-related adverse events are periodically reviewed and analysed by an independent DMC. Members of this board are not affiliated with any (interventional) cardiology site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC Charter.

11. Risk Analysis

The risk of shortening of DAPT after drug-eluting stent implantation has been assessed in the ZEUS using a permanent polymer stent and the Leaders Free trial using a biolimus-eluting coating-free stent. The ZEUS trial provided data showing that a BMS-like DAPT regimen

(30-day or even shorter) in patients receiving Endeavor sprint Zotarolimus-eluting stent (E-ZES) did not pose safety concerns while achieving superior clinical efficacy in patients whith high bleeding risk. More recently, the LEADERS FREE trial has been published where over 2,000 patients at HBR were randomly allocated to a polymer free biolimus A9 drug-coated stent (DCS) versus the corresponding bare metal stent platform followed by 30 day DAPT. This study provided consistent results to the ZEUS study showing not only improved efficacy in terms of lower target lesion revascularisation but also lower risk of myocardial infarction in patients received DCS.

In the current trial, the Ultimaster stent is used for treatment of coronary artery disease. The Ultimaster stent is a sirolimus-eluting stent with bioresorbable polymer. The drug elutes in the first 3 months with biodegradation of polylactide coating. Considering the fact the coating disappears over time, we assume that the thrombogenicity of the Ultimaster does not exceed the stent with permanent coating such as Endeavor stent used in ZEUS. Therefore the safety risk on the abbreviated DAPT regimen with the Ultimaster stent is considered to be minimal.

12. Monitoring

The CERC (Cardiovascular European Research Center, 7 rue du Théatre, 91300 Massy, France) is responsible for clinical monitoring in all countries except for the Netherlands and Belgium. In these countries, Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for clinical monitoring. The details of operating procedures for monitoring are described in a separate Clinical Monitoring Plan.

13. Quality control and quality assurance

13.1 Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB) and competent authorities (CA) and other regulatory bodies if required per local regulations.
The trial will only start at a clinical site after favourable opinion of the study has been obtained from all concerned regulatory bodies. Any additional requirements imposed by the authorities shall be implemented.

The study will be performed in accordance with the protocol and with the principles enunciated in the current version of the Declaration of Helsinki as well as the applicable local regulations.

13.2 Data Recording

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.
For all data captured in the eCRF, the location of the source should be documented on a list of source documents, which will be stored in the investigator site file at each study site.

13.3 Quality Assurance and Monitoring

Monitoring the clinical investigation at the study site is the responsibility of the monitoring organisation through trained and qualified Clinical Research Associates (CRAs).

14. Data management and Quality Assessment

14.1 Data management

14.1.1 Data handling and record keeping

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (secuTrial). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated Oracle database.
Responsibility for hosting the EDC system and the database lies with Inselspital Bern.

14.1.2 Confidentiality, Data Protection

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.
All data entered into the CRFs are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail). A multi-level back-up system is implemented.

14.1.3 Archiving and Destruction

At interim and final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables. The study database with all archive tables will be securely stored by Inselspital Bern. The sponsor also keeps the Trial Master File and interim and final reports both in electronic and in hard copy form for at least 10 years.

14.1.4 Electronic and Central Data Validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.

14.2 On-site Audits

To ensure compliance with the Declaration of Helsinki and applicable national/local regulatory requirements, a member of the Sponsor's or a designated CRO's quality assurance unit, may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator agrees to cooperate with the

Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide may inspect the investigator during and after the study. The investigator should contact the sponsor immediately if this occurs, and must cooperate with the regulatory authority inspections as required.

15. Adjudication of events

The events are adjudicated by the clinical event committee (CEC) comprised of qualified physicians who are not investigators in the trial. The CEC is responsible for adjudicating all potential endpoint events, including death, bleeding, myocardial infarction, stent thrombosis, stroke, and coronary revascularization The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

16. ORGANISATION

16.1 Sponsor

In this investigator-initiated trial, the European Cardiovascular Research Institute (ECRI) will act as Sponsor (ECRI-9 B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands,). The Sponsor's responsibilities are described in chapter 20

16.2 Executive Committee

The Executive Committee is responsible of the overall management of the study. Their names, roles and responsibilities are described in a separate Executive Steering Committee Charter.

16.3 Operational Committee

The operational committee is responsible for daily management of study execution in operational level under supervision of executive committee.

16.4 Steering Committee

The Steering Committee is comprised of the executive committee and national lead investigators. Their names, roles and responsibilities are described in a separate Steering Committee Charter.

16.5 National lead investigators

National lead investigators will be assigned by the Sponsor. During the regulatory submissions, they help to guide the other sites in their country, where required. In case of study management issues (e.g. protocol-related questions), national lead investigators support the sites and help them to solve any other problems that are particular to their clinic. The names of the national lead investigators and their roles and responsibilities are listed in the Appendix of the separate Steering Committee Charter.

16.6 Data Monitoring Committee

The DMC is described in section 10. The composition, guiding policies and operating procedures governing the DMC are described in a separate DMC Charter.

16.7 Data Management, Central Data Review and statistical analysis

Data management, central data review and statistical analysis will be conducted by the independent Clinical Trials Unit (CTU) in Bern, Switzerland (Universität Bern, CTU Bern, Finkenhubelweg 11, 3012 Bern, Switzerland).

16.8 Site Management and Monitoring

The CRO CERC (Cardiovascular European Research Center, 7 rue du Théatre, 91300 Massy, France) will be responsible for site management and monitoring except for the Netherlands and Belgium, where the CRO Cardialysis will be responsible for these activities.

16.9 Safety Reporting

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for entering endpoint-related events from the eCRF in a safety database.

16.10 Clinical event committee

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for organizing Clinical event committee.

16.11 Core Laboratories

In order to characterise the details of the treated coronary lesion and PCI procedure, angiographic recording of the index procedure and any planned staged procedure will be collected at each site and sent centrally to Bern (Universität Bern, CTU Bern, Finkenhubelweg 11, 3012 Bern, Switzerland).

17. DATA HANDLING AND RECORD KEEPING

17.1 Source Documentation (SD)

Regulations require that investigators maintain information in the patient's medical records that corroborate data collected in the electronic Case Report Form (eCRF). In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained and made available as required by monitors and/or regulatory inspectors:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol inclusion and exclusion criteria;
- Dated and signed notes on the day of entry into the study, protocol number, clinical site, patient number assigned and a statement that informed consent was obtained;
- Notations on abnormal lab results;
- Serious adverse events reported and their resolution, including supporting documents such as discharge summaries, cath lab reports, ECGs, lab results;
- Notes regarding protocol-required and prescription medications taken during the study (including dose, start and stop dates);
- Study patient's condition upon completion of or withdrawal from the study.

17.2 Case Report Form Completion

All required data are accurately recorded by authorised personnel documented on the authorised signature log in the eCRF.

17.3 Record Retention

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator for a minimum 2 years following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian, if applicable.

18. PUBLICATION POLICY

The Steering Committee and investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings.

The MASTER DAPT is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with Terumo company. All public presentations and manuscript generation and submissions will be led under the auspices of the two coordinating Principal Investigators who will organise and lead a Publications Committee. However, this study represents a joint effort between investigators, ECRI and collaborators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

The final locked database will be housed at the data management centre, CTU Bern. CTU Bern will not publicly release data or study-related material, presentations, or manuscripts without the express permission of the two coordinating Principal Investigators. Two coordinating Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The authors on the primary manuscript include the steering committee members and investigators according to the number of patients and quality of data. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-centre results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted.

All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the Steering Committee for review and approval including the choice of authors prior to submission for publication or presentation.

19. INVESTIGATOR RESPONSIBILITIES

19.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly.

19.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to patient enrolment:

- Signed Protocol Signature Page
- Recent signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Copy of the written favourable EC/IRB opinion.
- Signed Investigator Site Agreement.

19.3 Regulatory Approvals

Before commencing subject recruitment, written approvals from all concerned regulatory bodies must be available. It is the responsibility of the principal investigator to obtain written favorable opinion of the EC / IRB and to provide the sponsor with copies of any study-related communication with the EC / IRB. The EC / IRB favorable opinion must contain following information:

- Statement of EC/IRB approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval
- Identification of the approved Principal Investigator
- Signature of the EC/IRB chairperson
- Identification of the approved documents on which the opinion was based
- Acknowledgement of the Co-Investigators (if applicable)
- EC/IRB favourable opinion of the informed consent form (if applicable)
- EC/IRB approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC/IRB and written favourable opinion obtained prior to implementation. Protocol amendments will be submitted to the EC/IRB in accordance with local regulation. .

Investigator will perform safety reporting as specified in 9.2.

19.4 Informed Consent

Study subjects must provide written informed consent using an EC/IRB-approved informed consent form. The study must be explained to the study subjects in lay language. The investigator, or representative, must be available to answer all of the study subject's study-related questions. Study subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

19.5 Protocol Deviation

Investigator will document and explain any Protocol Deviation that occurred during the course of the study.

19.6 Reporting Requirements

Reporting to the EC/IRB and/or Competent Authority is performed if required according to applicable local regulations.

Type of CRF/Report	Completed by Site Within	Process
Serious Adverse Events	Ongoing Basis	Collected in patient hospital file
Endpoint related events	as soon as possible	Enter eCRF pages as soon as possible of knowledge of event
Randomization (study regimen assignment)	Immediate	Enter eCRF randomization page
eCRF (Baseline, In-hospital summary, Follow-up, Non-compliance, Reconciliation Form, Patient Withdrawal)	Ongoing basis	Collected in the eCRF
ECGs and Angiographic Films	Ongoing basis	Collected by site and transferred to Core lab within 7 days
Annual Reports	Annually, as requested by EC/IRB	Copy to be provided to Sponsor and EC/IRB
Final Report	Within 3 months of study completion or termination	Copy to be provided to Sponsor and EC/IRB

Site responsibilities for submitting data and reports:

19.7 Audits / Inspection

In the event that audits are initiated by the Sponsor (or its designee) or national/international regulatory authorities, the investigator allows access to the original medical records and provides all requested information.
In the event that audits are initiated by a regulatory authority, the investigator will immediately notify the Sponsor.

20. SPONSOR RESPONSIBILITIES

20.1 Role of ECRI

As Sponsor, ECRI has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant competent authorities.

General duties

Prior commencing the subject recruitment the sponsor shall submit any required application to all concerned regulatory bodies and ensure that respective written approvals are obtained and documented. Any amendment to the protocol, will be submitted to the concerned regulatory bodies in accordance with the applicable regulatory requirements and written approval obtained prior to implementation.

Selection of clinical investigators and sites

The Sponsor will select qualified investigators and facilities which have adequate study patient population to meet the requirements of the investigation.

Training of investigator and site personnel

The training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor, or designee, and may be conducted during an investigator meeting, a site initiation visit, or other appropriate training sessions.

Documentation

The Sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents;

- All study relevant documents (protocol, Instruction for use, EC/IRB approval and comments, competent authority notification and comments, patient information and informed consent template, relevant correspondence, etc.)
- Signed and dated Case Report Forms
- Records of any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

20.2 Supplemental Applications

As appropriate, the Sponsor will submit changes to the study protocol to the investigators to obtain EC/IRB re-approval.

20.3 Submitting Reports

The Sponsor will submit the appropriate reports identified by the regulations. This includes unanticipated adverse device effects, withdrawal of any EC/IRB approval, yearly summary of serious adverse events, interim (if any) and final reports.

20.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, unanticipated adverse device effects, SAEs and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator Site Agreements according to sponsor specific requirements in compliance with Declaration of Helsinki.

20.5 Audit

The Sponsor is responsible for auditing the study to ensure compliance with Declaration of Helsinki and/or applicable local regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit and may arrange to conduct an on-site audit to assess the performance of the study at the study site and of the study documents originating there.

20.6 Confidentiality

All data and information collected during this study related to the participating subject will comply with the standards for protection of privacy based on applicable local/ national requirements for subject's confidentiality. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study subjects' names. Access to study subject files will be limited to authorised personnel of the Sponsor, the investigator, and research staff. Authorised regulatory personnel have the right to inspect and copy all records pertinent to this study, but all efforts must be made to remove the subject's personal data.

APPENDIX I Summary of follow up visits

Day 0: PCI	**V1: 30 days**	**V2: 90 days**	**V3: 180 days**	**V4: 365 days**	**V5: 450 days**
	+14 days	*60±14 days post randomization*	*120±14 days post randomization*	*335+14 days post randomization*	*420+14 days post randomization*
Type of contact	Visit	Visit or Phone and Letter*	Visit or Phone and Letter*	Visit	Phone
Inclusion/ exclusion criteria	X				
Informed consent**	X				
Physical examination	X				
Medical and cardiac history	X				
Peri-procedural PCI data	X				
Randomization	X				
Electrocardiogram (12 lead ECG)	X***				
Medication regimen	X	X	X	X	X
Anginal status	X	X	X	X	X
Serious adverse event monitoring	X****	X	X	X	X
Blood sampling	X***				

*) A letter with details of randomized duration regimen is sent to the patient, which will be brought to the treating physician to ensure the implementation of randomized regimen.
**) Informed consent can be obtained at any time between the percutaneous coronary intervention (PCI) and 30-44-days randomization visit (V1)
***) Only in the centers where this is a part of usual clinical practice
****) Serious adverse event monitoring starts immediately after informed consent.

APPENDIX II Definitions

BLEEDING

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification.[59]

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 health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria: Requiring non-surgical, medical intervention by a health care professional Leading to hospitalization of increased level of care Prompting evaluation
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 hemoglobin 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 LP Intra-ocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period* Chest tube output ≥ 2 L within a 24 hour period
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

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL hemoglobin). † Cell saver products will not be counted.

TIMI Bleeding Criteria [39, 60, 61]

Non-CABG related bleeding

- **Major**
  - Any intracranial bleeding (excluding microhemorrhages < 10mm evident only on gradient-echo MRI)
  - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5g/dL
  - Fatal bleeding (bleeding that directly results in death within 7 days
- **Minor**
  - Clinically overt (including imaging), resulting in hemoglobin drop of 3 to < 5g/dL
- **Other non-major or minor**
  - Any overt bleeding event that does not meet the criteria above

Bleeding in the setting of CABG

- Fatal bleeding (bleeding that directly results in death)
- Perioperative intracranial bleeding
- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
- Chest tube output >2 L within a 24-h period

GUSTO Bleeding Criteria [46]

- **Severe or life-threatening**
  - Intracerebral hemorrhage
  - Resulting in substantial hemodynamic compromise requiring treatment
- **Moderate**
  - Requiring blood transfusion but not resulting in hemodynamic compromise
- **Mild**
  - Bleeding that does not meet above criteria

DEATH

All deaths will be categorized as cardiovascular, non-cardiovascular or undetermined based on the definitions below. [62]

Cardiovascular death:
Cardiovascular Death is defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other cardiovascular causes.

Death due to Acute Myocardial Infarction:
Death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

Sudden Cardiac Death:
Death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).
- Death after unsuccessful resuscitation from cardiac arrest. Death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology.
- Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General Considerations
A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."

Typical scenarios include:

- Subject well the previous day but found dead in bed the next day
- Subject found dead at home on the couch with the television on
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

Death due to Heart Failure or Cardiogenic Shock:
Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin or
- Oliguria (urine output < 30 mL/hour) or
- Altered sensorium or
- Cardiac index < 2.2 L/min/m²

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Death due to Cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

Death due to Other Cardiovascular Causes: Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death:
Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause.

- The following categories may be collected:
- Non-Malignant Causes
- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Haemorrhage*, excluding haemorrhagic strokes and bleeding in the setting of coronary revascularization
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction)
- Neurological process that is not a stroke or haemorrhage
- Other non-cardiovascular, specify: _____

*Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal hematoma following PCI is considered CV death. Death due to intracerebral haemorrhage is considered CV death.

Malignant Causes

Death results directly from the cancer;
OR
Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy);
OR
Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently should be further classified (worsening prior malignancy; new malignancy).

Undetermined cause of death:
Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

For each death event an assessment will be made as to whether the event was caused, on the basis of the totality of the evidence, by a bleeding (ie a fatal bleeding occurred) or not.

MYOCARDIAL INFARCTION

For the primary analysis, MI endpoint will be defined based on the third universal definition of myocardial infarction with the exception of periprocedural MI after PCI, which will be defined according to the SCAI definition. [63, 64]

For secondary analyses, PCI-related MI according to the Third Universal MI definition (type 4a) will be also adjudicated.

1. Spontaneous MI (>48 hours after intervention, MI type 1)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:[63]:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB
- Development of new Q waves in the ECG
  Evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a *target* or *non-target vessel or lesion* in most cases.

Type 2 MI

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3 MI

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Type 4a MI (NOT USED for primary analysis; see definition below)

Type 4 MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

In addition, at least one of the following is required:
- symptoms suggestive of myocardial ischaemia
- new ischaemic ECG changes
- angiographic findings consistent with a procedural complication
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

Type 4b MI
Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

Type 4c MI

A spontaneous MI where a restenosis is the only angiographic explanation

Type 5 MI
Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline cTn values (≤URL).

In addition, at least one of the following is required:
- new pathological Q waves or new LBBB
- angiographic documented new graft or new native coronary artery occlusion
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

2. Periprocedural MI after PCI (within 48 hours after PCI)

Periprocedural MI is defined based on the SCAI definitions as follows:[64]

1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, *OR* in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. .
2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above *plus* new ST-segment elevation or depression *plus* signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Target-vessel vs. non-target-vessel MI:
Any MI not clearly attributable to a non-target vessel will be considered as target-vessel MI.

STENT THROMBOSIS

Stent Thrombosis is defined by the Academic Research Consortium[62] as follows:

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
- Nonocclusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream
- Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)
‡Intracoronary thrombus

Probable stent thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days.
- Irrespective of the time after the index procedure, any myocardial infarction (MI), which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis:

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of hemorrhage or infarction.

CNS includes brain, spinal cord and retina.

Classification:

Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as"Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or

In absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.

Note, Hemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischemic stroke

Cerebral Hemorrhage

Hemorrhages in the CNS are classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke. The diagnoses included in this section are intracerebral hemorrhage (intraparenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and nonaneurysmal).

Stroke caused by intracerebral hemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid hemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma. Hemorrhages may be further classified according to location (example, supratentorial, subtentorial, etc.)

Stroke not otherwise specified

An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

URGENT CORONARY REVASCULARIZATION

According to the Academic Research Consortium [62] urgent coronary revascularization is defined as follows:

One or more episodes of rest pain, presumed to be ischemic in origin, which results in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST segment changes (a new ST segment shift > 0.05 mV (0.5 mm) on a 12-lead ECG), indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will be initiated within 24 hours of the last episode of ischemia and not be identified as planned/staged. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guide wire removal. CABG initiated

within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, will also be considered a urgent coronary revascularization endpoint.

For each urgent coronary revascularization endpoint, an assessment will be also made as to whether this is related to the target vessel and/or the target lesion as follows:

Target Lesion Revascularization (TLR)
TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent/scaffold.

Target Vessel Revascularization (TVR)
TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches, and the target lesion itself

APPENDIX III: Abbreviations and Acronyms

ACS	Acute Coronary Syndrome
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
CRA	Clinical Research Associate
(e)CRF	(electronic)Case Report Form
DAPT	Dual AntiPlatelet Therapy
DES	Drug-Eluting Stent
DMC	Data Monitoring Committee
DTI	Direct Thrombin Inhibitor
EC	Ethics Committee
ECG	Electrocardiography
ISR	In-Stent Restenosis
IRB	Institutional Review Board
IV	IntraVenous
GP	GlycoProtein
HIT	Heparin-Induced Thrombocytopenia
IFU	Instruction For Use
IRB	Institutional Review Board
LAD	Left Anterior Descending artery
LCA	Left Coronary Artery
LCX	Left Circumflex artery
MACE	Major Adverse Cardiac Events
MACCE	Major Adverse Cardiac and Cerebral Event
MCB	Major or clinically relevant non-major bleeding
MI	Myocardial Infarction
NACE	Net Adverse Clinical Endpoint
NOAC	New Oral Anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEACS	Non-ST segment Elevation Acute Coronary Syndrome
(N)STEMI	(Non-)ST segment Elevation Myocardial Infarction
OAC	Oral Anticoagulant
PAR	Protease Activated Receptor
PCI	Percutaneous Coronary Intervention
RCA	Right Coronary Artery
(S)AE	(Serious) Adverse Event
SAPT	Single AntiPlatelet Therapy
SD	Source Documentation
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularisation
TVF	Target Vessel Failure
UA	Unstable Angina
UFH	UnFractionated Heparin
ULN	Upper Limit of Normal

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Statistical Analysis Plan

Administrative Information

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Contents

1. Introduction

1.1. Background and rationale

High bleeding risk population represents a significant proportion of coronary artery disease (CAD) patients undergoing coronary stent implantation. Decisions regarding the duration of dual antiplatelet therapy (DAPT) after stent implantation are difficult, especially after implantation of newer generation drug eluting stents (DES) due to conflicting results from recent trials.

The current ESC guidelines on DAPT indicate that in patients at high bleeding risk (HBR), shorter DAPT duration (<6 months) should or might be considered after DES implantation (Class of recommendation: IIa/IIb). Similarly, the more recent American guidelines on DAPT duration, stated that in patients treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 or 6 months may be reasonable (Class of recommendation IIb). Both the European and American guidelines acknowledge that limited data is currently available to sustain this practice and call for dedicated DAPT studies in HBR patients.

Therefore, further randomized trials are needed to appraise the optimal DAPT duration in HBR patients treated with contemporary DES.

1.2. Objectives

The objective is to compare, within current guidelines (GL) and instructions for use (IFU), an abbreviated versus a prolonged DAPT duration after bioresorbable polymer coated Ultimaster (TANSEI) sirolimus-eluting stent implantation in patients presenting HBR features.

The study was designed to test the following hypotheses:

1) Abbreviated DAPT (one month) is non-inferior to a prolonged DAPT regimen in terms of NACE
2) Abbreviated DAPT (one month) is non-inferior to a prolonged DAPT regimen in terms of MACCE
3) Abbreviated DAPT (one month) is superior to a prolonged DAPT regimen in terms of MCB

These hypotheses are tested in a hierarchical order, in order to preserve type I error rate, meaning that if the first test fails the study will be interpreted as not supportive of the abbreviated DAPT over prolonged DAPT, and subsequently the second and third tests result will be presented as exploratory. Likewise, if the first test passes and the second test fails, the third test result will be presented as exploratory.

If the NACE and MACE are claimed as non-inferior according to the margins and procedures described below, than both endpoints will also be tested for superiority using Hochberg-Benjamini approach to evaluate the two superiority p-values.

All patients in the FAS dataset will be considered in each step of the analysis.

2. Study methods

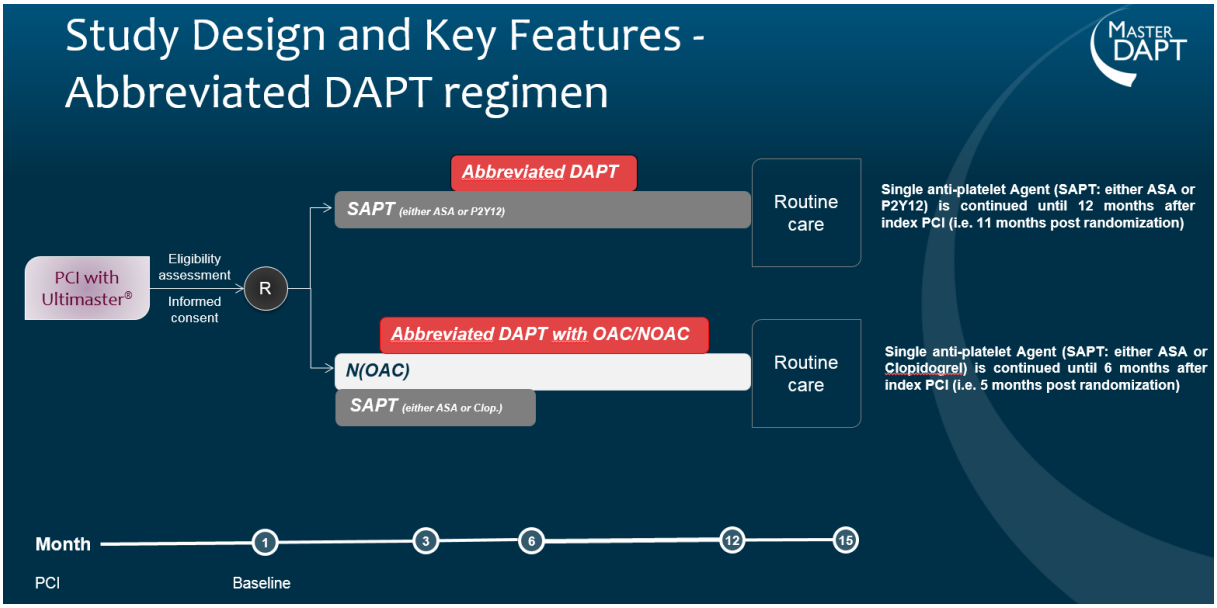
2.1. Trial design

An Investigator-initiated, multi-center, randomized clinical trial in HBR patients after PCI with Ultimaster (TANSEI) bioresorbable polymer coated sirolimus-eluting stent implantation. Open-label non-inferiority (in NACE and MACCE) and superiority (in MCB) study, parallel group design.

Patients, study personnel, monitors and central data monitors are not blinded to the randomized regimen the patient receives. The CEAC is blinded to the randomized regimen the patient receives.

2.1.1. Abbreviated DAPT regimen

The experimental, so called **Abbreviated DAPT regimen** is illustrated in this figure:

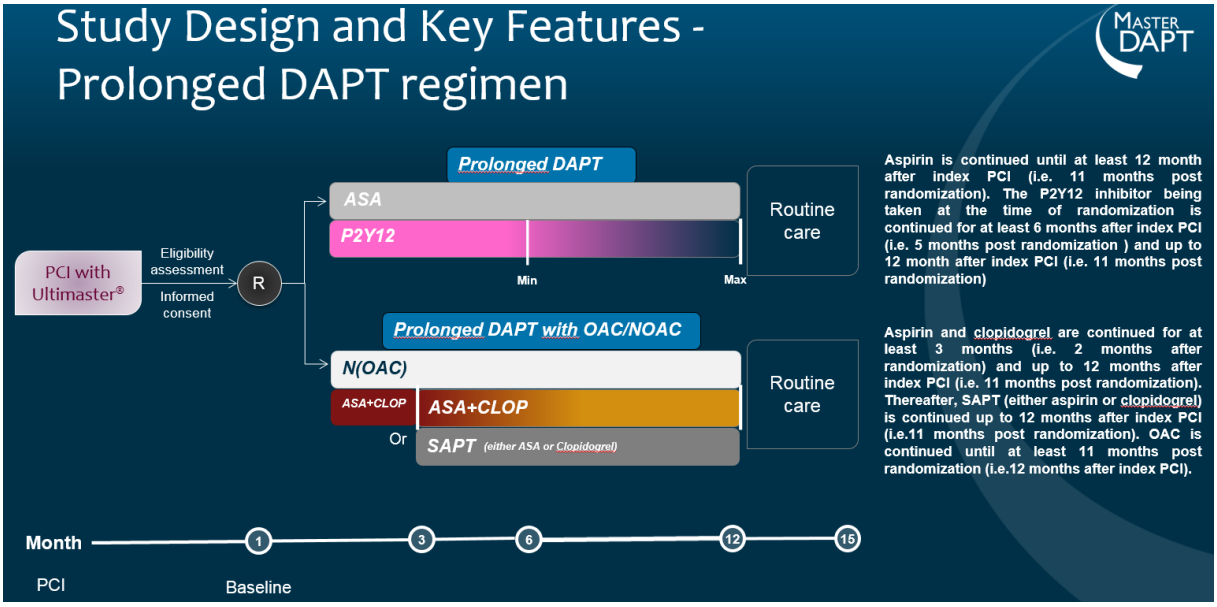


R = randomization at M1 visit, which is conducted 30 to 44 days after the index PCI (last PCI with Ulitmaster stent).

Note that patients receive DAPT up to M1 and then continue with SAPT; for patients without indication to (N)OAC, SAPT will be maintained for another 11 months (up to M12 visit); for patients with indication for (novel) oral anticoagulation (N)OAC (vitamin K antagonist OAC or novel anticoagulation NOAC) SAPT will be maintained for another 5 months (up to M6 visit).

2.1.2. Prolonged DAPT regimen

The control, so called **Prolonged DAPT regimen** is illustrated in this figure:



 = randomization at M1 visit, which is conducted 30 to 44 days after the index PCI (last PCI with Ulitmaster stent).

Note that patients receive DAPT up to M1 and then continue with DAPT post-randomization as follows: for patients without indication to (N)OAC, DAPT must be continued for at least 5 months (up to M6 visit), and up to 11 months post-randomization (at discretion of the treating physician). For patients on (N)OAC, DAPT must be continued for at least 2 months, and up to 11 months post-randomization (at discretion of the treating physician). This flexibility has been implemented to be able to accommodate in the control group the variable DAPT durations observed across studies and registries, especially among those with indication to (N)OAC as well as for allowing clinicians in the control group to accommodate the duration on DAPT based on ischemic risk according to their experience and practice. Before randomization, clinicians are asked to pre-specify the anticipated DAPT duration they would select, had the patient been randomized to prolonged DAPT.

2.2. Randomization

Randomization is performed at the one-month randomization visit, scheduled between 30 and 44 days post index PCI. Patients can be randomized only if all inclusion criteria are met and if no exclusion criteria apply. Patient can be only randomized in the presence of written informed consent.

The randomization procedure is programmed into the eCRF. After confirmation of selection criteria and presence of informed consent, the investigator triggers the randomization procedure, after which randomization to either abbreviated DAPT or prolonged DAPT is divulged. The randomization is stratified per site, by a history of acute myocardial infarction (within 12 months prior to the index procedure) and use of OAC.

If the subject is randomized to abbreviated DAPT, the Investigator takes the necessary measures so that the abbreviated DAPT regimen is implemented without any undue delay. If the subject is randomized to maintain the DAPT regimen, the existing DAPT regimen is continued.

2.3. Sample size

The study includes 2 x 2150 (i.e. 4,300) patients. Sample size calculations have been made for a formal sample size of 2 x 2040 evaluable patients. This allows for attrition rate of 5%.

The assumed event rates under prolonged DAPT are 12% for NACE, 8% for MACCE and 6.5% for MCB. All tests are carried out with a one-side type I error rate of 0.025.

With this sample size, the study has:

- >90% power to establish non-inferiority in NACE with a non-inferiority margin of 3.6%
- >80% power to establish non-inferiority in MACCE with a non-inferiority margin of 2.4%
- >90% power to establish superiority in MCB if abbreviated DAPT reduces the MCB rate from 6.5% to 4.2%, which corresponds to a 35% relative risk reduction.

Abbreviated DAPT is the experimental regimen and Prolonged DAPT is the reference regimen.

2.4. Framework and outcomes

The first test presented is the non-inferiority test of NACE comparing Abbreviated DAPT vs Prolonged DAPT regimen, with a non-inferiority margin of 3.6%.
If the first test fails, the main trial result will be interpreted accordingly, and the second and third tests will be interpreted in light of the finding of failure of the first test.

The second test presented is the non-inferiority test of MACCE comparing Abbreviated DAPT regimen vs Prolonged DAPT regimen, with a non-inferiority margin of 2.4%. If the second test fails, the third test will be interpreted in light of the finding of failure of the second test.

The third test presented is superiority in MCB comparing Abbreviated DAPT regimen vs Prolonged DAPT regimen.

2.5. Statistical interim analyses and stopping guidance

No interim analyses are planned and stopping guidance is provided in the Data Monitoring Committee documentation.

2.6. Timing of final analysis

Final analysis of all primary endpoints and secondary endpoints will be conducted after receiving the CEAC confirmed events (external database export in SAS format provided by Cardialysis – Rotterdam).

Events which are not confirmed by the CEAC are not reported in the publication. A merging with the investigator reported events will be conducted to check whether all events have been assessed by the CEAC (confirmed plus not confirmed). Investigator reported events are adjudicated by the CEAC according to the CEAC charter. Other SAEs related to the DAPT regimen, which are not primary or secondary outcomes, will be reported separately on request only.

2.7. Timing of outcome assessments

All CEAC confirmed adjudicated events occurring between randomization at M1 visit up to and including 335 days post-randomization will be reported.

The first event of each type per patient only will be reported, except if stated otherwise for specific sub-studies or sub-analyses where the occurrence of multiple events will be accounted for (e.g. if the patient xxxx-yy-zz-nnnn had two BARC 3a bleeding between randomization and 335 days after randomization, only the first BARC3a bleeding will be reported).

2.8. Assessment of objectives

The main analyses evaluate the occurrence of the primary endpoints between randomization and 11 months thereafter. This covers the time frame in which the patients are allocated to the experimental or control treatment regimens.

The analyses of primary and secondary endpoints between 11 months and 15 months after randomization is not specifically covered in this statistical analysis plan. This covers the period when the patients are no longer on the randomized study regimen, and accordingly take medications according to routine care.

All event analyses are based on the Clinical Event Committee CEAC (external database export in SAS format provided by Cardialysis – Rotterdam) adjudicated events.
Investigators are instructed to interview each patient carefully at each study visit to determine if serious adverse event may have occurred. When endpoint-related suspected events (including death, myocardial infarction, stent thrombosis, stroke, and bleeding events [BARC 2, 3 or 5]) occur, they are entered into the eCRF as soon as possible after the study staff have become aware of those, including their judgement.

The above events are adjudicated by the CEAC using anonymised source documents, and adjudicated events only will be used for all statistical analyses. For the primary and second objectives, adjudicated events occurring beyond 11 months after randomization will be censored. Adjudicated events occurring up to and including 335 days after randomization will be reported. Adjudicated events reported between 11 months (336 days) and 15 months (up to and including 365+90=455 days) will be be used for secondary analyses assessing the outcomes of switching from study regimens to routine care (e.g. DAPT or SAPT discontinuation in patients without or with OAC indication, respectively, allocated to the control group).

There will be a substudy related to the systemic embolism event rate in patients with concomitant OAC indication. Each event related to systemic embolism reported in the eCRF will be adjudicated by the CEAC.

2.9. Changes of the primary objective during the conduct of the study

No changes in the primary and secondary objectives during the conduct of the study are expected to occur.

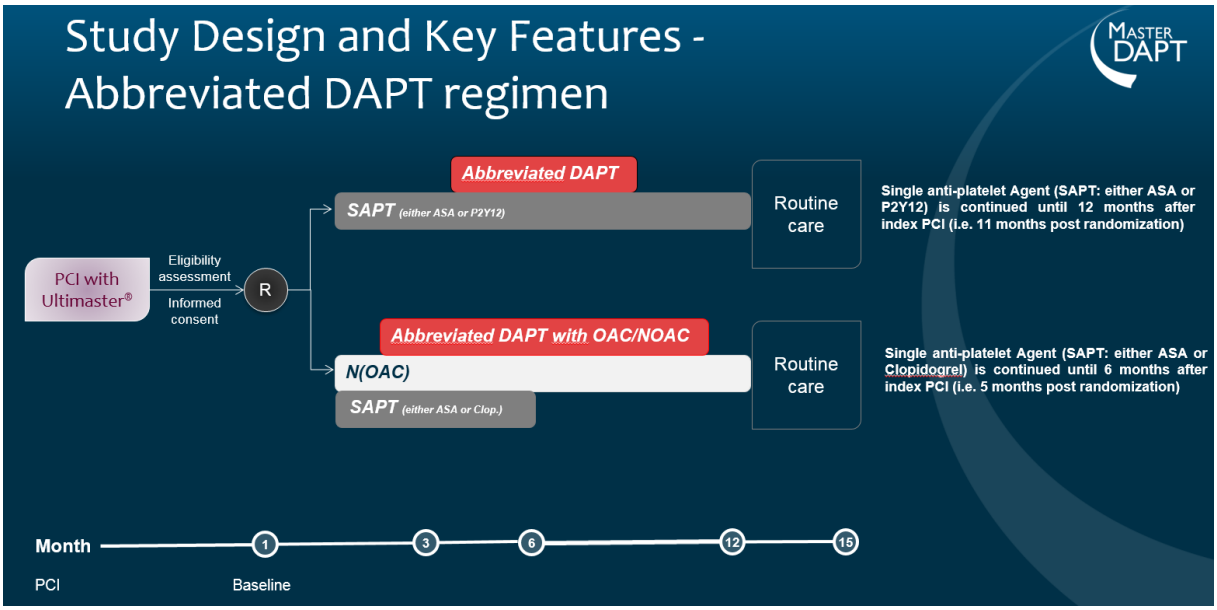
3. Statistical principles

3.1. Confidence intervals and p-values

Ninety-five percent confidence intervals will be reported throughout. Level of statistical significance, two-sided Type I, is set at 5% throughout. The non-inferiority tests are calculated using the confidence intervals of the risk difference Abbreviated DAPT vs Prolonged DAPT with a one-side type I error rate of 2.5%, which is equivalent to a two-sided type I error rate of 5%.

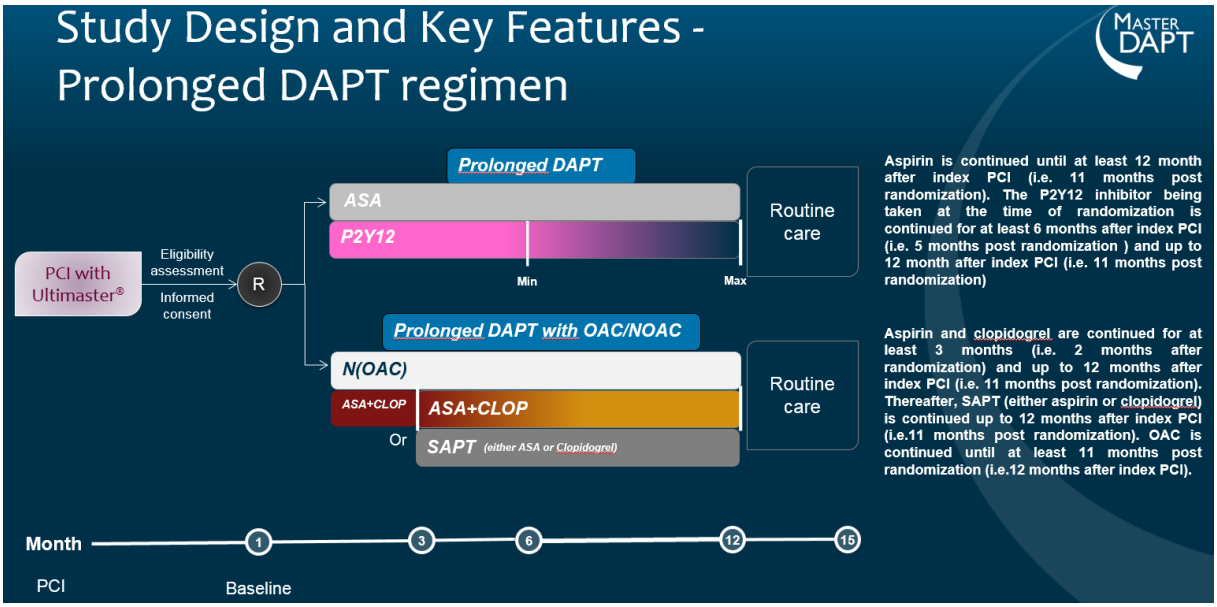
3.2. Evaluation of regimen adherence

The following figure highlights the protocol mandated treatment regimens with regards to the **Abbreviated DAPT** arm.



In particular, patients without OAC indication at the time of randomization should receive a single antiplatelet medication (aspirin, clopidogrel, prasugrel or ticagrelor) from randomization onwards until 11 months post-randomization. Patients with OAC should receive a single antiplatelet medication (aspirin or clopidogrel) up to 5 months post-randomization.

The following figure highlights the protocol mandated treatment regimens with regards to the **Prolonged DAPT** arm.



Patients **without OAC** should receive two concomitant antiplatelet medications consisting of aspirin with either clopidogrel, prasugrel or ticagrelor from randomization onwards until at least **5 months** post-randomization. Afterwards it is allowed to stop the P2Y12 inhibitor, whereas aspirin needs to be continued until 11 months post-randomization (it is also allowed to stop the P2Y12 inhibitor at any time from 5 to 11 months post-randomization).

Patients **with OAC** should receive two antiplatelet medications (aspirin with clopidogrel) from randomization onwards until at least **2 months** post-randomization. Afterwards it is allowed to stop clopidogrel, whereas aspirin needs to be continued until 11 months post-randomization;,it is also allowed to stop aspirin and continue clopidogrel until 11 months post-randomization. Hence, it is allowed to stop one of the antiplatelets at any time between 2 months and 11 months of randomization, as long as the other antiplatelet is continued.

3.3. Adherence to study regimen

3.3.1. Assessment of regimens

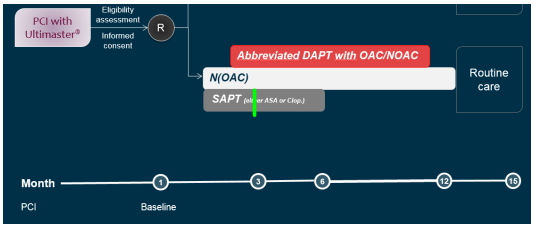
There are scheduled follow-up visits at 90, 180, 365, and 450 days after the index procedure; which is 60, 150, 335 and 425 days after randomization, respectively. At each follow-up the investigator collects information about the regimen inquiring actual and prior use of study medication(s)). Sites are then asked to update the adherence form for each antiplatelet and OAC medication accordingly by indicating the exact start date (first dose taken) and stop date (last dose taken), including clarifying the decision maker (i.e. who decided the start or stop) and why each study medication was started or stopped.

These start-stop sequences are similarly collected for every change in dosing, with each start date (first dose taken) and stop date (last dose taken) of the new drug regimen, including who decided the start or stop with dosage, why the medication dosage was terminated (stopped) or changed to new dosage (started). Note that vitamin K-antagonists do not have a dosage change but INR values are to be collected.

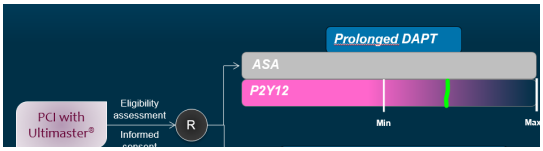
Adherence forms are built accordingly with repetitive start-stop sequences of each antiplatelet drug and each type of OAC.

3.3.2. Adherence to SAPT and DAPT regimen when antiplatelets are exchanged

It is allowed to switch antiplatelet(s) within a SAPT or a DAPT regimen: the patient is considered adherent if the switching was seamless and did not lead to a change from SAPT to DAPT, did not lead to a change from SAPT to no APT, did not lead to a change from DAPT to SAPT and did not lead to a change from DAPT to no APT; i.e. when the patient remained on SAPT or DAPT according to the regimen that should have been prescribed according to randomized arm and timing from randomization (Examples 1 and 2).



Example 1. Patient changed from SAPT consisting of aspirin to SAPT consisting of clopidogrel at 3 months and as such remains consistently on SAPT according to the randomized arm (green line).



Example 2. Patient changed from DAPT consisting of aspirin + clopidogrel DAPT consisting of aspirin + ticagrelor DAPT at 9 months and remains on DAPT in keeping with the prolonged regimen arm (green line). The patient could also continue with aspirin only, this would also be allowed from 5 months after randomization onwards.

It is allowed to stop APT for up to 2 days during APT switch (i.e. fulfilling NARC type 2 non adherence pattern, which is based on the half-life of the pharmacological effects of the P2Y12 inhibitors involved, Table 1).

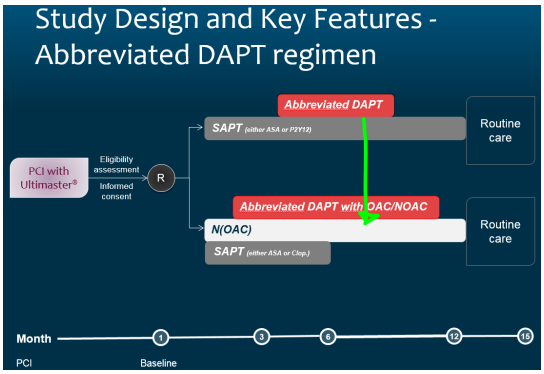
Table 1. Half-life of the pharmacological effects of the APT medications

	Abbreviated DAPT regimen		**Prolonged DAPT regimen**	
Antiplatelet	Not on OAC	On OAC	Not on OAC	OAC
Aspirin	**2 days**	**2 days**	**2 days**	**2 days**
Clopidogrel	**2 days**	**2 days**	**2 days**	**2 days**
Prasugrel	**2 days**	**2 days**	**2 days**	**2 days**
Ticagrelor	**2 days**	**2 days**	**2 days**	**2 days**

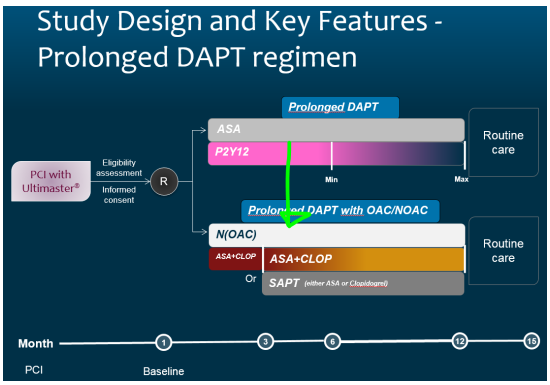
3.3.3. Adherence to SAPT and DAPT regimen in case of changes of OAC

It is allowed to replace one type of OAC with another type of OAC (e.g. Warfarin to Rivaroxaban), the patient should remain on their allocated regimen (i.e. abbreviated versus prolonged) during this switch.

Patients who receive OAC due to a new post-randomization OAC indication should continue according to the protocol-mandated OAC-stratum APT regimen (Examples 3 and 4) and must remain accordingly adherent:



Example 3. Patient receives OAC at 7 months, so switches accordingly (green arrow) and must immediately stop SAPT treatment.

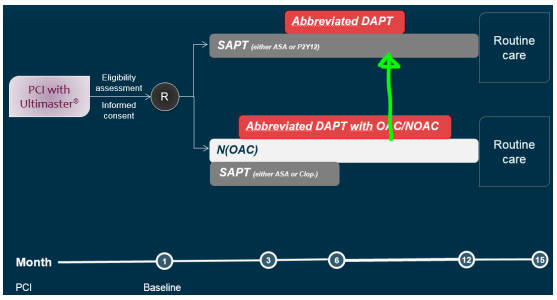


Example 4. Patient receives OAC at 4 months, so switches accordingly (green arrow) and can immediately stop DAPT treatment and continue with one APT only. If the patient was on aspirin + ticagrelor, then ticagrelor should be stopped and replaced by clopidogrel if a provision is made to continue DAPT otherwise he/she can continue with aspirin only or clopidogrel only (SAPT).

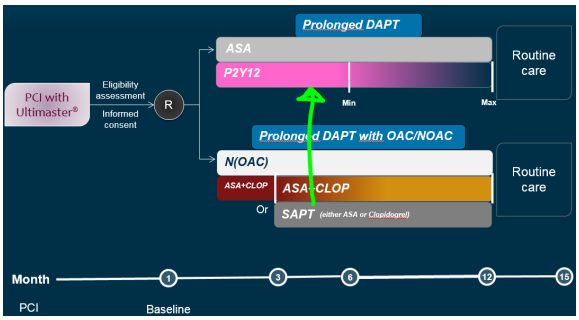
In the case a patient on OAC after randomization is taking one of the newer P2Y12 inhibitors (ticagrelor or prasugrel), following the right duration of the regimen, we will consider this patient adherent.

It is allowed to have a 14-day time period to implement the correct switching after an OAC indication has arisen during the course of the study.

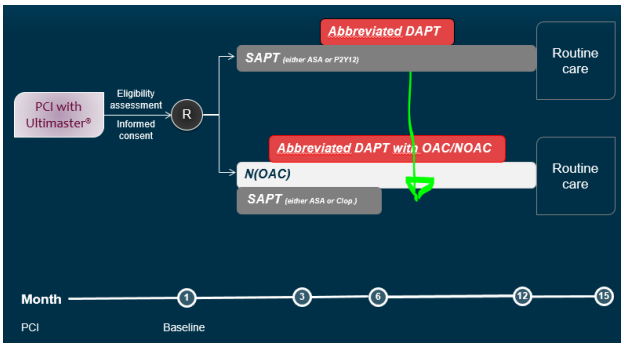
Patients with OAC indication who have been randomized into the study are allowed to stop OAC if no further OAC treatment is deemed indicated, and patient should restart SAPT as necessary (Example 5) or restart DAPT as necessary (Example 6, in both examples in case OAC stopped after randomization):



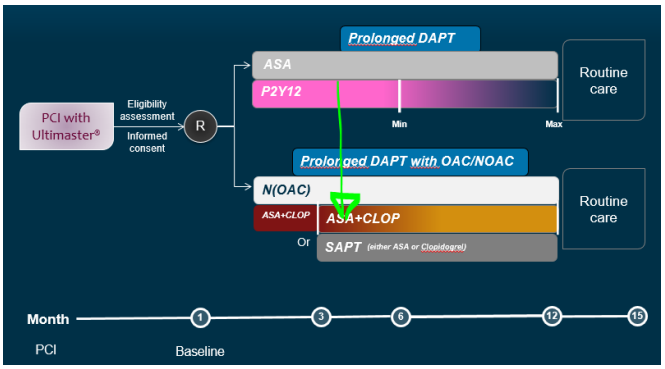
Example 5. Patient stops OAC at 8 months, so should restart aspirin (SAPT) or clopidogrel (SAPT). It is also allowed to implement a SAPT regimen or a DAPT regimen.



Example 6. Patient stops OAC at 4 months while on SAPT consisting of aspirin, so should change to aspirin + clopidogrel (DAPT). It is also allowed to start another P2Y12 inhibitor with aspirin DAPT. If the patient is on aspirin + clopidogrel (DAPT), then this regimen should now be continued for at least 5 months post-randomization.



Example 7. Patient starts on OAC at 8 months, so should stop SAPT. If the patient starts on OAC before 6 months a change from PY212 to Clopidogrel is required.

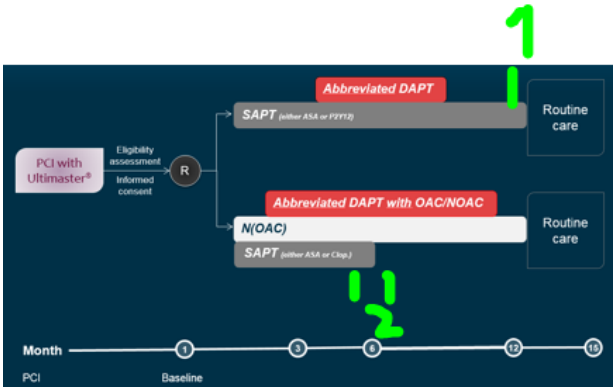


Example 8. Patient starts with OAC at 4 months and should change from P2Y12 to Clopidogrel. It is also allowed for the patient to switch to SAPT (Aspirin or Clopidogrel). However, in the case a patient on OAC after randomization is taking one of the newer P2Y12 inhibitors (ticagrelor or prasugrel), following the right duration of the regimen, we will consider this patient adherent.

It is allowed to have a 14 days time period to make the correct switch after the OAC was newly added or removed.

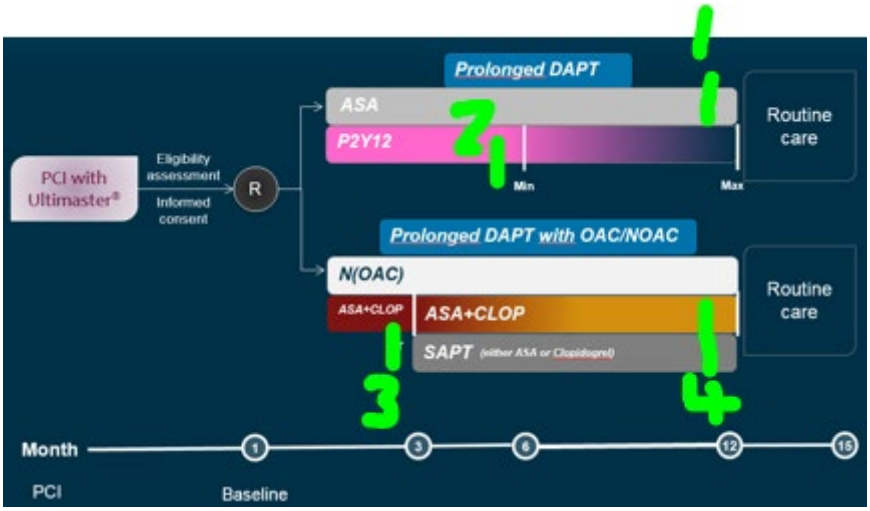
3.3.4. Adherence to SAPT and DAPT regimen in case of too early or too late stops

Patients who are randomized to **Abbreviated DAPT** regimen are permitted to implement the allocated regimen with an allowance of 14 days (i.e. at M6 plus/minus 14 days = 136 to 164 days post-randomization; e.g. at M12 335 days minus 14 days = 321 days post-randomization; see Example 9).



Example 9. Case 1: patient can stop 321 days post-randomization with SAPT or later (as afterwards there will be routine care with no APT, SAPT or DAPT as chosen by the investigator). Case 2. patient must stop SAPT within window of 136 to 164 days post-randomization (150 days ± 14 days).

Patients who are randomized to **Prolonged DAPT** regimen are permitted to prematurely stop one medication as long as this happens within a 14 day window from the due date (e.g. at M3 76 days or later post-randomization; e.g. at M6 136 days or later post-randomization; at M12 321 days or later post-randomization, see Example 10).



Example 10. Case 1: patient can stop 321 days post-randomization with aspirin or later, irrespective of P2Y12 intake (as afterwards there will be routine care with no APT, SAPT or DAPT as chosen by the investigator). Case 2. patient can stop P2Y12 inhibitor 136 days or later post-randomization (note that the patient would only be non-adherent if also aspirin would be stopped). Case 3: patient can stop 76 days post-randomization with aspirin or clopidogrel (note that the patient would only be non-adherent if also the other APT would be stopped). Case 4. patient can stop all APTs at 321 days or later post-randomization.

3.3.5. Adherence to SAPT and DAPT regimen after events

If any of the following events occur, the following rules for the randomized treatment regimens apply (+ days denotes how many days of a regimen might be added after the event, each addition has again a window of ±14 days as applicable; ≥ denotes minimum additional days allowed or more, Table 2).

Table 2, APT regimen(s) allowed after each type of event, with routine care meaning according to the discretion of the local investigator.

	Abbreviated DAPT regimen		**Prolonged DAPT regimen**	
Event number and Type	Not on OAC	On OAC	Not on OAC	OAC
A. Repeat PCI	**+30 days DAPT**	**+30 days DAPT**	*≥180 days DAPT*	*≥90 days DAPT*
B. Stent thrombosis	**routine care**	**routine care**	**routine care**	**routine care**
C. Myocardial infarction	**routine care**	**routine care**	**routine care**	**routine care**
D. First occurrence of a BARC type 2 bleeding	**routine care** until event resolved*	**routine care** until event resolved*	**routine care** until event resolved*	**routine care** until event resolved*
From the 2nd BARC 2	**routine care**	**routine care**	**routine care**	**routine care**
E. BARC 3 to 5 bleeding	**routine care**	**routine care**	**routine care**	**routine care**
F. Stroke	**routine care**	**routine care**	**routine care**	**routine care**
G. Other contraindications for the randomized DAPT regimen				
H. Temporary discontinuation*	**+7 days routine care***	**+7 days routine care***	**+7 days routine care***	**+7 days routine care***
I. Dyspnea on ticagrelor	**See 3.3.5 I**	**See 3.3.5 I**	**See 3.3.5 I**	**See 3.3.5 I**

bold changes will be re-coded as the patient being adherent (APT change is allowed), the *italic* changes do not affect the adherence assessment of the indicated regimen (so they are relevant for patient safety but the adherence assessment is not affected as already allowed by randomized regimen), empty cells means that the event does not affect the regimen (e.g. P2Y12 switch or no clear and derivable recommendations).

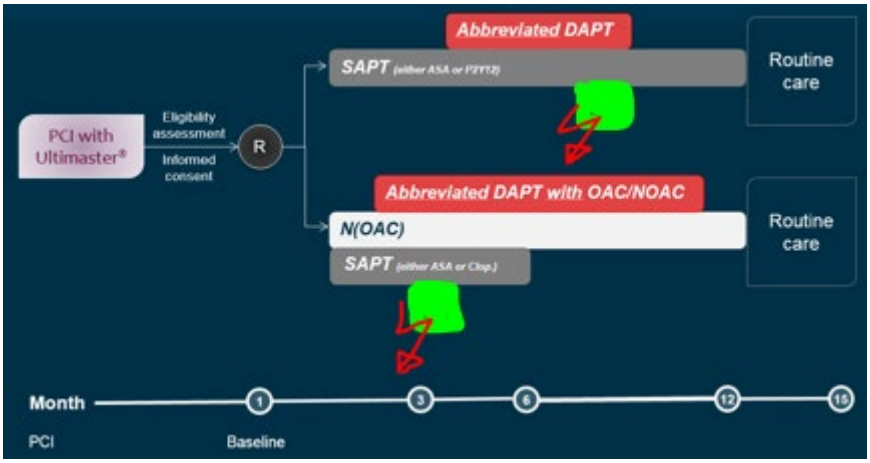
*only discontinuations due to **surgery or non-revascularisation intervention requiring (temporary) stop or dosage change** are counted as such, in most cases the patient will receive no APT or SAPT during this temporary stop. If the patient does not restart the regimen after 7 days, the 0 to 7 days are coded as adherent, but day 8 and later are coded as non-adherent. Event resolved: date the site reports that the bleeding event was resolved. If the patient has another BARC 2 bleeding, it is allowed to do routine care after this second BARC2 event (note that this is different from the protocol, which says: "the randomized treatment regimen is adhered to as much as possible", regardless of how many BARC 2 bleedings occurred).

See for detailed descriptions per event the next pages (event **A** to **I**).

A. Elective repeat PCI

Antiplatelet treatment should be prescribed as local practice:

- **Abbreviated DAPT**: If not on OAC, a P2Y12 or aspirin is added for one month to the pre-existing SAPT (i.e. a DAPT regimen is re-instituted for 1 month). If on OAC, DAPT with aspirin and clopidogrel is re-instituted for 1 month and thereafter clopidogrel or aspirin is continued for 5 months. See Example 11.



Example 11. In both cases the patient is on one month of DAPT after the repeat PCI (red flash), allowed is 16 to 44 days of DAPT (±14 days window), afterwards on SAPT.

- **Prolonged DAPT**: If not on OAC, treatment with aspirin and a P2Y12 inhibitor is continued or started for at least 6 months (i.e. a DAPT regimen is re-instituted for 6 months). If on OAC, aspirin and clopidogrel are re-instituted for at least 3 months. There is no Example, as Prolonged DAPT allows for DAPT from randomization to 11 months by default, and restart of DAPT after SAPT does not affect adherence to this regimen.

B. Definite stent thrombosis

Further antithrombotic treatment is as per current guidelines and institutional recommendations.

C. Non-fatal myocardial infarction and no definite stent thrombosis

Antiplatelet treatment should be prescribed as per local practice, we recommend:

- **Abbreviated DAPT**: If not on OAC, a P2Y12 or aspirin is added for one month to the pre-existing SAPT (i.e. a DAPT regimen is re-instituted for 1 month). If on OAC, aspirin and clopidogrel are re-instituted for 1 month and thereafter clopidogrel or aspirin is continued for 5 months.
- **Prolonged DAPT**: If not on OAC, treatment with a P2Y12 inhibitor is continued or started for at least 6 months (i.e. a DAPT regimen is re-instituted for 6 months). If on OAC, aspirin and clopidogrel are re-instituted for at least 3 months.

D. BARC 2 bleeding

Routine care is allowed until the site reports that the BARC2 bleeding has been resolved. In case the patient experiences another, second, BARC2 bleeding: routine care is allowed afterwards until the end of the regimen.

E. BARC 3 to 5 bleeding

The management of antithrombotic treatment including discontinuation or down titration of previously prescribed agents or switching to a different regimen is at the discretion of the treating physician, meaning routine care is allowed.

F. Stroke

The management of antithrombotic treatment including discontinuation or down titration of previously prescribed agents or switching to a different regimen is at the discretion of the treating physician, meaning routine care.

G. Other contraindications for the randomized DAPT regimen

No changes in APT use are allowed in the context of the adherence and statistical analyses as defined in this statistical analysis plan. Note that physicians are allowed to do further treatment at their discretion.

H. Temporary discontinuation (e.g. Surgery, tooth extraction etc.)

The randomized trial regimen is resumed as soon as the indication of temporary discontinuation is resolved. The item will be derived from **surgery or non-revascularisation intervention requiring (temporary) stop or dosage change** (with stop date in Adherence form APT) and the next re-start of APT (next start date in the same Adherence form APT), the period between this stop and re-start will be considered as the patient being adherent **if lasting up to 7 days**. The restart of the regimen should be within these 7 days, if not the 8th day and later is regarded as the patient being non-adherent - until the regimen is correctly restarted.

I. Dyspnea on ticagrelor

Ticagrelor is replaced preferably with prasugrel, or clopidogrel if prasugrel is not an option. When ticagrelor is switched to clopidogrel, loading dose of clopidogrel (3/600mg) is given. When ticagrelor is switched to prasugrel, the administration of prasugrel loading dose is at discretion of the physician. See chapter 3.3.2.

3.3.6. Temporary and permanent changes

We consider a patient completely adherent to the regimen when the patient is taking the allocated antiplatelet therapy (or allowed routine care or allowed altered therapy as specified above), excluding the following three scenarios:

1. When a patient is off pharmacological effect of the drug due to a temporary discontinuation. In this case, the interruption length allowed is a maximum of 2 days:

	Allowed days of interruption	Number of pills per day
Aspirin	2	1
Clopidogrel	2	1
Prasugrel	2	1
Ticagrelor	2	2

2. When a patient had permanent discontinuation.
3. When a patient adds APT to no APT (so is now wrongly on SAPT), when a patient adds APT to SAPT (so is now wrongly on DAPT), when this is not allowed by routine care and also not allowed as altered therapy, as defined above.

3.3.7. Adherence to NOAC dosages

A descriptive table of NOAC dosages use per randomized arm and per visit will be produced as Supplement material. Over- and under-dosing includes off-label too high or too low dosages of NOACs (e.g. low dosage not explained by the dose reduction criteria for each of the prescribed NOAC agent). The protocol mandated NOAC regimens are as follows:

- Apixaban 5mg b.i.d or Apixaban 2.5 mg b.i.d. if at least two of the following: Age ≥ 80 years, body weight ≤ 60 kg or serum creatinine level ≥ 1.5 mg/dL (133 µmol/L);
- Dabigatran 150 mg b.i.d. Dose reduction to Dabigatran 110 mg b.i.d. is recommended if Age ≥ 80 years or if the patient receives concomitant Verapamil. Dose reduction to Dabigatran 110 mg b.i.d. may be considered if the Age is between 75-80 years, CrCL 30-50 mL/min, for patients with gastritis, esophagitis or gastroesophageal reflux, or other patients at increased risk of bleeding.
- Edoxaban 60 mg q.d. or Edoxaban 30 mg q.d. if any of the following criteria apply: CrCl of 15–50 mL/min, or body weight ≤ 60 kg, or concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole.
- Rivaroxaban 20 mg q.d. Rivaroxaban 15 mg q.d. if CrCl 30–49 mL/min.

3.3.8. Adherence categories

We divide the patients in 3 groups based on adherence; the first group will be type 2/3 patients (type 2 or 3 NARC, type 2 is temporary discontinuation, type 3 is permanent discontinuation, these two NARC levels are non-adherent patients), the second group consists of permanently adherent patients (referred to as “type 0” NARC patients and includes routine care, if allowed as described above), the third group of patients with ≤2 days interruptions/over-dosing/under-dosing (referred to as type 1 NARC patients, during wash-out of the pharmacological effect). See for the NARC classification Valgimigli et al. 2018.

Adherence will be computed per patient and per day as follows:

1. Compute permanent stop first at time t (t is three days after last intake, i.e. allowing two days as window to account for the residual pharmacological effect of the discontinued treatment in keeping with section 3.3.6) at time t. All days at t and later the patient is coded as non-adherent, except if routine care or altered therapy is allowed as specified above in Chapters 3.3.1 to 3.3.6.
2. Compute for each day whether partially adherent (at day t not taken, at day t-2 to t+2 not always taken, but total period t-2 to t+2 includes a maximum of 5 days interruption). Take into consideration ±2 days windows etc. as specified above. Again a reminder that routine care or altered is allowed as specified above in Chapters 3.3.1 to 3.3.6.
3. Remaining days are then fully adherent days (if no other APTs are added not according to the regimen). And also here a reminder that this may include days that the patient is on routine care or altered therapy, if allowed as specified above in Chapters 3.3.1 to 3.3.6.

3.3.9. APT treatment categories

We acknowledge and are fully aware that lumping patients into type 2/3, type 0 or type 1 categories neglects the fact that we may cluster patients into the same group who may have completely different adherence patterns, e.g. patients with a shorter or longer time period of full adherence (type 0) followed by a permanent discontinuation will all be merged together under type 2.

Therefore, we will also assess for each patient the percentage of days he/she was receiving:
1. **treatment as per protocol**
Includes taking no APT, SAPT or DAPT according to Chapters 3.3.1 to 3.3.4, i.e. allows switches and changes within certain windows, but does not allow over-dosing, under-dosing nor non-regimen explainable additions or removals of APTs.
2. **over-treatment allowed**
Includes over-dosing, adding APTs to the treatment strategy, as allowed in the definitions of Chapters 3.3.1 to 3.3.6.
3. **over-treatment not-allowed**
Includes over-dosing, adding APTs to the treatment strategy, but each of them are not allowed according to the regimen as explained in Chapters 3.3.1 to 3.3.6.
4. **under-treatment allowed**
Includes under-dosing, removing APTs from the treatment strategy as allowed in the definitions of Chapters 3.3.1 to 3.3.6.
5. **under-treatment not allowed**
Includes under-dosing, removing APTs from the treatment strategy, but each of them are not allowed according to the regimen as explained in Chapters 3.3.1 to 3.3.6.

The percentages are calculated from day 0 (randomization) up to 335 days post-randomization (or last day of adherence assessment if <335 days); and these five percentages can be used for more detailed across patient assessments (either cross-sectional or cumulative over time)

3.3.10. OAC treatment categories

Over- and under-dosing includes off-label too high or too low dosages of NOACs as described in section 3.3.7.

For vitamin-K-antagonist patients will be classified as treatment as per protocol if they are within their pre-specified target therapy INR 65% of the time or more. Conversely, if they are within target therapy less than 65% of the time, they will be classified as not on treatment.

3.3.11. Treatment graphs

Cross sectional analysis of treatments

The cross-sectional assessment of treatments for the first 11 months after randomization calculates the proportion of the five treatment categories (Chapter 3.3.9) on a per patient per day basis, i.e. at day 0 (randomization), 1, 2, 3 … 335 days post-randomization, overall and per randomized regimen arm divided by OAC no or yes.

Cumulative analysis of treatments

The cumulative assessment of treatments for the first 11 months after randomization will be considered in addition to the cross-section adherence analysis. First the percentage of the time that each patient is in each of the five treatment categories is analyzed (Chapter 3.3.9), and the mean and CI over the population is then computed.

3.4. Exposure to APT study drugs within the regimens

3.4.1. Extent of APT exposure

All patients are on DAPT (Aspirin and Clopidogrel/Prasugrel/Ticagrelor) between index PCI and randomization (occurs 30-44 days after index PCI).

At 30 days to 44 days after the index PCI (M1), patients are randomized to either Abbreviated DAPT regimen or Prolonged DAPT regimen and the exposure to study drugs is as follows from M1 onwards:

Abbreviated DAPT (experimental arm):

- Not on OAC: DAPT is discontinued and a single P2Y12 inhibitor (Clopidogrel or Prasugrel or Ticagrelor) is continued until at least 11 months post randomization (i.e.12 months after index PCI).
- On OAC: DAPT is discontinued and either aspirin or clopidogrel is continued until 5 months post randomization (i.e. 6 months after index PCI). OAC or NOAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).

Prolonged DAPT (control arm):

- Not on OAC: Aspirin is continued until at least 11 months post randomization (i.e.12 months after index PCI). The P2Y12 inhibitor being taken at the time of randomization is continued for at least 5 months and up to 11 months post randomization (i.e.12 months after index PCI).
- On OAC: Aspirin and Clopidogrel are continued for at least 2 months (i.e. 3 months after index PCI) and up to 11 months post randomization (i.e. 12 months after index PCI). Thereafter, SAPT (either Aspirin or Clopidogrel) is continued up to 11 months post randomization (i.e.12 months after index PCI). OAC or NOAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).

3.4.2. Duration of APT exposure

For at least 1 year (11 months after randomization), afterwards patients receive routine care and may continue with no APT, or change to SAPT or change to DAPT. See for details of which exposures are allowed for each regimen section 3.3.

3.4.3. Antiplatelet and OAC daily dosages

Study regimens are implemented by regular drug prescription. The investigators provide the necessary prescription to the study participants. The followings are recommended according to the current guidelines and local practice.

- Aspirin is prescribed in standard dose of at least 75 mg/day and up to 162 mg/day.
- Clopidogrel is prescribed in standard dose of 75 mg once daily.
- Prasugrel is prescribed in standard dose of 10mg/day or 5mg/ day in patients weighing less than 60 kg or who are over 75 years old. In regions where other standard dose exists (i.e. Japan), prasugrel dosage is adjusted according to the locally approved dose.
- Ticagrelor is prescribed in standard dose of 180 mg/day (90mg bid).
- Vitamin K antagonist is dosed to keep INR within guidelines.
- NOACs (rivaroxaban, edoxaban, dabigatran and apixaban) are given in locally approved doses.
- Switching from Vitamin K antagonist to NOACs or vice-versa is not allowed unless there are clinical and well documented reasons for doing so. Similarly, switching from NOACs to VKA during the course of the study is not allowed, unless dictated by a clinical and documented reason (e.g. change in renal function during the course of the investigation), which will be captured in the eCRF.
- Prescribed units of aspirin, clopidogrel, prasugrel, ticagrelor and OAC are recorded in the eCRF. Patients are queried on general drug adherence.

Analyses of dosages used by the patients and per medication type will be provided on request.

3.5. Definition of populations for analysis

All patients undergoing PCI with an Ultimaster (TANSEI) stent will be individually invited to participate in the MASTER-DAPT Trial, and can potentially be enrolled if they satisfy all inclusion and exclusion criteria.

3.5.1. Full analysis set (FAS)

Full analysis population (FAS) consists of all randomized subjects.

Subjects are analysed according to the group to which they were assigned by the randomization process, using the intention-to-treat principle (i.e. intention to implement the allocated regimen).

3.5.2. Per-protocol population (PP)

Per-protocol (PP) population consists of randomized patients who met the following criteria.

• No violation of inclusion/exclusion criteria (HBR) at the time of randomization

• Randomized treatment was implemented within 7 days after randomization (on treatment within 7 days after randomization)

In particular, the following patients are excluded from the PP population

- Not at HBR
- Not treated with Ultimaster (TANSEI) stent
- Received other stents than Ultimaster (TANSEI) stents within 6 months of qualifying procedure.
- Received treatment for an in-stent restenosis or in-stent thrombosis

3.5.3. Non-randomized population

The non-randomised population consists of all patients with full written consent, where all the data up to and including the Randomization assessment will be collected inside the EDC (Demographics, History, HBR criteria, PCIs with Lesions and APT after PCI), but these patients were not randomized due to various reasons (i.e. death before M1, withdrew consent before randomization, lost to follow-up at M1, no longer eligible at M1), i.e. these patients cannot be used for the comparison Abbreviated DAPT regimen vs Prolonged DAPT regimen. It includes patients who were randomized mistakenly due to a clerical error, and these patients have been moved to the non-randomised population with a Note to File by CTU Central Data Monitoring and Management team, after received confirmation of the site and the local CRA.

3.5.4. Definitions of sub-group populations

Results of the subgroups may be presented in separate publications.

The following main subgroups are defined (the first two items are used to stratify the randomization):

Oral anticoagulation (Yes vs No)

History of acute MI within 12 months (Yes vs No)

Indication for PCI (ACS vs Stable CAD)

DAPT score (High ≥2 vs Low <2)

> See for DAPT score: Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al; DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016; 315(16): 1735-1749.

PRECISE DAPT score (0-24 vs ≥25)

Gender (Male vs Female)

Creatinine clearance (≥60 ml/min vs <60 ml/min)

Age (≥75 years vs <75 years)

Diabetes mellitus (Yes vs No)

Additional subgroups/dedicated analyses, which will not be reported in the main study results manuscript(s), are defined according to each of the **single** HBR criteria (if not outlined above), i.e.:

Recent (<12 months) or Post-PCI non-access site bleeding episode, which required medical attention Yes/No

Previous bleeding episode(s) which required hospitalization and the underlying cause is not been definitely treated Yes/No

Systemic conditions associated with increased bleeding risk Yes/No

Documented anaemia or transfusion within 4 weeks before randomization Yes/No

Need for chronic treatment with steroids or NSAIDs Yes/No

Diagnosed malignancy (other than skin) considered at high bleeding risk Yes/No

Stroke at any time, or TIA in the previous 6 months before first PCI Yes/No]

Presence or absence of concomitant heart valve disease;

Fulfillment of at least one criterion of complex PCI as defined by Giustino et al JACC (2016);

Syntax score before the procedure

Residual Syntax score (both as per investigator reported Syntax score or by core-lab analysis if and when available)

Type of DAPT before randomization in terms of aspirin+clopidogrel versus aspirin+ticagrelor or aspirin+prasugrel), type of selected SAPT (aspirin versus each type of P2Y12 inhibitor)

HBR criteria according to the Academic Research Consortium initiative

Stratified analyses based on bleeding and ischemic PARIS score

Performance and value in risk stratification of the PRECISE OAC.

4. Trial population

4.1. Screening data

Full screening data will be collected for all sites within one week windows per site only, and analyses of high bleeding risk criteria (HBR criteria) as defined for the MASTER DAPT trial will be provided on request.

For a subset of these HBR patients with full written consent all the data up to and including the Randomization assessment will be collected inside the EDC (Demographics, History, HBR criteria, PCIs with Lesions and APT after PCI), but these patients were not randomized due to various reasons (i.e. death before M1, withdrew consent before randomization, lost to follow-up at M1, no longer eligible at M1). The non-randomised population will be compared to the randomized population on request (with p-values for comparison of e.g. history, risk factors and HBR), using the applicable shell tables.

4.2. Patient flow

A CONSORT style flow chart will be produced.

5. Analysis

5.1. Outcome definitions

This study has three primary endpoints:

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

The primary objective is to assess the primary endpoints between randomization and 11 months (equals 335 days) thereafter.

The secondary endpoints of the study are the following:

1) The individual components of each composite primary endpoints
2) The composite of cardiovascular death, MI, and stroke

5.2. Analysis methods

Tables and figures will be presented for of a number of variables for the comparison between patients on abbreviated DAPT and prolonged DAPT. In the tables either the mean and standard deviation, or the number of patients and the percentage of the total population will be presented for each variable. Due to the time varying nature of the primary and secondary endpoints, figures of these endpoints (either exact values or estimates) over time will be included (Kaplan-Meier plots).

All patients will be analysed by intention-to-treat (FAS) and reported according to their randomized arm, irrespective of the treatment they received. The differences in the rates of the primary endpoints (standard DAPT to abbreviated DAPT) will be reported as the cumulative incidence from the date of randomization to 335 days after randomization using the Kaplan-Meier approach.

The main analysis will consider the occurrence of primary endpoints between randomization and 11 months (335 days) thereafter. In secondary analyses, the occurrence of primary endpoints between 11 months and 15 months after index PCI can be evaluated, i.e. when the patients are on routine care medications.

The analyses of the primary endpoints are performed in the FAS population under application of the Intention-to-treat principle that is, events are counted irrespective of their occurrence relative to termination of randomized APT regimen. Follow-up is censored at the last date of known outcome status or at 11 months since randomization, whichever comes first.

Incidence rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to 335 days after randomization (~1 year post index PCI) by the Kaplan-Meier method. Incidence rate differences, comparing Abbreviated DAPT vs Prolonged DAPT regimen , are defined as the cumulative incidence under abbreviated DAPT minus that under standard DAPT, estimated using the Com-Nougue et al. methodology (with Greenwood estimators of the standard error).

Hazard ratios with 95% confidence intervals comparing Abbreviated DAPT vs Prolonged DAPT regimen are computed using the Cox regression method, using the stratification factors as

covariates (i.e. recent myocardial infarction - within 12 months before the first PCI and OAC at randomization).

5.2.1. Adjustment of covariates

The primary and secondary endpoints will be analyzed adjusted for the two stratification factors used at randomization (acute MI with 12 months yes/no; clinical indication for OAC yes/no).

5.2.2. Pooling of sites

The randomization is stratified by site (in addition to history of MI and use of OAC), ensuring that approximately equal numbers of patients are randomized to Abbreviated and Prolonged DAPT regimen at each site. Since a large number of centers are participating in the study with potentially few randomized patients per site and probably no primary or secondary endpoints recorded at some sites, a correction for the effect of site will not be included in the analyses.

5.2.3. Assessment of statistical assumptions

The proportional hazards tests will be used to test whether the hazard ratio remains stable over time.

5.3. Missing data

Patients will be censored at the last valid contact or at the date of consent withdrawal if alive; and at the date of death if deceased. Consent withdrawal on the date of randomization will be counted as one day at risk for the primary and secondary endpoints.

5.4. Per-protocol analyses

Per-protocol population (PP) analyses will be conducted for the three primary endpoints only (NACE, MACE and MCB).

Per-protocol analyses in the per-protocol population (PP) will be conducted including each patient during the time period when the patient is on treatment, and censoring each patient at the moment when he or she is off treatment, for the three primary endpoints only (NACE, MACE and MCB).

For example, censoring will occur when routine care or DAPT is not allowed as specified in Chapter 3, so the patient is expected to (still) follow the regimen.

It includes *for example*:

- Discontinuation of DAPT was not implemented in patients randomized to abbreviated DAPT at M1 visit, ±14 days window.
- Permanent discontinuation of DAPT in patients randomized to prolonged DAPT occurring before 5 months post-randomization (±14 days) in patients not on OAC, or before 2 months in patients with OAC (±14 days), not allowed as defined in Chapter 3.

5.5. Harms

The investigator monitors the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after randomization. Any records of any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation are collected and stored.

Only endpoint-related SAEs need to be reported during the study, unless they are considered related to the duration of the DAPT treatment.

A table for endpoint related adverse events will be produced. For other events, a Supplementary Material table will be produced if applicable and requested. Listing of adverse events per patient are provided on request.

5.6. Statistical software

Statistical analyses will be performed with Stata version 15.1 or higher, or R version 3.4 or higher in case a specific statistical procedure is not available within the Stata software.

6. Display items

6.1. Demographics and baseline characteristics

Please note that P-values, standard errors, and confidence intervals are not to be shown in baseline tables according to the CONSORT Statement, since any significant difference can be explained by the play of chance if the randomization was performed properly.

A table of baseline characteristics and medical history will be produced.

6.2. PCIs and Lesions

A table of procedural and lesion characteristics will be produced.

6.3. Adherence to regimen

A table for adherence to the study medications will be produced, optionally (or additionally) as a line or stacked bar figure.

6.4. Clinical endpoints

The p-value of the non-inferiority test Abbreviated DAPT regimen vs Prolonged DAPT regimen comparing the risk difference - using the 95% confidence interval of this risk difference with the margin - of the **Co-primary composite endpoint of all-cause death, myocardial infarction, stroke and bleeding events defined as BARC 3 or 5 (NACE)** will be produced for the main text and Abstract.

The p-value of the non-inferiority test Abbreviated DAPT regimen vs Prolonged DAPT regimen comparing the risk difference - using the 95% confidence interval of this risk difference with the margin - of the **Co-primary composite endpoint of all-cause death, myocardial infarction, stroke (MACCE)** will be produced for the main text and Abstract.

The p-value of the superiority test Abbreviated DAPT regimen vs Prolonged DAPT regimen comparing the risk difference - using the 95% confidence interval of this risk difference with the margin - of the **Co-primary composite endpoint of type 2, 3 and 5 BARC bleeding events (MCB)** will be produced for the main text and Abstract.

Note that certain journals will not accept p-values for secondary outcomes, but it is suggested to present all p-values initially for informational purposes, including a superiority test *pro-forma* of the two co-primary composite endpoints separately.

6.5. Subgroup analyses

Pre-specified subgroup analyses of the three co-primary endpoints will be performed, but it is expected that some of these figures will be moved to the Supplementary Information of the publication.

As mentioned in chapter 5.2, confidence intervals for the cumulative incidence rate differences comparing Abbreviated DAPT vs Prolonged DAPT regimen, are calculated according to the approach of Com-Nogue et al., accordingly p-values for a modifying effect of the subgroup on this difference are computed (i.e. interaction p-values).

6.6. Medications

All full tabulation of medications will be produced. Note that for APTs and OACs the medication will be regarded as taken when taken inside a ±14 days window around the visit: if this leads to multiple P2Y12 inhibitors taken due to a switch around the visit, then the P2Y12 inhibitor closest to the exact day will be reported (e.g. clopidogrel on 50 days, ticagrelor on 51 days, ticagrelor is closer to 60 days post-randomization so reported as taken, whereas clopidogrel is reported as not taken). Again, 2 months = 2x30 days = 60 days, 5 months = 5x30 days = 150 days and 11 months = 335 days after randomization.

7. References

Literature

Com-Nougue C, Rodary C, Patte C. 1993. How to establish equivalence when data are censored: a randomized trial of treatments for B non-Hodgkin lymphoma. Statistics in Medicine 12: 1353-64.

Giustino G et al. 2016. Efficacy and safety of dual antiplatelet therapy after complex PCI. JACC 68: 1851-1864.

Kernan et al. 1999. Stratified randomization for clinical trials. Journal of Clinical Epidemiology 52: 19-26.

Valgimigli et al. 2018. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC), European Heart Journal.

Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al. 2016. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 315: 1735-1749.

Data Management Plan

MASTER DAPT Data Management Plan (dynamic document)

8. Appendix I: Abbreviations

ACS	Acute Coronary Syndrome
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
CEAC	Clinical Event Adjudication Committee
CRA	Clinical Research Associate
(e)CRF	(electronic) Case Report Form
DAPT	Dual AntiPlatelet Therapy
DES	Drug-Eluting Stent
DMC	Data Monitoring Committee
DTI	Direct Thrombin Inhibitor
EC	Ethics Committee
ECG	Electrocardiography
ISR	In-Stent Restenosis
IRB	Institutional Review Board
IV	IntraVenous
GP	GlycoProtein
HBR	High Bleeding Risk
HIT	Heparin-Induced Thrombocytopenia
IFU	Instruction For Use
IRB	Institutional Review Board
LAD	Left Anterior Descending artery
LCA	Left Coronary Artery
LCX	Left Circumflex artery
MACE	Major Adverse Cardiac Events
MACCE	Major Adverse Cardiac and Cerebral Event
MCB	Major or clinically relevant non-major bleeding
MI	Myocardial Infarction
NACE	Net Adverse Clinical Endpoint
NOAC	New Oral Anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEACS	Non-ST segment Elevation Acute Coronary Syndrome
(N)STEMI	(Non-)ST segment Elevation Myocardial Infarction
OAC	Oral Anticoagulant
PAR	Protease Activated Receptor
PCI	Percutaneous Coronary Intervention
RCA	Right Coronary Artery
(S)AE	(Serious) Adverse Event
SAPT	Single AntiPlatelet Therapy
SD	Source Documentation
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularisation
TVF	Target Vessel Failure
UA	Unstable Angina
UFH	UnFractionated Heparin
ULN	Upper Limit of Normal
Ultimaster	Ultimaster© (TANSEI) drug-eluting stent developed by Terumo

9. Appendix II: visit plan

SUMMARY OF FOLLOW-UP VISITS

Day 0: PCI	**V1: 30 days**	**V2: 90 days**	**V3: 180 days**	**V4: 365 days**	**V5: 450 days**
	+14 days	*60±14 days post randomization*	*150±14 days post randomization*	*335+14 days post randomization*	*420+14 days post randomization*
Type of contact	Visit	Visit or Phone and Letter*	Visit or Phone and Letter*	Visit	Phone
Inclusion/ exclusion criteria	X				
Informed consent**	X				
Physical examination	X				
Medical and cardiac history	X				
Peri-procedural PCI data	X				
Randomization	X				
Electrocardiogram (12 lead ECG)	X***				
Medication regimen	X	X	X	X	X
Anginal status	X	X	X	X	X
Serious adverse event monitoring	X****	X	X	X	X
Blood sampling	X***				

*) A letter with details of randomized duration regimen is sent to the patient, which will be brought to the treating physician to ensure the implementation of randomized regimen.
**) Informed consent can be obtained at any time between the percutaneous coronary intervention (PCI) and 30-44-days randomization visit (V1)
***) Only in the centers where this is a part of usual clinical practice
****) Serious adverse event monitoring starts immediately after informed consent.

UNIVERSITÄT BERN

Faculty of Medicine

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Statistical Analysis Plan

Administrative Information

Project number:	**634**
Study title:	**MASTER DAPT**
Trial registration number:	NCT03023020
SAP version:	Version 3 Valid from: 05.06.2020
Protocol version:	Version 1.0 dated November 2, 2016

Authored by

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Revision history

Revision	Justification	Timing
v2	Pages 1-39: added minor additional wording to clarify sentences, including the Examples used to illustrate adherences	25.11.2019

v2	Page 5-6: Added definition of per-protocol population used for non-inferiority testing of primary endpoint	25.11.2019
v2	Mikael Sunnaker has left CTU Bern, deleted	25.11.2019
v2	Page 22-23, 32-35: added reasonable adherence definition in concordance with contemporary trials published in the same field	25.11.2019
v2	Page 23: Rivaroxaban dosage recommendations adapted to latest guidelines	25.11.2019
v2	Page 28-30: added planned substudies	25.11.2019
v3	Appendix III: SARS-CoV-2	05.06.2020

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Contents

1. Introduction

1.1. Background and rationale

High bleeding risk population represents a significant proportion of coronary artery disease (CAD) patients undergoing coronary stent implantation. Decisions regarding the duration of dual antiplatelet therapy (DAPT) after stent implantation are difficult, especially after implantation of newer generation drug eluting stents (DES) due to conflicting results from recent trials.

The current ESC guidelines on DAPT indicate that in patients at high bleeding risk (HBR), shorter DAPT duration (<6 months for stable coronary artery disease patients or <12 months for acute coronary artery disease patients) should or might be considered after DES implantation (Class of recommendation: IIa/IIb). Similarly, the more recent American guidelines on DAPT duration, stated that in patients treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 or 6 months may be reasonable (Class of recommendation IIb). Both the European and American guidelines acknowledge that limited data is currently available to sustain this practice and call for dedicated DAPT studies in HBR patients.

Therefore, further randomized trials are needed to appraise the optimal DAPT duration in HBR patients treated with contemporary DES.

1.2. Objectives

The objective is to compare, within current guidelines (GL) and instructions for use (IFU), an abbreviated versus a prolonged DAPT duration after bioresorbable polymer coated Ultimaster (TANSEI) sirolimus-eluting stent implantation in patients presenting HBR features.

The study was designed to test the following hypotheses:

1) Abbreviated DAPT (one month) is non-inferior to a prolonged DAPT regimen in terms of net adverse clinical events (NACE)
2) Abbreviated DAPT (one month) is non-inferior to a prolonged DAPT regimen in terms of major adverse cardio or cerebrovascular event (MACCE)
3) Abbreviated DAPT (one month) is superior to a prolonged DAPT regimen in terms of major or non-major clinical relevant bleeding (MCB)

These hypotheses are tested in a hierarchical order, in order to preserve type I error rate, meaning that if the first test fails the study will be interpreted as not supportive of the abbreviated DAPT over prolonged DAPT, and subsequently the second and third tests result will be presented as exploratory. Likewise, if the first test passes and the second test fails, the third test result will be presented as exploratory.

If the NACE and MACE are claimed as non-inferior according to the margins and procedures described below, than both endpoints will also be tested for superiority using Hochberg-Benjamini approach to evaluate the two superiority p-values.

Per-protocol analyses (i.e. restricting the analyses to the per-protocol population) will be the primary analyses for non-inferiority testing (which will be also corroborated by non-inferiority testing the FAS/ITT dataset) whereas all patients in the FAS dataset will be considered for all primary and secondary superiority analyses. A per protocol analysis will be also performed for the superiority testing of abbreviated DAPT over prolonged DAPT on MCB in order to

complement the ITT approach on the same endpoint (Please see section 3.5.2 for the definition of the per protocol population).

2. Study methods

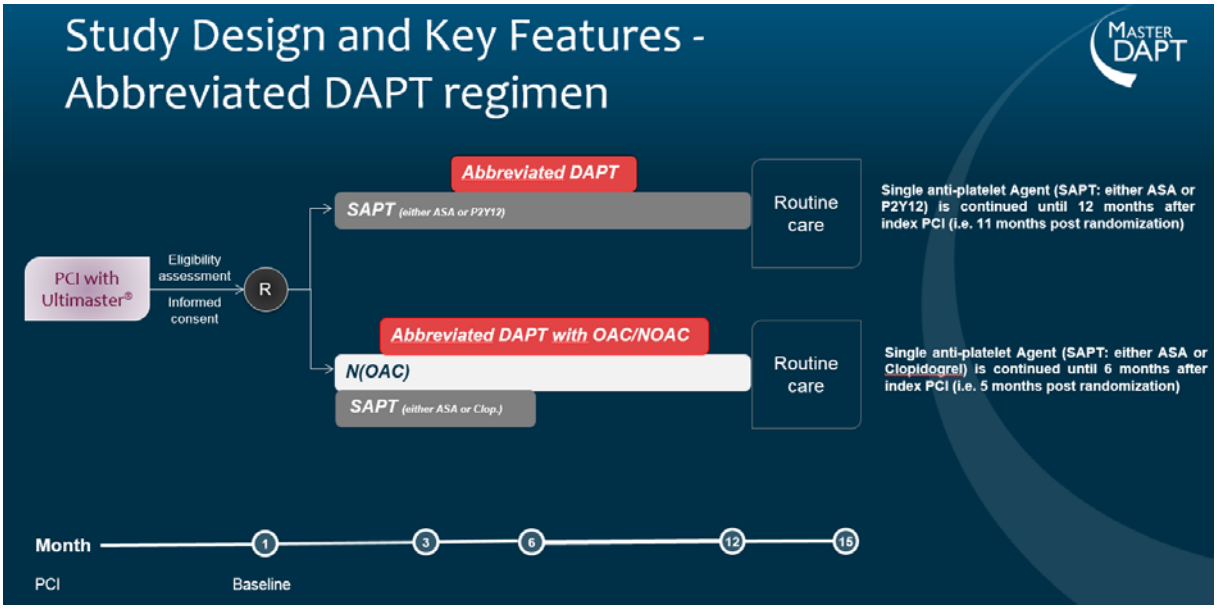
2.1. Trial design

An Investigator-initiated, multi-center, randomized clinical trial in HBR patients after PCI with Ultimaster (TANSEI) bioresorbable polymer coated sirolimus-eluting stent implantation. Open-label non-inferiority (in NACE and MACCE) and superiority (in MCB) study, parallel group design.

Patients, study personnel, monitors and central data monitors are not blinded to the randomized regimen the patient receives. The clinical event adjudication committee (CEAC) is blinded to the randomized regimen the patient receives.

2.1.1. Abbreviated DAPT regimen

The experimental, so called **Abbreviated DAPT regimen** is illustrated in this figure:

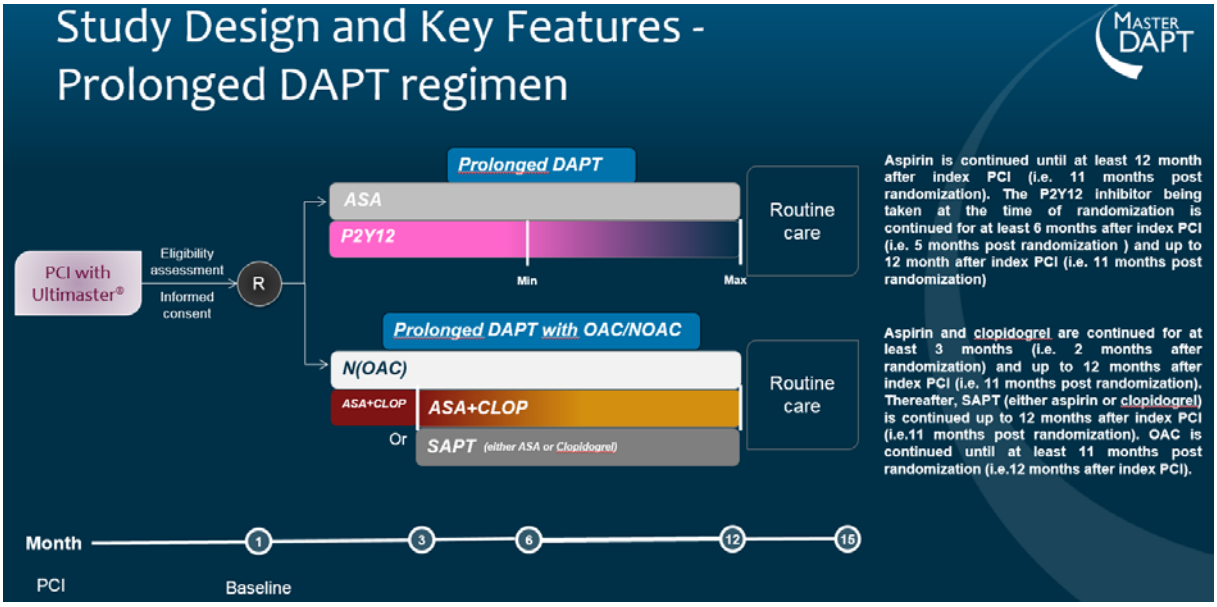


R = randomization at M1 visit, which is conducted 30 to 44 days after the index PCI (last PCI with Ulitmaster stent).

Note that patients receive DAPT up to 1 month (M1) and then continue with single antiplatelet therapy (SAPT); for patients without indication to (N)OAC, SAPT will be maintained for another 11 months (up to M12 visit); for patients with indication for (novel) oral anticoagulation (N)OAC (vitamin K antagonist OAC or novel anticoagulation NOAC) SAPT will be maintained for another 5 months (up to M6 visit).

2.1.2. Prolonged DAPT regimen

The control, so called **Prolonged DAPT regimen** is illustrated in this figure:



 = randomization at M1 visit, which is conducted 30 to 44 days after the index PCI (last PCI with Ultimaster stent).

Note that patients receive DAPT up to M1 and then continue with DAPT post-randomization as follows: for patients without indication to (N)OAC, DAPT must be continued for at least 5 months (up to M6 visit), and up to 11 months post-randomization (at discretion of the treating physician). For patients on (N)OAC, DAPT must be continued for at least 2 months, and up to 11 months post-randomization (at discretion of the treating physician). This flexibility has been implemented to be able to accommodate in the control group the variable DAPT durations observed across studies and registries, especially among those with indication to (N)OAC as well as for allowing clinicians in the control group to accommodate the duration on DAPT based on ischemic risk according to their experience and practice. Before randomization, clinicians are asked to pre-specify the anticipated DAPT duration they would select, had the patient been randomized to prolonged DAPT.

2.2. Randomization

Randomization is performed at the one-month randomization visit, scheduled between 30 and 44 days post index PCI. Patients can be randomized only if all inclusion criteria are met and if no exclusion criteria apply. Patient can be only randomized in the presence of written informed consent.

The randomization procedure is programmed into the eCRF. After confirmation of selection criteria and presence of informed consent, the investigator triggers the randomization procedure, after which randomization to either abbreviated DAPT or prolonged DAPT is divulged. The randomization is stratified per site, by a history of acute myocardial infarction (within 12 months prior to the index procedure) and use of OAC.

If the subject is randomized to abbreviated DAPT, the Investigator takes the necessary measures so that the abbreviated DAPT regimen is implemented without any undue delay. If the subject is randomized to maintain the DAPT regimen, the existing DAPT regimen is continued.

2.3. Sample size

The study includes 2 x 2150 (i.e. 4,300) patients. Sample size calculations have been made for a formal sample size of 2 x 2040 evaluable patients. This allows for attrition rate of 5%.

The assumed event rates under prolonged DAPT are 12% for NACE, 8% for MACCE and 6.5% for MCB. All tests are carried out with a one-side type I error rate of 0.025.

With this sample size, the study has:

- >90% power to establish non-inferiority in NACE with a non-inferiority margin of 3.6%
- >80% power to establish non-inferiority in MACCE with a non-inferiority margin of 2.4%
- >90% power to establish superiority in MCB if abbreviated DAPT reduces the MCB rate from 6.5% to 4.2%, which corresponds to a 35% relative risk reduction.

Abbreviated DAPT is the experimental regimen and Prolonged DAPT is the reference regimen.

2.4. Framework and outcomes

The first test presented is the non-inferiority test of NACE comparing Abbreviated DAPT vs Prolonged DAPT regimen, with a non-inferiority margin of 3.6%.
If the first test fails, the main trial result will be interpreted accordingly, and the second and third tests will be interpreted in light of the finding of failure of the first test.

The second test presented is the non-inferiority test of MACCE comparing Abbreviated DAPT regimen vs Prolonged DAPT regimen, with a non-inferiority margin of 2.4%. If the second test fails, the third test will be interpreted in light of the finding of failure of the second test.

The third test presented is superiority in MCB comparing Abbreviated DAPT regimen vs Prolonged DAPT regimen.

2.5. Statistical interim analyses and stopping guidance

No interim analyses are planned and stopping guidance is provided in the Data Monitoring Committee documentation.

2.6. Timing of final analysis

Final analysis of all primary endpoints and secondary endpoints will be conducted after receiving the CEAC confirmed events (external database export in SAS format provided by Cardialysis – Rotterdam).

Events which are not confirmed by the CEAC are not reported in the publication. A merging with the investigator reported events will be conducted to check whether all events have been assessed by the CEAC (confirmed plus not confirmed). Investigator reported events are adjudicated by the CEAC according to the CEAC charter. Other SAEs related to the DAPT regimen, which are not primary or secondary outcomes, will be reported separately on request only.

2.7. Timing of outcome assessments

All CEAC confirmed adjudicated events occurring between randomization at M1 visit up to and including 335 days post-randomization will be reported.

The first event of each type per patient only will be reported, except if stated otherwise for specific sub-studies or sub-analyses where the occurrence of multiple events will be accounted for (e.g. if the patient xxxx-yy-zz-nnnn had two BARC 3a bleeding between randomization and 335 days after randomization, only the first BARC3a bleeding will be reported).

2.8. Assessment of objectives

The main analyses evaluate the occurrence of the primary endpoints between randomization and 11 months thereafter. This covers the time frame in which the patients are allocated to the experimental or control treatment regimens.

The analyses of primary and secondary endpoints between 11 months and 15 months after randomization is not specifically covered in this statistical analysis plan. This covers the period when the patients are no longer on the randomized study regimen, and accordingly take medications according to routine care.

All event analyses are based on the Clinical Event Committee CEAC (external database export in SAS format provided by Cardialysis – Rotterdam) adjudicated events.
Investigators are instructed to interview each patient carefully at each study visit to determine if serious adverse event may have occurred. When endpoint-related suspected events (including death, myocardial infarction, stent thrombosis, stroke, and bleeding events [BARC 2, 3 or 5]) occur, they are entered into the eCRF as soon as possible after the study staff have become aware of those, including their judgement.

The above events are adjudicated by the CEAC using anonymised source documents, and adjudicated events only will be used for all statistical analyses. For the primary and second objectives, adjudicated events occurring beyond 11 months after randomization will be censored. Adjudicated events occurring up to and including 335 days after randomization will be reported. Adjudicated events reported between 11 months (336 days) and 15 months (up to and including 365+90=455 days) will be used for secondary analyses assessing the outcomes of switching from study regimens to routine care (e.g. DAPT or SAPT discontinuation in patients without or with OAC indication, respectively, allocated to the control group).

There will be a substudy related to the systemic embolism event rate in patients with concomitant OAC indication. Each event related to systemic embolism reported in the eCRF will be adjudicated by the CEAC.

2.9. Changes of the primary objective during the conduct of the study

No changes in the primary and secondary objectives during the conduct of the study are expected to occur.

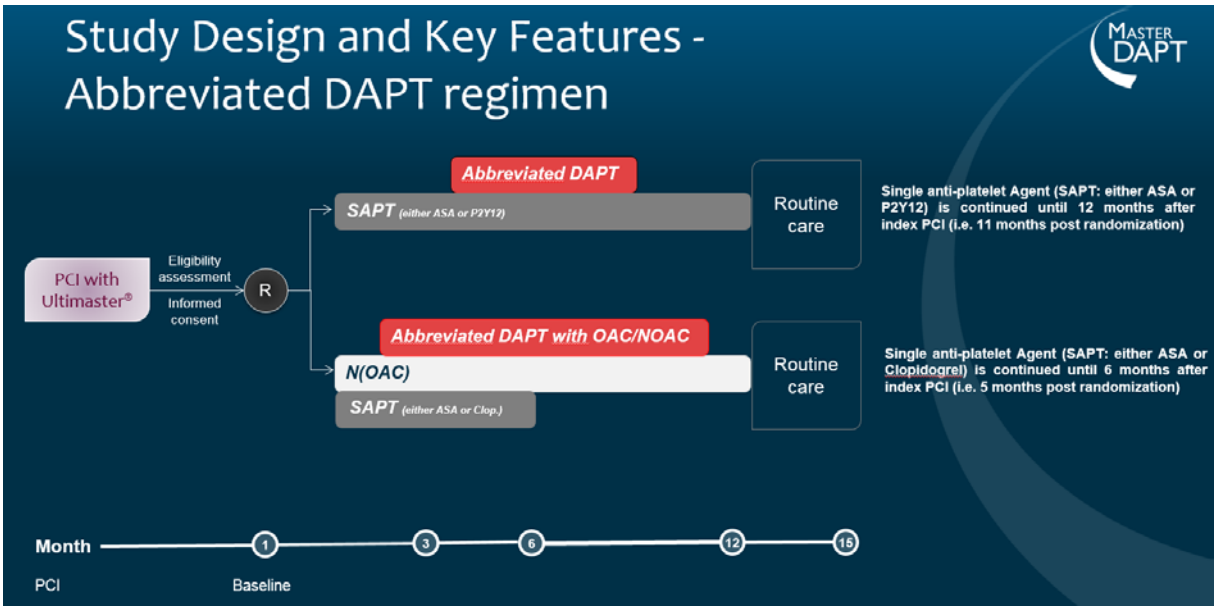
3. Statistical principles

3.1. Confidence intervals and p-values

Ninety-five percent confidence intervals will be reported throughout. Level of statistical significance, two-sided Type I, is set at 5% throughout. The non-inferiority tests are calculated using the confidence intervals of the risk difference Abbreviated DAPT vs Prolonged DAPT with a one-side type I error rate of 2.5%, which is equivalent to a two-sided type I error rate of 5%.

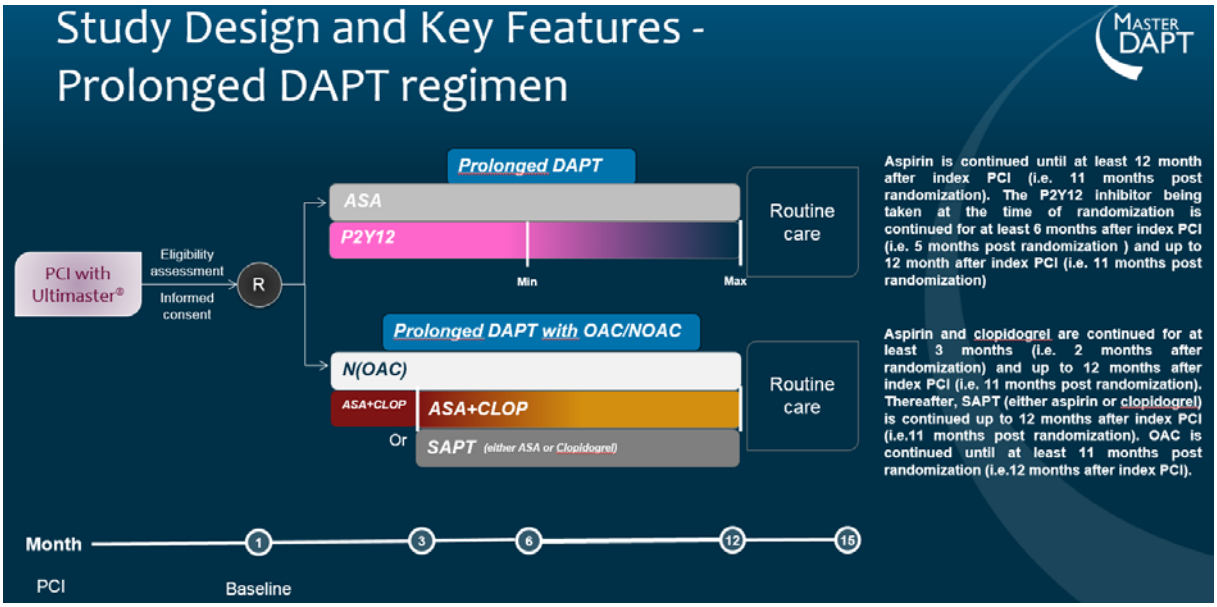
3.2. Evaluation of regimen adherence

The following figure highlights the protocol mandated treatment regimens with regards to the **Abbreviated DAPT** arm.



In particular, patients without OAC indication at the time of randomization should receive a single antiplatelet medication (aspirin, clopidogrel, prasugrel or ticagrelor) from randomization onwards until 11 months post-randomization. Patients with OAC should receive a single antiplatelet medication (aspirin or clopidogrel) up to 5 months post-randomization.

The following figure highlights the protocol mandated treatment regimens with regards to the **Prolonged DAPT** arm.



Patients **without OAC** should receive two concomitant antiplatelet medications consisting of aspirin with either clopidogrel, prasugrel or ticagrelor from randomization onwards until at least **5 months** post-randomization. Afterwards it is allowed to stop the P2Y12 inhibitor, whereas aspirin needs to be continued until 11 months post-randomization (it is also allowed to stop the P2Y12 inhibitor at any time from 5 to 11 months post-randomization).

Patients **with OAC** should receive two antiplatelet medications (aspirin with clopidogrel) from randomization onwards until at least **2 months** post-randomization. Afterwards it is allowed to stop clopidogrel, whereas aspirin needs to be continued until 11 months post-randomization;,it is also allowed to stop aspirin and continue clopidogrel until 11 months post-randomization. Hence, it is allowed to stop one of the antiplatelets at any time between 2 months and 11 months of randomization, as long as the other antiplatelet is continued.

3.3. Adherence to study regimen

3.3.1. Assessment of regimens

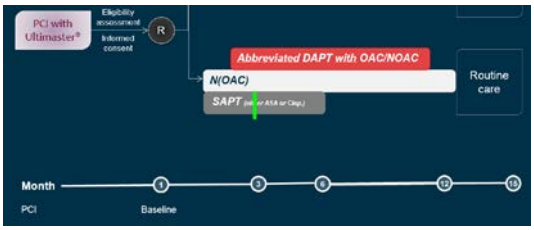
There are scheduled follow-up visits at 90, 180, 365, and 450 days after the index procedure; which is 60, 150, 335 and 425 days after randomization, respectively. At each follow-up the investigator collects information about the regimen inquiring actual and prior use of study medication(s)). Sites are then asked to update the adherence form for each antiplatelet and OAC medication accordingly by indicating the exact start date (first dose taken) and stop date (last dose taken), including clarifying the decision maker (i.e. who decided the start or stop) and why each study medication was started or stopped.

These start-stop sequences are similarly collected for every change in dosing, with each start date (first dose taken) and stop date (last dose taken) of the new drug regimen, including who decided the start or stop with dosage, why the medication dosage was terminated (stopped) or changed to new dosage (started). Note that vitamin K-antagonists do not have a dosage change but INR values are to be collected.

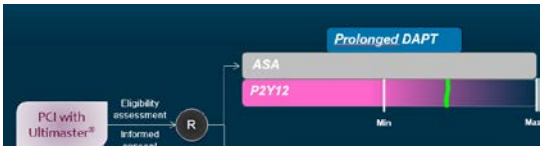
Adherence forms are built accordingly with repetitive start-stop sequences of each antiplatelet drug and each type of OAC.

3.3.2. Adherence to SAPT and DAPT regimen when antiplatelet medications are exchanged

It is allowed to switch antiplatelet(s) within a SAPT or a DAPT regimen: the patient is considered adherent if the switching was seamless and did not lead to a change from SAPT to DAPT, did not lead to a change from SAPT to no APT, did not lead to a change from DAPT to SAPT and did not lead to a change from DAPT to no APT; i.e. when the patient remained on SAPT or DAPT according to the regimen that should have been prescribed according to randomized arm and timing from randomization (Examples 1 and 2).



Example 1. Patient changed from SAPT consisting of aspirin to SAPT consisting of clopidogrel at 3 months and as such remains consistently on SAPT according to the randomized arm (green line).



Example 2. Patient changed from DAPT consisting of aspirin + clopidogrel to DAPT consisting of aspirin + ticagrelor at 9 months and remains on DAPT in keeping with the prolonged regimen arm (green line). The patient could also continue with aspirin only, because a SAPT is allowed in the prolonged DAPT arm from 5 months onwards from randomization (in patients without concomitant OAC indication).

It is allowed to stop APT for up to 2 days during APT switch (i.e. fulfilling NARC type 2 non adherence pattern, which is based on the half-life of the pharmacological effects of the P2Y12 inhibitors involved, Table 1).

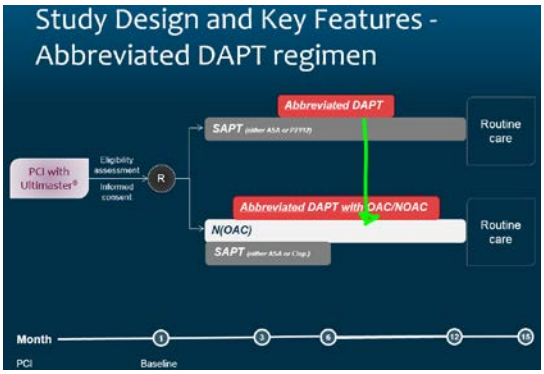
Table 1. Half-life of the pharmacological effects of the APT medications

	Abbreviated DAPT regimen		**Prolonged DAPT regimen**	
Antiplatelet	Not on OAC	On OAC	Not on OAC	OAC
Aspirin	**2 days**	**2 days**	**2 days**	**2 days**
Clopidogrel	**2 days**	**2 days**	**2 days**	**2 days**
Prasugrel	**2 days**	**2 days**	**2 days**	**2 days**
Ticagrelor	**2 days**	**2 days**	**2 days**	**2 days**

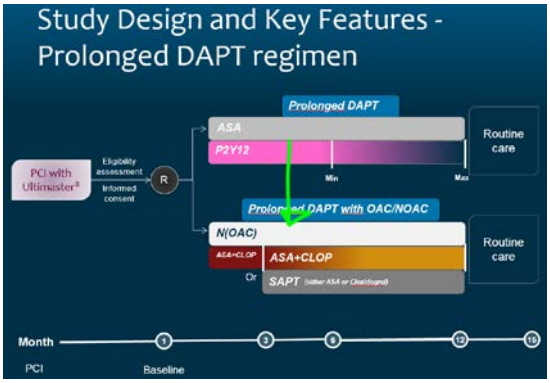
3.3.3. Adherence to SAPT and DAPT regimen in case of changes of OAC

It is allowed to replace one type of OAC with another type of OAC (e.g. Warfarin to Rivaroxaban), the patient should remain on their allocated regimen (i.e. abbreviated versus prolonged) during this switch.

Patients who receive OAC due to a new post-randomization OAC indication should continue according to the protocol-mandated OAC-stratum APT regimen (Examples 3 and 4) and must remain accordingly adherent:



Example 3. A patient who was previously randomized to abbreviated DAPT, receives OAC at 7 months because of a new indication (e.g. new onset atrial fibrillation), so he/she switches accordingly (green arrow) and must immediately stop SAPT treatment. If the same patient develops a new OAC indication 45 days after randomization, SAPT needs to be implemented in conjunction with OAC until 5 months after randomization and then dropped.

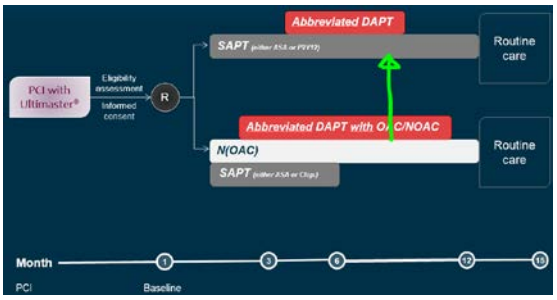


Example 4. A patient who was previously randomized to prolonged DAPT receives OAC at 4 months because of a new indication (e.g. new onset atrial fibrillation), so he/she switches accordingly (green arrow) and can immediately stop DAPT treatment and continue with one APT only. Note that 2 months after randomization DAPT can be stopped or further continued at discretion of the investigator. Therefore, If the patient was on aspirin + ticagrelor, then ticagrelor should be stopped and replaced by clopidogrel if a provision is made to continue DAPT, otherwise he/she can continue with aspirin only or clopidogrel only (SAPT). Finally, if the investigator decides not to prolong DAPT any further, then ticagrelor could also be immediately stopped and the patient continue with ASA and OAC until 11 months after randomization.

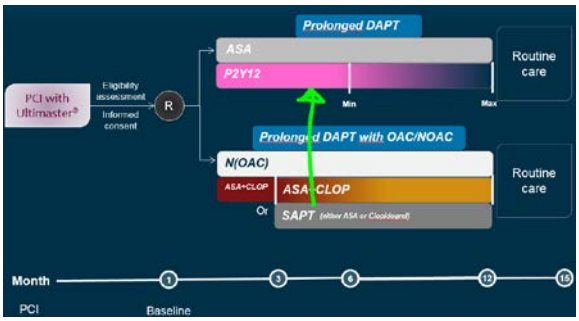
In the case a patient on OAC after randomization is taking one of the newer P2Y12 inhibitors (ticagrelor or prasugrel), following the right duration of the regimen, we will consider this patient adherent.

It is allowed to have a 14-day time period to implement the correct switching after an OAC indication has arisen during the course of the study.

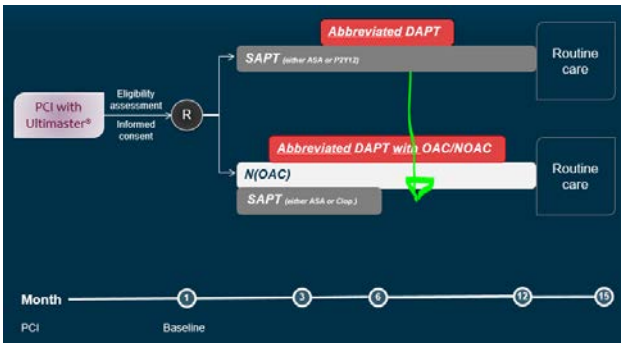
Patients with OAC indication who have been randomized into the study are allowed to stop OAC if no further OAC treatment is deemed indicated, and patient should restart SAPT as necessary (Example 5) or restart DAPT as necessary (Example 6, in both examples in case OAC stopped after randomization):



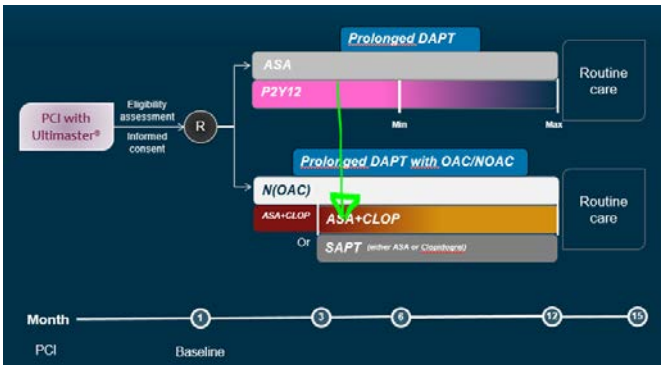
Example 5. A patient who was previously randomized to abbreviated DAPT, stops OAC at 8 months because this treatment is no longer indicated against the anticipated treatment duration at the time of inclusion, so should restart aspirin (SAPT) or clopidogrel (SAPT) or ticagrelor (SAPT) or prasugrel (SAPT).



Example 6. A patient who was previously randomized to prolonged DAPT, stops OAC at 4 months while on SAPT consisting of aspirin, so he/she should change to aspirin + one of the oral P2Y12 inhibitor (DAPT) and continued for at least 5 months after randomization or longer at discretion of the investigator.



Example 7. A patient who was previously randomized to abbreviated DAPT, starts on OAC at 8 months because of a new indication (e.g. new onset atrial fibrillation), so he/she should stop SAPT. If the patient starts on OAC before 5 months after randomization, SAPT with either ASA or clopidogrel should be continued in association to OAC until the completion of 5 months after randomization.

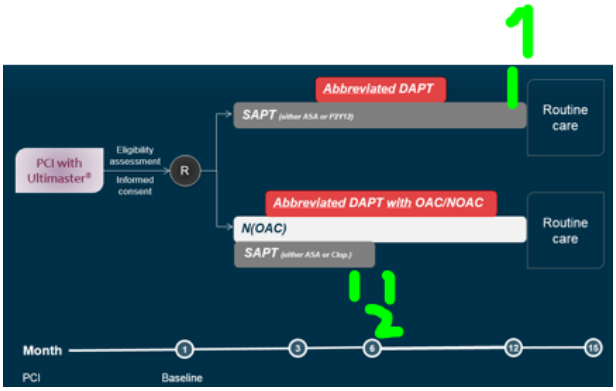


Example 8. A patient, who was previously randomized to prolonged DAPT and was taking either ASA+ticagrelor or ASA+prasugrel, starts with OAC at 4 months because of a new indication arose (e.g. new onset atrial fibrillation) should change from ticagrelor or prasugrel to clopidogrel if the investigator wants to continue SAPT with a P2Y12 inhibitor or drop ticagrelor or prasugrel and continue SAPT with ASA. He/she is also to switch to SAPT (Aspirin or Clopidogrel). Finally, at discretion of the investigator, a DAPT regimen, in the form of ASA plus clopidogrel, can be also implemented in conjunction with OAC up to 11 months after randomization. Despite the protocol recommendations concerning the use of ASA alone or clopidogrel alone or their combination in association to OAC, If a patient on OAC after randomization is taking one of the newer P2Y12 inhibitors (ticagrelor or prasugrel), and follows the right duration of the regimen, this patient will still be considered protocol adherent.

It is allowed to have a 14 days time period to make the correct switch after the OAC was newly added or removed.

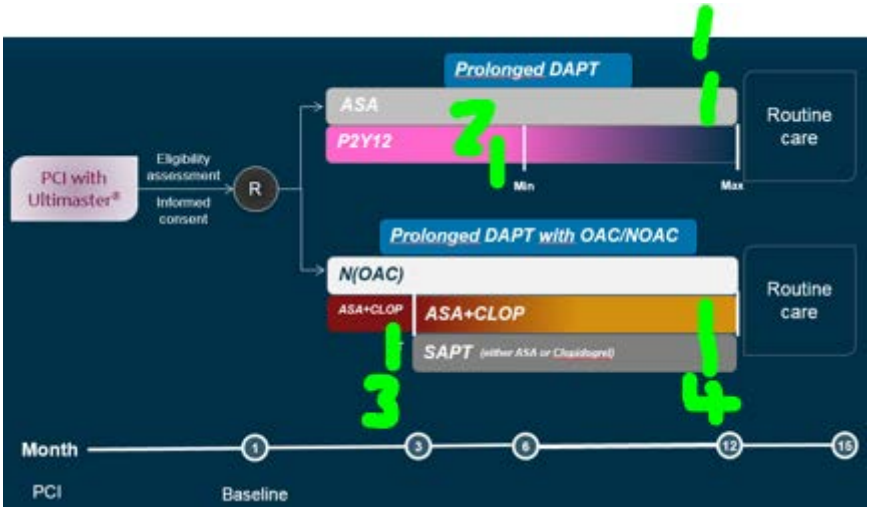
3.3.4. Adherence to SAPT and DAPT regimen in case of too early or too late stops

Patients who are randomized to **Abbreviated DAPT** regimen are permitted to implement the allocated regimen with an allowance of 14 days (i.e. at M6 plus/minus 14 days = 136 to 164 days post-randomization; e.g. at M12 335 days minus 14 days = 321 days post-randomization; see Example 9).



Example 9. Case 1: patient can stop 321 days post-randomization with SAPT or later (as afterwards there will be routine care with no APT, SAPT or DAPT as chosen by the investigator). Case 2. patient must stop SAPT within window of 136 to 164 days post-randomization (150 days ± 14 days).

Patients who are randomized to **Prolonged DAPT** regimen are permitted to prematurely stop one medication as long as this happens within a 14 day window from the due date (e.g. at M3 76 days or later post-randomization; e.g. at M6 136 days or later post-randomization; at M12 321 days or later post-randomization, see Example 10).



Example 10. Case 1: patient can stop 321 days post-randomization with aspirin or later, irrespective of P2Y12 intake (as afterwards there will be routine care with no APT, SAPT or DAPT as chosen by the investigator). Case 2. patient can stop P2Y12 inhibitor 136 days or later post-randomization (note that the patient would only be non-adherent if also aspirin would be stopped). Case 3: patient can stop 76 days post-randomization with aspirin or clopidogrel (note that the patient would only be non-adherent if also the other APT would be stopped). Case 4. patient can stop all APTs at 321 days or later post-randomization.

3.3.5. Adherence to SAPT and DAPT regimen after events

If any of the following events occur, in the opinion of the investigator (i.e. IR-event), the following rules for the randomized treatment regimens apply (+ days denotes how many days of a regimen might be added after the event, each addition has again a window of ±14 days as applicable; ≥ denotes minimum additional days allowed or more, Table 2).

Table 2, APT regimen(s) allowed after each type of event, with routine care meaning according to the discretion of the local investigator.

	Abbreviated DAPT regimen		**Prolonged DAPT regimen**	
Event number and Type according to the Investigator	Not on OAC	On OAC	Not on OAC	OAC
A. Repeat PCI	**+30 days DAPT**	**+30 days DAPT**	**≥180 days DAPT**	**≥90 days DAPT**
B. Stent thrombosis	**routine care**	**routine care**	**routine care**	**routine care**
C. Myocardial infarction	**routine care**	**routine care**	**routine care**	**routine care**
D. First occurrence of a BARC type 2 bleeding	**routine care** until event resolved***1**	**routine care** until event resolved***1**	**routine care** until event resolved***1**	**routine care** until event resolved***1**
From the 2nd BARC 2	**routine care**	**routine care**	**routine care**	**routine care**
E. BARC 3 to 5 bleeding	**routine care**	**routine care**	**routine care**	**routine care**
F. Stroke	**routine care**	**routine care**	**routine care**	**routine care**
G. Other contraindications for the randomized DAPT regimen				
H. Temporary discontinuation*2	**+7 days routine care*2**	**+7 days routine care*2**	**+7 days routine care*2**	**+7 days routine care*2**
I. Dyspnea on ticagrelor	**See 3.3.5 I**	**See 3.3.5 I**	**See 3.3.5 I**	**See 3.3.5 I**

bold changes will be re-coded as the patient being adherent (APT change is allowed), the *italic* changes do not affect the adherence assessment of the indicated regimen (so they are relevant for patient safety but the adherence assessment is not affected as already allowed by randomized regimen), empty cells means that the event does not affect the regimen (e.g. P2Y12 switch or no clear and derivable recommendations).

*1: only discontinuations due to **surgery or non-revascularisation intervention requiring (temporary) stop or dosage change** are counted as such, in most cases the patient will receive no APT or SAPT during this temporary stop. If the patient does not restart the regimen after 7 days, the 0 to 7 days are coded as adherent, but day 8 and later are coded as non-adherent.

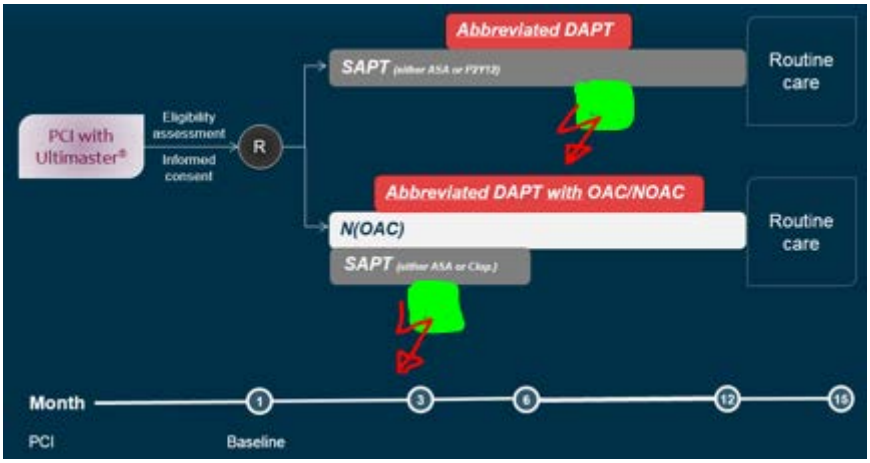
*2: Event resolved: date the site reports that the bleeding event was resolved. If the patient has another BARC 2 bleeding, it is allowed to do routine care after this second BARC2 event (note that this is different from the protocol, which says: "the randomized treatment regimen is adhered to as much as possible", regardless of how many BARC 2 bleedings occurred).

See for detailed descriptions per event the next pages (event **A** to **I**).

A. Elective repeat PCI

Antiplatelet treatment should be prescribed as local practice:

- **Abbreviated DAPT**: If not on OAC, a P2Y12 or aspirin is added for one month to the pre-existing SAPT (i.e. a DAPT regimen is re-instituted for 1 month). If on OAC, DAPT with aspirin and clopidogrel is re-instituted for 1 month and thereafter clopidogrel or aspirin is continued for 5 months. See Example 11.



Example 11. In both cases the patient is on one month of DAPT after the repeat PCI (red flash), allowed is 16 to 44 days of DAPT (±14 days window), afterwards on SAPT.

- **Prolonged DAPT**: If not on OAC, treatment with aspirin and a P2Y12 inhibitor is continued or started for at least 6 months (i.e. a DAPT regimen is re-instituted for 6 months). If on OAC, aspirin and clopidogrel are re-instituted for at least 3 months. There is no Example, as Prolonged DAPT allows for DAPT from randomization to 11 months by default, and restart of DAPT after SAPT does not affect adherence to this regimen.

B. Definite stent thrombosis

Further antithrombotic treatment is as per current guidelines and institutional recommendations.

C. Non-fatal myocardial infarction and no definite stent thrombosis

Antiplatelet treatment should be prescribed as per local practice, we recommend:

- **Abbreviated DAPT**: If not on OAC, a P2Y12 or aspirin is added for one month to the pre-existing SAPT (i.e. a DAPT regimen is re-instituted for 1 month). If on OAC, aspirin and clopidogrel are re-instituted for 1 month and thereafter clopidogrel or aspirin is continued for 5 months.
- **Prolonged DAPT**: If not on OAC, treatment with a P2Y12 inhibitor is continued or started for at least 6 months (i.e. a DAPT regimen is re-instituted for 6 months). If on OAC, aspirin and clopidogrel are re-instituted for at least 3 months.

D. BARC 2 bleeding

Routine care is allowed until the site reports that the BARC2 bleeding has been resolved. In case the patient experiences another, second, BARC2 bleeding: routine care is allowed afterwards until the end of the regimen.

E. BARC 3 to 5 bleeding

The management of antithrombotic treatment including discontinuation or down titration of previously prescribed agents or switching to a different regimen is at the discretion of the treating physician, meaning routine care is allowed.

F. Stroke

The management of antithrombotic treatment including discontinuation or down titration of previously prescribed agents or switching to a different regimen is at the discretion of the treating physician, meaning routine care.

G. Other contraindications for the randomized DAPT regimen

No changes in APT use are allowed in the context of the adherence and statistical analyses as defined in this statistical analysis plan. Note that physicians are allowed to do further treatment at their discretion.

H. Temporary discontinuation (e.g. Surgery, tooth extraction etc.)

The randomized trial regimen is resumed as soon as the indication of temporary discontinuation is resolved. The item will be derived from **surgery or non-revascularisation intervention requiring (temporary) stop or dosage change** (with stop date in Adherence form APT) and the next re-start of APT (next start date in the same Adherence form APT), the period between this stop and re-start will be considered as the patient being adherent **if lasting up to 7 days**. The restart of the regimen should be within these 7 days, if not the 8th day and later is regarded as the patient being non-adherent - until the regimen is correctly restarted.

I. Dyspnea on ticagrelor

Ticagrelor is replaced preferably with prasugrel, or clopidogrel if prasugrel is not an option. When ticagrelor is switched to clopidogrel, loading dose of clopidogrel (3/600mg) is given. When ticagrelor is switched to prasugrel, the administration of prasugrel loading dose is at discretion of the physician. See chapter 3.3.2.

3.3.6. Temporary and permanent changes

Two definitions of adherence to protocol-mandated anti-platelet therapy are pre-specified, including a reasonable adherence pattern, which constitutes the primary adherence definition and a perfect adherence pattern, which is based on the Non Academic research consortium (NARC) consensus paper and constitutes a secondary adherence definition.
We consider a patient reasonably adherent (**reasonable adherence pattern**) to the regimen when the patient is exposed the allocated anti-platelet therapy (i.e. DAPT, SAPT or no APT) (or allowed routine care or allowed altered therapy as specified above in the sections 3.3.1 to 3.3.6) for at least 80% of the time from randomization to 11 months follow-up or until last known medication status or until death, whatever comes first (i.e. if NARC 2 or NARC 3 categories will be met for less than 80% of the time from randomization to the 11 month visit or until last known medication status or until death, whatever comes first). Exposure will be analyzed taking into account the half-life of anti-platelet agents and not simply the amount of skipped or taken pills. After 2 consecutive skipped intakes of aspirin, clopidogrel and prasugrel or after 4 consecutive skipped intakes of ticagrelor, the patient will be considered not exposed to the pharmacological effect of the corresponding APT. Similarly, patients taking a DAPT regimen instead of SAPT or no APT or a SAPT instead of no APT or DAPT will be considered non-adherent starting from the first day of intake of the non protocol mandated APT regimen until 2 days after the wrong APT regimen has been discontinued.
We consider a patient completely adherent (**perfect adherence pattern**) to the regimen when the patient is taking the allocated antiplatelet therapy (or allowed routine care or allowed altered therapy as specified above in the sections 3.3.1 to 3.3.6), excluding the following three scenarios:

1. When a patient is off pharmacological effect of the drug due to a temporary discontinuation. In this case, the interruption length allowed is a maximum of 2 days:

	Allowed days of interruption	Number of pills per day
Aspirin	2	1
Clopidogrel	2	1
Prasugrel	2	1
Ticagrelor	2	2

2. When a patient had permanent discontinuation 3 days or longer before the end of study visit.
3. When a patient adds APT to no APT (so is now wrongly on SAPT), when a patient adds APT to SAPT (so is now wrongly on DAPT), when this is not allowed by routine care and also not allowed as altered therapy, as defined above in the sections 3.3.1 to 3.3.6.

3.3.7. Adherence to NOAC dosages

A descriptive table of NOAC dosages use per randomized arm and per visit will be produced as Supplement material. Over- and under-dosing includes off-label too high or too low dosages of NOACs (e.g. low dosage not explained by the dose reduction criteria for each of the prescribed NOAC agent). The protocol mandated NOAC regimens are as follows:

- Apixaban 5 mg b.i.d or Apixaban 2.5 mg b.i.d. if at least two of the following: Age ≥ 80 years, body weight ≤ 60 kg or serum creatinine level ≥ 1.5 mg/dL (133 µmol/L);
- Dabigatran 150 mg b.i.d. Dose reduction to Dabigatran 110 mg b.i.d. is recommended if Age ≥ 80 years or if the patient receives concomitant Verapamil. Dose reduction to Dabigatran 110 mg b.i.d. may be considered if the Age is between

75-80 years, CrCL 30-50 mL/min, for patients with gastritis, esophagitis or gastroesophageal reflux, or other patients at increased risk of bleeding.

- Edoxaban 60 mg q.d. or Edoxaban 30 mg q.d. if any of the following criteria apply: CrCl of 15–50 mL/min, or body weight ≤ 60 kg, or concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole.
- Rivaroxaban 20 mg q.d or Rivaroxaban 15 mg q.d. if CrCl 30–49 mL/min. However, the use of Rivaroxaban 15 mg q.d. or Rivaroxaban 10 mg if CrCl 30–49 mL/min is not regarded as a protocol violation.

3.3.8. Adherence categories

We divide the patients in 3 groups based on adherence; the first group will be NARC type 2/3 patients (type 2 is temporary discontinuation, type 3 is permanent discontinuation, these two NARC levels are non-adherent patients according to the perfect adherence pattern but may still qualify as adherent patients according to the primary reasonable adherence definition taking into account the duration of NARC 2 and/or 3 patterns). The second group consists of permanently adherent patients (referred to as “type 0” NARC patients and includes routine care, if allowed as described above). The third group consists of patients with ≤2 days interruptions/over-dosing/under-dosing (referred to as type 1 NARC patients, during wash-out of the pharmacological effect). See for the NARC classification Valgimigli et al. 2018.

Based on the above-described metrics, patients will be classified as perfectly adherent if not fulfilling NARC 2 or greater categories (i.e. including patients with NARC 0 or NARC 1). Patients will also be classified as reasonably adherent if NARC 2 or NARC 3 categories will be met for less than 80% of the time from randomization to the 11 month visit. We also pre-specify to explore adherence as continuous variable calculating the amount of time exposed or not exposed to the protocol mandated specific APT regimen (i.e. DAPT, SAPT or no APT) from randomization to end of study visit.

Adherence will be computed per patient and per day as follows:
1. Compute permanent stop first at time t (t is three days after last intake, i.e. allowing two days as window to account for the residual pharmacological effect of the discontinued treatment in keeping with section 3.3.6) at time t. All days at t and later the patient is coded as non-adherent, except if routine care or altered therapy is allowed as specified above in Chapters 3.3.1 to 3.3.6.
2. Compute for each day whether partially adherent (at day t not taken, at day t-2 to t+2 not always taken, but total period t-2 to t+2 includes a maximum of 5 days interruption). Take into consideration ±2 days windows etc. as specified above. Again a reminder that routine care or altered is allowed as specified above in Chapters 3.3.1 to 3.3.6.
3. Remaining days are then fully adherent days (if no other APTs are added not according to the regimen). And also here a reminder that this may include days that the patient is on routine care or altered therapy, if allowed as specified above in Chapters 3.3.1 to 3.3.6.

3.3.9. APT treatment categories

We acknowledge and are fully aware that lumping patients into type 2/3, type 0 or type 1 categories neglects the fact that we may cluster patients into the same group who may have completely different adherence patterns, e.g. patients with a shorter or longer time period of full adherence (type 0) followed by a permanent discontinuation will all be merged together under type 2.

Therefore, we will also assess for each patient the percentage of days he/she was receiving:
1. **treatment as per protocol**
Includes taking no APT, SAPT or DAPT according to Chapters 3.3.1 to 3.3.4, i.e. allows switches and changes within certain windows, but does not allow over-dosing, under-dosing nor non-regimen explainable additions or removals of APTs.
2. **over-treatment allowed**
Includes over-dosing, adding APTs to the treatment strategy, as allowed in the definitions of Chapters 3.3.1 to 3.3.6.
3. **over-treatment not-allowed**
Includes over-dosing, adding APTs to the treatment strategy, but each of them are not allowed according to the regimen as explained in Chapters 3.3.1 to 3.3.6.
4. **under-treatment allowed**
Includes under-dosing, removing APTs from the treatment strategy as allowed in the definitions of Chapters 3.3.1 to 3.3.6.
5. **under-treatment not allowed**
Includes under-dosing, removing APTs from the treatment strategy, but each of them are not allowed according to the regimen as explained in Chapters 3.3.1 to 3.3.6.

The percentages are calculated from day 0 (randomization) up to 335 days post-randomization (or last day of adherence assessment if <335 days); and these five percentages can be used for more detailed across patient assessments (either cross-sectional or cumulative over time)

3.3.10. OAC treatment categories

Over- and under-dosing includes off-label too high or too low dosages of NOACs as described in section 3.3.7.
For vitamin-K-antagonist patients will be classified as treatment as per protocol if they are within their pre-specified target therapy INR 65% of the time or more. Conversely, if they are within target therapy less than 65% of the time, they will be classified as not on treatment.

3.3.11. Treatment graphs

Cross sectional analysis of treatments

The cross-sectional assessment of treatments for the first 11 months after randomization calculates the proportion of the five treatment categories (Chapter 3.3.9) on a per patient per day basis, i.e. at day 0 (randomization), 1, 2, 3 … 335 days post-randomization, overall and per randomized regimen arm divided by OAC no or yes.

Cumulative analysis of treatments

The cumulative assessment of treatments for the first 11 months after randomization will be considered in addition to the cross-section adherence analysis. First the percentage of the time that each patient is in each of the five treatment categories is analyzed (Chapter 3.3.9), and the mean and CI over the population is then computed.

3.4. Exposure to APT study drugs within the regimens

3.4.1. Extent of APT exposure

All patients are on DAPT (Aspirin and Clopidogrel/Prasugrel/Ticagrelor) between index PCI and randomization (occurs 30-44 days after index PCI).

At 30 days to 44 days after the index PCI (M1), patients are randomized to either Abbreviated DAPT regimen or Prolonged DAPT regimen and the exposure to study drugs is as follows from M1 onwards:

Abbreviated DAPT (experimental arm):

- Not on OAC: DAPT is discontinued and a single P2Y12 inhibitor (Clopidogrel or Prasugrel or Ticagrelor) is continued until at least 11 months post randomization (i.e.12 months after index PCI).
- On OAC: DAPT is discontinued and either aspirin or clopidogrel is continued until 5 months post randomization (i.e. 6 months after index PCI). OAC or NOAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).

Prolonged DAPT (control arm):

- Not on OAC: Aspirin is continued until at least 11 months post randomization (i.e.12 months after index PCI). The P2Y12 inhibitor being taken at the time of randomization is continued for at least 5 months and up to 11 months post randomization (i.e.12 months after index PCI).
- On OAC: Aspirin and Clopidogrel are continued for at least 2 months (i.e. 3 months after index PCI) and up to 11 months post randomization (i.e. 12 months after index PCI). Thereafter, SAPT (either Aspirin or Clopidogrel) is continued up to 11 months post randomization (i.e.12 months after index PCI). OAC or NOAC is continued until at least 11 months post randomization (i.e.12 months after index PCI).

3.4.2. Duration of APT exposure

For at least 1 year (11 months after randomization), afterwards patients receive routine care and may continue with no APT, or change to SAPT or change to DAPT. See for details of which exposures are allowed for each regimen section 3.3.

3.4.3. Antiplatelet and OAC daily dosages

Study regimens are implemented by regular drug prescription. The investigators provide the necessary prescription to the study participants. The followings are recommended according to the current guidelines and local practice.

- Aspirin is prescribed in standard dose of at least 75 mg/day and up to 162 mg/day.
- Clopidogrel is prescribed in standard dose of 75 mg once daily.
- Prasugrel is prescribed in standard dose of 10mg/day or 5mg/ day in patients weighing less than 60 kg or who are over 75 years old. In regions where other standard dose exists (i.e. Japan), prasugrel dosage is adjusted according to the locally approved dose.
- Ticagrelor is prescribed in standard dose of 180 mg/day (90mg bid).
- Vitamin K antagonist is dosed to keep INR within guidelines.

- NOACs (rivaroxaban, edoxaban, dabigatran and apixaban) are given in locally approved doses.
- Switching from Vitamin K antagonist to NOACs or vice-versa is not allowed unless there are clinical and well documented reasons for doing so. Similarly, switching from NOACs to VKA during the course of the study is not allowed, unless dictated by a clinical and documented reason (e.g. change in renal function during the course of the investigation), which will be captured in the eCRF.
- Prescribed units of aspirin, clopidogrel, prasugrel, ticagrelor and OAC are recorded in the eCRF. Patients are queried on general drug adherence.

Analyses of dosages used by the patients and per medication type will be performed for sub-analyses but are not meant to be included in the primary study publications.

3.5. Definition of populations for analysis

All patients undergoing PCI with an Ultimaster (TANSEI) stent will be individually invited to participate in the MASTER-DAPT Trial, and can potentially be enrolled if they satisfy all inclusion and exclusion criteria.

3.5.1. Full analysis set (FAS)

Full analysis population (FAS) consists of all randomized subjects.

Subjects are analysed according to the group to which they were assigned by the randomization process, using the intention-to-treat principle (i.e. intention to implement the allocated regimen).

3.5.2. Per-protocol population (PP)

Per-protocol (PP) population consists of randomized patients who met the following criteria:

• No violation of inclusion/exclusion criteria (HBR) at the time of randomization

• Randomized protocol-mandated treatment was initiated within 14 days after randomization (on treatment within 14 days after randomization or allowed routine care or allowed altered therapy as specified above in the sections 3.3.1 to 3.3.6)

In particular, the following patients are excluded from the PP population

- Not at HBR
- Not treated with Ultimaster (TANSEI) stent
- Received other stents than Ultimaster (TANSEI) stents within 6 months of qualifying procedure.
- Received treatment for an in-stent restenosis or in-stent thrombosis

3.5.3. Non-randomized population

The non-randomised population consists of all patients with full written consent, where all the data up to and including the Randomization assessment will be collected inside the EDC (Demographics, History, HBR criteria, PCIs with Lesions and APT after PCI), but these patients were not randomized due to various reasons (i.e. death before M1, withdrew consent before randomization, lost to follow-up at M1, no longer eligible at M1), i.e. these patients cannot be used for the comparison Abbreviated DAPT regimen vs Prolonged DAPT regimen. It includes patients who were randomized mistakenly due to a clerical error, and these patients have been moved to the non-randomised population with a Note to File by CTU Central Data Monitoring and Management team, after received confirmation of the site and the local CRA.

3.5.4. Definitions of sub-group populations and sub-studies

Results of the subgroups may be presented in separate publications.

The following main subgroups are defined (the first two items are used to stratify the randomization):

Oral anticoagulation (Yes vs No)

History of acute MI within 12 months (Yes vs No)

Indication for PCI (ACS vs Stable CAD)

DAPT score (High ≥2 vs Low <2)

> See for DAPT score: Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al; DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016; 315(16): 1735-1749.

PRECISE DAPT score (0-24 vs ≥25)

Sex (Male vs Female)

Creatinine clearance (≥60 ml/min vs <60 ml/min)

Age (≥75 years vs <75 years)

Diabetes mellitus (Yes vs No)

Additional subgroups/dedicated analyses, which will not be reported in the main study results manuscript(s), are defined according to each of the **single** HBR criteria (if not outlined above), i.e.:

Recent (<12 months) or Post-PCI non-access site bleeding episode, which required medical attention Yes/No

Previous bleeding episode(s) which required hospitalization and the underlying cause is not been definitely treated Yes/No

Systemic conditions associated with increased bleeding risk Yes/No

Documented anaemia or transfusion within 4 weeks before randomization Yes/No

Need for chronic treatment with steroids or NSAIDs Yes/No

Diagnosed malignancy (other than skin) considered at high bleeding risk Yes/No

Stroke at any time, or TIA in the previous 6 months before first PCI Yes/No]

Additional sub-studies will focus on the following analyses:

Presence or absence of concomitant heart valve disease;

Geographic area and ethnicity

Fulfillment of at least one criterion of complex PCI as defined by Giustino et al JACC (2016);

Syntax score before the procedure

Residual Syntax score (both as per investigator reported Syntax score or by core-lab analysis if and when available)

Impact of residual lumen stenosis narrowing or post-treatment minimal lumen diameter on outcomes and treatment effect

Type of DAPT before randomization in terms of aspirin+clopidogrel versus aspirin+ticagrelor or aspirin+prasugrel), type of selected SAPT (aspirin versus each type of P2Y12 inhibitor)

HBR criteria according to the Academic Research Consortium initiative and their prospective validation

Stratified analyses based on bleeding and ischemic PARIS score

Performance and value in risk stratification of the PRECISE OAC.

History of MI at any time prior to randomization.

According to the anticipated benefits and risks of DAPT as declared by investigators at the time of randomization and according to their judgment on perceived ischemic and bleeding risks.

Impact of concomitant medications (e.g. proton pump inhibitor, high intensity statins) on outcomes

Left main or proximal LAD stenting Yes/No

Impact of age as continuous variable on ischemic/bleeding risks and on treatment effect

Impact of Hb as continuous variable on ischemic/bleeding risks and on treatment effect

Impact of whole blood count (i.e. integrating Hb, WBC and PLT) on outcomes and treatment effects

Impact of renal function as continuous variable on ischemic/bleeding risks and on treatment effect

Impact of hospital PCI volume on outcomes and treatment effects

Impact of operator experience on outcomes and treatment effects

Impact of coronary artery diameters and presence or absence of coronary ectasia as declared by the investigators or as defined based on absolute coronary diameters on outcomes and treatment effects

Stratified analyses based on geographic location/ethnicity with a special focus on Asian versus western populations.

Impact of prior PCI or prior CABG on outcomes and treatment effects.

Impact of dose of NOAC or TTR on outcomes and treatment effects

Impact of mean platelet volumes on outcomes and treatment effects.

Impact of glycaemia at the time of PCI on outcomes and treatment effects.

Impact of BMI on outcomes and treatment effects.

Impact of bleeding and ischemic events and type thereof on mortality

Impact of HASBLED on outcomes and treatment effects.

Impact of history of Heart failure and LVEF on outcomes and treatment effect

Impact of co-morbidities, including computation of the Charlson index on outcomes and treatment effects.

Impact of adherence on allocated treatment on outcomes and treatment effects.

Impact of bleeding complications after PCI on the risks of recurrent bleeding or ischemic events at follow-up

Impact of ischemic complications (e.g. ACS, reinterventon, stent thrombosis or ischemic stroke) after PCI on the risks of recurrent bleeding or ischemic events at follow-up

Impact on bleeding and ischemic events of routine medical care implemented 11 months after randomization with a focus on the occurrence of an ischemic rebound in those who discontinued DAPT or SAPT.

Cumulative bleeding and ischemic risks of the randomized population, stratified by allocated study group, at 15-month follow-up (i.e. combining both the protocol-mandated study regimen as well as the effect of transitioning to routine care afterwards. All analyses will be performed in the ITT as well as in the PP populations as well as factoring in adherence data.

Cost-effectiveness analysis will be performed to assess the impact of allocated treatment to resource utilization and overall heath care expenditure.

Development of the PRECISE DAPT II score in an attempt to explore the additional value of covariates which were not included in the generation and validation of PRECISE DAPT, such as history of cancer, stroke, platelet count and mean platelet volume, use and type of OAC etc.

On-treatment analysis according to the perfect and reasonably perfect adherence pattern or other derived adherence pattern also contrasting investigator-reported versus CEC adjudicated events to justify deviation from the protocol-mandated treatment.

4. Trial population

4.1. Screening data

Full screening data will be collected from sites willing to participate for at least one week window capturing all PCI and analysed based upon presence or absence of high bleeding risk criteria (HBR criteria) as defined for the MASTER DAPT trial and type thereof. .

For all consented patients all data up to and including the Randomization assessment will be collected inside the EDC (Demographics, History, HBR criteria, PCIs with Lesions and APT after PCI) (Screened population). The screened but not randomized population will consist of all consented, and eligible, but not randomized patients due to various reasons (i.e. death before M1, withdrew consent before randomization, lost to follow-up at M1, no longer eligible at M1). The non-randomised population will be compared to the randomized population on request (with p-values for comparison of e.g. history, risk factors and HBR), using the applicable shell tables.

4.2. Patient flow

A CONSORT style flow chart will be produced.

5. Analysis

5.1. Outcome definitions

This study has three primary endpoints:

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

The primary objective is to assess the primary endpoints between randomization and 11 months (equals 335 days) thereafter.

The secondary endpoints of the study are the following:

1) The individual components of each composite primary endpoints
2) The composite of cardiovascular death, MI, and stroke

5.2. Analysis methods

Tables and figures will be presented for of a number of variables for the comparison between patients on abbreviated DAPT and prolonged DAPT. In the tables either the mean and standard deviation, or the number of patients and the percentage of the total population will be presented for each variable. Due to the time varying nature of the primary and secondary endpoints, figures of these endpoints (either exact values or estimates) over time will be included (Kaplan-Meier plots).

All patients will be analysed by intention-to-treat (FAS) and reported according to their randomized arm, irrespective of the treatment they received. The differences in the rates of the primary endpoints (standard DAPT to abbreviated DAPT) will be reported as the cumulative incidence from the date of randomization to 335 days after randomization using the Kaplan-Meier approach.

The main analysis will consider the occurrence of primary endpoints between randomization and 11 months (335 days) thereafter. In secondary analyses, the occurrence of primary endpoints between 11 months and 15 months after index PCI can be evaluated, i.e. when the patients are on routine care medications.

The non-inferiority primary analyses of the primary endpoints are performed in the per-protocol population (non-inferiority analyses based on the FAS dataset will be performed as secondary analyses to corroborate the findings in the PP) whereas superiority analyses are performed in the FAS dataset (i.e. all randomised patients). Follow-up is censored at the last date of known outcome status or at 11 months since randomization, whichever comes first. All adjudicated events occurring since randomisation until 335 days post-randomisation are considered in the per-protocol population analyses and in the FAS dataset analyses.

Incidence rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to 335 days after randomization (~1 year post index PCI) by the Kaplan-Meier method. Incidence rate differences, comparing Abbreviated DAPT vs Prolonged DAPT regimen, are defined as the cumulative incidence under abbreviated DAPT minus that under standard DAPT, estimated using the Com-Nougue et al. methodology (with Greenwood estimators of the standard error).

Hazard ratios with 95% confidence intervals comparing Abbreviated DAPT vs Prolonged DAPT regimen are computed using the Cox regression method, using the stratification factors as covariates (i.e. recent myocardial infarction - within 12 months before the first PCI and OAC at randomization).

5.2.1. Adjustment of covariates

The primary and secondary endpoints will be analyzed adjusted for the two stratification factors used at randomization (acute MI with 12 months yes/no; clinical indication for OAC yes/no).

5.2.2. Pooling of sites

The randomization is stratified by site (in addition to history of MI and use of OAC), ensuring that approximately equal numbers of patients are randomized to Abbreviated and Prolonged DAPT regimen at each site. Since a large number of centers are participating in the study with potentially few randomized patients per site and probably no primary or secondary endpoints recorded at some sites, a correction for the effect of site will not be included in the analyses.

5.2.3. Assessment of statistical assumptions

The proportional hazards tests will be used to test whether the hazard ratio remains stable over time.

5.3. Missing data

Patients will be censored at the last valid contact or at the date of consent withdrawal if alive; and at the date of death if deceased. Consent withdrawal on the date of randomization will be counted as one day at risk for the primary and secondary endpoints.

5.4. Per-protocol analyses

Per-protocol population (PP) analyses will be conducted for the three primary endpoints only (NACE, MACE and MCB). Per-protocol analyses will be considered the primary analyses for NACE AND MACE non-inferiority testing (and non-inferiority testing replicated in all randomised patients will be considered as corroborative) whereas for superiority analyses, testing on FAS will be considered as primary and PP analyses as corroborative.

5.5. On-treatment analyses

On-treatment analyses will be conducted in the FAS and per protocol populations for all primary, secondary or exploratory endpoints as sensitivity analyses intended to be reported separately from the main study publications.

On-treatment analyses will be conducted including each patient during the time period when the patient is on treatment, and censoring each patient at the moment when he or she is off treatment, for endpoint of interest.

For example, censoring will occur when routine care or DAPT is not allowed as specified in Chapter 3, so the patient is expected to (still) follow the regimen.

It includes *for example*:

- Discontinuation of DAPT was not implemented in patients randomized to abbreviated DAPT at M1 visit, ±14 day window.

- Permanent discontinuation of DAPT in patients randomized to prolonged DAPT occurring before 5 months post-randomization (±14 days) in patients not on OAC, or before 2 months in patients with OAC (±14 days), not allowed as defined in Chapter 3.

5.6. Harms

The investigator monitors the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after randomization. Any records of any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation are collected and stored.

Only endpoint-related SAEs need to be reported during the study, unless they are considered related to the duration of the DAPT treatment.

A table for endpoint related adverse events will be produced. For other events, a Supplementary Material table will be produced if applicable and requested. Listing of adverse events per patient are provided on request.

5.7. Statistical software

Statistical analyses will be performed with Stata version 15.1 or higher, or R version 3.4 or higher in case a specific statistical procedure is not available within the Stata software.

6. Display items

6.1. Demographics and baseline characteristics

Please note that P-values, standard errors, and confidence intervals are not to be shown in baseline tables according to the CONSORT Statement, since any significant difference can be explained by the play of chance if the randomization was performed properly.

A table of baseline characteristics and medical history will be produced.

6.2. PCIs and Lesions

A table of procedural and lesion characteristics will be produced.

6.3. Adherence to regimen

A table for adherence to the study medications will be produced, optionally (or additionally) as a line or stacked bar figure.

6.4. Clinical endpoints

The p-value of the non-inferiority test Abbreviated DAPT regimen vs Prolonged DAPT regimen comparing the risk difference - using the 95% confidence interval of this risk difference with the margin - of the **Co-primary composite endpoint of all-cause death, myocardial infarction, stroke and bleeding events defined as BARC 3 or 5 (NACE)** will be produced for the main text and Abstract.

The p-value of the non-inferiority test Abbreviated DAPT regimen vs Prolonged DAPT regimen comparing the risk difference - using the 95% confidence interval of this risk difference with the margin - of the **Co-primary composite endpoint of all-cause death, myocardial infarction, stroke (MACCE)** will be produced for the main text and Abstract.

The p-value of the superiority test Abbreviated DAPT regimen vs Prolonged DAPT regimen comparing the risk difference - using the 95% confidence interval of this risk difference with the margin - of the **Co-primary composite endpoint of type 2, 3 and 5 BARC bleeding events (MCB)** will be produced for the main text and Abstract.

Note that certain journals will not accept p-values for secondary outcomes, but it is suggested to present all p-values initially for informational purposes, including a superiority test *pro-forma* of the two co-primary composite endpoints separately.

6.5. Subgroup analyses

Pre-specified subgroup analyses of the three co-primary endpoints will be performed, but it is expected that some of these figures will be moved to the Supplementary Information of the publication.

As mentioned in chapter 5.2, confidence intervals for the cumulative incidence rate differences comparing Abbreviated DAPT vs Prolonged DAPT regimen, are calculated according to the approach of Com-Nogue et al., accordingly p-values for a modifying effect of the subgroup on this difference are computed (i.e. interaction p-values).

6.6. Medications

All full tabulation of medications will be produced. Note that for APTs and OACs the medication will be regarded as taken when taken inside a ±14 days window around the visit: if this leads to multiple P2Y12 inhibitors taken due to a switch around the visit, then the P2Y12 inhibitor closest to the exact day will be reported (e.g. clopidogrel on 50 days, ticagrelor on 51 days, ticagrelor is closer to 60 days post-randomization so reported as taken, whereas clopidogrel is reported as not taken). Again, 2 months = 2x30 days = 60 days, 5 months = 5x30 days = 150 days and 11 months = 335 days after randomization.

7. References

Literature

Com-Nougue C, Rodary C, Patte C. 1993. How to establish equivalence when data are censored: a randomized trial of treatments for B non-Hodgkin lymphoma. Statistics in Medicine 12: 1353-64.

Giustino G et al. 2016. Efficacy and safety of dual antiplatelet therapy after complex PCI. JACC 68: 1851-1864.

Kernan et al. 1999. Stratified randomization for clinical trials. Journal of Clinical Epidemiology 52: 19-26.

Valgimigli et al. 2018. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC), European Heart Journal.

Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al. 2016. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 315: 1735-1749.

Data Management Plan

MASTER DAPT Data Management Plan (dynamic document)

8. Appendix I: Abbreviations

ACS	Acute Coronary Syndrome
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
CEAC	Clinical Event Adjudication Committee
CRA	Clinical Research Associate
(e)CRF	(electronic) Case Report Form
DAPT	Dual AntiPlatelet Therapy
DES	Drug-Eluting Stent
DMC	Data Monitoring Committee
DTI	Direct Thrombin Inhibitor
EC	Ethics Committee
ECG	Electrocardiography
ISR	In-Stent Restenosis
IRB	Institutional Review Board
IV	IntraVenous
GP	GlycoProtein
HBR	High Bleeding Risk
HIT	Heparin-Induced Thrombocytopenia
IFU	Instruction For Use
IRB	Institutional Review Board
LAD	Left Anterior Descending artery
LCA	Left Coronary Artery
LCX	Left Circumflex artery
MACE	Major Adverse Cardiac Events
MACCE	Major Adverse Cardiac and Cerebral Event
MCB	Major or clinically relevant non-major bleeding
MI	Myocardial Infarction
NACE	Net Adverse Clinical Endpoint
NOAC	New Oral Anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEACS	Non-ST segment Elevation Acute Coronary Syndrome
(N)STEMI	(Non-)ST segment Elevation Myocardial Infarction
OAC	Oral Anticoagulant
PAR	Protease Activated Receptor
PCI	Percutaneous Coronary Intervention
RCA	Right Coronary Artery
(S)AE	(Serious) Adverse Event
SAPT	Single AntiPlatelet Therapy
SD	Source Documentation
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularisation
TVF	Target Vessel Failure
UA	Unstable Angina
UFH	UnFractionated Heparin
ULN	Upper Limit of Normal
Ultimaster	Ultimaster© (TANSEI) drug-eluting stent developed by Terumo

9. Appendix II: visit plan

SUMMARY OF FOLLOW-UP VISITS

Day 0: PCI	**V1: 30 days**	**V2: 90 days**	**V3: 180 days**	**V4: 365 days**	**V5: 450 days**
	+14 days	*60±14 days post randomization*	*150±14 days post randomization*	*335+14 days post randomization*	*420+14 days post randomization*
Type of contact	Visit	Visit or Phone and Letter*	Visit or Phone and Letter*	Visit	Phone
Inclusion/ exclusion criteria	X				
Informed consent**	X				
Physical examination	X				
Medical and cardiac history	X				
Peri-procedural PCI data	X				
Randomization	X				
Electrocardiogram (12 lead ECG)	X***				
Medication regimen	X	X	X	X	X
Anginal status	X	X	X	X	X
Serious adverse event monitoring	X****	X	X	X	X
Blood sampling	X***				

*) A letter with details of randomized duration regimen is sent to the patient, which will be brought to the treating physician to ensure the implementation of randomized regimen.
**) Informed consent can be obtained at any time between the percutaneous coronary intervention (PCI) and 30-44-days randomization visit (V1)
***) Only in the centers where this is a part of usual clinical practice
****) Serious adverse event monitoring starts immediately after informed consent.

10. Appendix III: SARS-CoV-2

From December 2019 onwards the SARS-CoV-2 pandemic has swept over the globe (COVID-19 corona-virus), with 6 416 828 confirmed cases and killing 382 867 people (as of 5 june 2020, see https://www.who.int/emergencies/diseases/novel-coronavirus-2019). To estimate the effect of this pandemic on the MASTER DAPT trial the following additions were made to the data capture: (1) for each country the date of the first confirmed case was recorded (so called country case date) using WHO data; (2) for each event occurring on or after this country case date it was recorded whether the event was related to SARS-CoV-2 (and if yes, when diagnosed and with which diagnostic methodology – PCR or antibodies).

A Supplementary Table of all events related to the SARS-CoV-2 will be produced.

A Supplementary Table of the primary outcomes and components will be produced (at 335 days of follow-up) comparing abbreviated DAPT versus prolonged DAPT using robustified Cox's regressions, stratifying the time at risk for each patient before and on/after the country case date, testing for an interaction effect between ***period*** (on/after vs before country case date) x randomized regimen (abbreviated DAPT vs prolonged DAPT), using once the ITT and once the per-protocol population. Note that patients reaching the 335 days follow-up time before the country case date will only contribute time at risk for the ***period*** before the pandemic reached their country; whereas all other patients can in principle contribute to both time periods. Non-fatal events will be counted separately for each patient and ***period***.