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Abbreviated or Standard Antiplatelet Therapy in Patients at High Bleeding Risk: Final 15-month Results of the MASTER-DAPT Trial

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**A complete list of the investigators in the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen Trial is provided in the Data Supplement.*

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ABSTRACT

Background. The risks and benefits of an abbreviated compared with standard antiplatelet therapy (APT) after 12 months in high bleeding risk (HBR) patients after percutaneous coronary intervention (PCI) are unknown.

Methods. The MASTER DAPT trial randomized 4579 HBR patients to abbreviated (n=2295) or standard (n=2284) APT regimens. Coprimary outcomes were net adverse clinical outcomes (NACE, the composite of all-cause death, myocardial infarction, stroke, and Bleeding Academic Research Consortium [BARC] 3 or 5 bleeding); major adverse cardiac and cerebral events (MACCEs, all-cause death, myocardial infarction, and stroke); and BARC type 2, 3, or 5 bleeding. In this prespecified analysis, we report cumulative 15-month and 12-to-15-month outcomes after PCI, when routine care was allowed in both study arms.

Results. At 15 months, more patients in the standard group remained on dual or single APT, whereas NACE and MACCE did not differ with abbreviated versus standard APT (hazard ratio [HR], 0.92 [95% CI, 0.76-1.12]; P= 0.399 and HR, 0.94 [95% CI, 0.76-1.17]; P= 0.579; respectively) and during the routine care period (HR, 0.81 [95% CI, 0.50-1.30]; P= 0.387 and HR, 0.74 [95% CI, 0.43-1.26]; P= 0.268; respectively). BARC 2, 3 or 5 was lower with abbreviated APT at 15 months (HR, 0.68 [95% CI, 0.56-0.83]; P= 0.0001) and did not differ during the routine care period (HR, 0.81 [95% CI, 0.48-1.35]; P= 0.414). The treatment effects during routine care were entirely consistent with those observed within 12 months after PCI.

Conclusions. At 15 months, prior allocation to a standard APT regimen was associated with greater use of dual or single APT, suggesting a carry-over reflex during routine care; the rates of NACE and MACCE did not differ in the two study groups whereas the risk of major or nonmajor clinically relevant bleeding remained lower with abbreviated compared with standard APT in HBR patients with prior PCI.

Trial Registration: ClinicalTrials.gov number, NCT03023020.

KEYWORDS: high bleeding risk; antiplatelet therapy; dual antiplatelet therapy; percutaneous coronary intervention.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

MASTER-DAPT, Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen
PCI, percutaneous coronary intervention
APT, antiplatelet therapy
SAPT, single antiplatelet therapy
DAPT, dual antiplatelet therapy
OAC, oral anticoagulation
MACCE, major adverse cardiac and cerebral events
NACE, net adverse clinical outcomes
BARC, Bleeding Academic Research Consortium
NARC, nonadherence Academic Research Consortium
HR, hazard ratio
CI, confidence interval

CLINICAL PERSPECTIVE

WHAT IS NEW?

- The MASTER DAPT trial randomized high bleeding risk (HBR) patients free from recurrent ischemic events at 1 month to an abbreviated or a standard antiplatelet therapy (APT). This prespecified analysis investigated cumulative rates of ischemic and bleeding events at 15 months and during the routine care period.
- Patients at HBR frequently present characteristics of high thrombotic risk which expose them to the risk of adverse events after short DAPT discontinuation.
- At 15 months post-index PCI, ischemic and net risk did not differ with abbreviated APT which resulted in lower bleeding rates, whereas the rates of the 3 co-primary outcomes did not differ during the routine care period.

WHAT ARE THE CLINICAL IMPLICATIONS?

- A considerable proportion of HBR patients with or without clinical indication for oral anticoagulation still received single or dual APT after 12 months, respectively.
- Prior allocation to standard antiplatelet treatment was associated with more frequent prolongation of single or dual APT beyond 1 year, suggesting the existence of a carry-over reflex, whereby prior treatment is likely to be continued.
- An upfront decision-making with respect to APT duration and intensity remains key and should take not only ischemic but also bleeding risks into account.

INTRODUCTION

Patients undergoing percutaneous coronary intervention (PCI) with stent implantation require dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor to reduce the risk of recurrent ischemic events, such as stent thrombosis or myocardial infarction (MI) (1,2). However, DAPT inevitably associates with enhanced bleeding risk, whose magnitude is linearly related to its duration. In patients at high bleeding risk (HBR), shortening the duration of DAPT (e.g. 1 to 6 months) in contrast to standard therapy (6 to 12 months depending on clinical presentation) is one of the recommended bleeding avoidance strategies (1,3). However, HBR patients also present characteristics of high thrombotic risk (4) and concerns remain in the community for the risk of adverse ischemic events especially after a short course of DAPT.

The MASTER DAPT (*Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen)* showed in unselected HBR patients, who were free from recurrent ischemic and active bleeding events at 1 month after biodegradable polymer-coated sirolimus-eluting stent implantation, that immediate DAPT discontinuation versus treatment continuation up to 1 year was noninferior for net and major adverse cardiac or cerebrovascular events and was associated with lower major or clinically relevant nonmajor bleeding at 335 days(5,6). Patients in both treatment groups implemented routine clinical care thereafter and underwent a final study visit at 15 months, which was meant to capture cumulative ischemic and bleeding endpoints after cessation of DAPT or any antiplatelet therapy (APT), respectively in patients without or with oral anticoagulation, irrespective of prior treatment allocation, as endorsed by current guidelines. We report here the prespecified final results of the MASTER DAPT trial, including the treatment effects of transitioning from protocol-mandated to standard of care regimens after an abbreviated or prolonged anti-platelet therapy regimen in largely unselected HBR who had undergone PCI, with or without indication to oral anticoagulation (OAC).

METHODS

MASTER DAPT design

The MASTER DAPT trial is an investigator-initiated, multicenter, randomized, open- label, noninferiority trial with sequential superiority testing in a large cohort of HBR patients who underwent PCI with implantation of a biodegradable polymer-coated Ultimaster (*Terumo Corporation, Tokyo, Japan*) sirolimus-eluting stent (5–7). The trial was performed at 140 sites in 30 countries across Europe, South America, the Middle East, Asia, and Australia. The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent. The study design and main results of this trial have been previously published (5–7). Trial organization and participating sites are mentioned in the **Supplemental material**.

Study patients

Patients at HBR were considered to be candidates for participation in the trial if they had undergone PCI of all planned coronary artery stenoses with Ultimaster stent implantation for acute or chronic coronary syndromes and remained event-free (including a new acute coronary syndrome [ACS], symptomatic restenosis, stent thrombosis, stroke, or any revascularization resulting in the prolonged use of DAPT) at 1 month after the index procedure. Key exclusion criteria were the implantation of a stent other than the Ultimaster stent within 6 months before the index procedure, the implantation of a bioresorbable scaffold at any time before the index procedure, and treatment for in-stent restenosis or stent thrombosis. Detailed inclusion and exclusion criteria are presented in the **Supplemental material**.

Patients were considered at HBR if at least one of the following criteria applied: any OAC (vitamin-k antagonists or nonvitamin K antagonist oral anticoagulants) therapy for at least 12 months, recent (<12 months) non-access site bleeding episode(s) that required medical attention, previous bleeding episode(s) that required hospitalization if the underlying cause had not been definitively treated,

advanced age (≥75 years), systemic conditions associated with an increased bleeding risk (eg, hematologic disorders or any known coagulation disorder associated with increased bleeding risk), documented anemia (defined as repeated hemoglobin levels <11 g/dL or transfusion within 4 weeks before randomization), need for chronic treatment with steroids or nonsteroidal anti-inflammatory drugs (NSAIDs), diagnosed malignancy (other than skin), stroke at any time or transient ischemic attack in the previous 6 months, or predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score ≥ 25 (8).

Randomization and follow-up

Patients were centrally randomized (1:1 ratio) to an open-label abbreviated or standard APT regimen 30 to 44 days after the index procedure. Randomization was concealed using a web-based system; randomization sequences were computer generated, blocked, with randomly selected 10 block sizes of 2, 4, or 6, and were stratified by site, history of acute myocardial infarction within the past 12 months, and clinical indication for at least 12 months of OAC therapy. Follow-up visits occurred at 60±14 and 150±14 days after randomization, preferably as on-site visits, at 335±14 days and 425±14 days after randomization, exclusively as an on-site visit. Three independent clinical research organizations (CERC, Massy, France; Cardialysis, Rotterdam, the Netherlands; and CVQuest, Tokyo, Japan) performed on-site and remote monitoring visits, verified the source documents, and collected source material for event adjudication. All events were adjudicated by an independent adjudication committee that was unaware of the treatment allocations. Nonadherence to the allocated treatment regimen was evaluated according to the Non-adherence Academic Research Consortium (NARC) classification (9). All data were stored at a central database (CTU, Bern, Switzerland).

Randomized treatments

Patients randomly allocated to the abbreviated treatment group immediately discontinued DAPT and continued single antiplatelet therapy (SAPT) until study completion, except for those receiving OAC, who continued SAPT up to 6 months after the index procedure. Patients allocated to the standard treatment group continued DAPT for at least 5 additional months (6 months after the index procedure) or, for those receiving OAC, for at least 2 additional months (3 months after the index procedure) and continued thereafter on SAPT. Antiplatelet and anticoagulant treatments were dosed according to authorizations for use and locally approved regimens. Detailed information of the randomized treatments were previously reported (5,6).

Study outcomes

The three ranked co-primary outcomes were net adverse clinical events (NACE, a composite of death from any cause, MI, stroke, or major bleeding), major adverse cardiac or cerebral events (MACCEs, a composite of death from any cause, MI, or stroke), and major or clinically relevant non-major bleeding (composite of type 2, 3, or 5 Bleeding Academic Research Consortium [BARC] bleeding). The secondary outcomes included the individual components of the three co-primary outcomes; the composite of cardiovascular death, MI, and stroke; the composite of cardiovascular death, MI, definite or probable stent thrombosis, the composite of stroke and transient ischemic attack; and all bleeding events, adjudicated according to the BARC, TIMI and GUSTO classifications. All outcomes were prespecified. All analyses evaluated the occurrence of the adjudicated outcomes at 425 days (15 months) and between 335 and 425 days (routine care period) post-index PCI.

Statistical analysis

Data were analyzed according to the intention-to-treat principle. The Com-Nougue method (10) was used to analyze time-to-event and calculate event rates and P values. We report cause-specific

estimates throughout the article. For patients with a primary outcome, time-to- event was calculated as the difference between the date of occurrence of the outcome event and the date of randomization plus 1. For patients with an outcome event and complete follow- up until the end of day 425, time to censoring was calculated as 425 days. For patients with incomplete clinical follow-up, time to censoring was defined as the difference between the dates of last known clinical status and randomization plus 1. For the third coprimary end point, the occurrence of death was defined as a competing risk event, and follow-up was censored at the time of the occurrence of death. Kaplan-Meier curves were created for the first 2 (time-to-event) coprimary outcomes, and cause-specific Kaplan-Meier curves for the third coprimary end point (with censoring at the time of the competing risk event of unrelated death). Kaplan-Meier calculations included all (first) adjudicated outcome events that occurred at 425 days after randomization as between 335 and 425 days (routine care period) according to the randomized treatment assignment, irrespective of the dual antiplatelet regimen received at the time of the outcome event. Cause-specific hazard ratio (HRs) and 95% confidence interval (CIs) were generated for primary and secondary end points with the use of Cox proportional hazards regression analysis with censoring at end of study and at the time of the competing risk event of unrelated death as defined above. Landmark analyses are based on the timepoints patients were allowed to reduce APT per protocol (150 days post-randomization) and to switch to routine care medication (335 days post-randomization). We applied both univariate and multivariable logistic regression models to evaluate the use of APT at 425 days (15-month follow-up) with clinical and procedural characteristics.

P values for testing homogeneity of the hazard ratio in subgroups of patients were derived in Cox proportional hazards models with interaction terms for treatment group and sub- group membership. The analyses were done using Stata release 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

From February 28, 2017, to December 5, 2019, 5204 patients (at 140 sites in 30 countries) were screened and 4579, at a median of 34 days (interquartile range [IQR], 32–39) after stenting, were randomized to the abbreviated (2295 patients) or the standard (2284 patients) APT groups; a total of 2205 and 2186 patients started routine care at 12 months, respectively (**Figure S1**). Complete follow-up at 15 months was available for 99.8% of the patients in the abbreviated and 99.9% of the patients in the standard APT arms.

Detailed information on antiplatelet and OAC use at 15 months is shown in **Figure 1** and **Figure S2**. At 15 months, 4.2% and 16.2% of patients with and without OAC were on DAPT in the standard APT arm, respectively. The corresponding figures in the abbreviated APT group were 1.1% and 6.3%, respectively. SAPT was implemented in 26.9% and 82.6% of patients with and without OAC in the standard APT arm, respectively. The corresponding figures in the abbreviated APT group were 13.5% and 84.0%, respectively. A total of 68.9% of patients in the standard and 84.5% of patients in the abbreviated APT group were on OAC monotherapy, whereas in the non-OAC group, 1.2% of patients in the standard and 9.7% in the abbreviated ATP arm had no APT (**Tables S1** and **S2**). In both study groups, clopidogrel plus aspirin was the most common antiplatelet combination for DAPT whereas aspirin, followed by clopidogrel, monotherapy the most used SAPT.

Median durations of DAPT since coronary stenting (**Table S3**) were 35 days (IQR, 31–40) in patients with OAC and 35 days (IQR, 32–42) in patients without OAC in the abbreviated arm; and 97 days (IQR, 91–121) and 366 days (IQR, 192– 381), respectively, in the standard therapy group. Potential causes of DAPT continuation assessed at 15 months are shown in **Table S4,** with higher prior ischemic and net events in patients on DAPT at 15 months in the abbreviated and standard groups, both in patients with and without indication for OAC (**Tables S5 and S6**).

Predictors of intensified antiplatelet therapy in the routine care

Among OAC patients, those on SAPT had more frequent diabetes mellitus, hematological or coagulation disorders, chronic treatment with steroids or NSAIDs and higher PRECISE DAPT score values compared with no-APT patients; STEMI as indication for index PCI was more frequent, and the total number of revascularizations and treated lesions were higher in the SAPT compared with no APT groups (**Tables S7** and **S8)**.

Among non-OAC patients at day 335, those on DAPT were younger, less frequently Caucasian, with greater prevalence of high-ischemic risk features (diabetes mellitus, carotid vascular disease, prior MI, ACS and advanced Killip class at presentation) compared with the SAPT group. Patients treated with DAPT had also more frequently complex lesions (B2/C) involving the left main and underwent more frequent bifurcation or trifurcation stenting than patients treated with SAPT. DAPT-treated patients had more frequent liver disease, prior bleeding, and trended towards higher PRECISE DAPT score (**Tables S7 and S8)**.

Among patients with clinical indication for OAC (**Table S9**), prior allocation to abbreviated treatment and atrial fibrillation were the only variables associated with lower use of SAPT. Conversely, high ischemic risk characteristics such as carotid artery disease, higher prior MI, prior revascularization and higher PRECISE DAPT score or major bleeding at 425 days were associated with higher use SAPT use compared with no APT use (**Table S9)**. Among non-OAC patients, prior allocation to abbreviated treatment and advanced age were associated with higher SAPT use, whereas clinical and procedural features of high ischemic risk (diabetes, carotid artery disease, advanced Killip class, preprocedural TIMI flow < 3, MI and revascularization at 425 days) with greater use of DAPT (**Table S10)**.

Clinical outcomes at 15-month follow-up

Clinical outcomes at 15 months are shown in **Table 1** and **Table S11**. Net adverse clinical events occurred in 199 (8.7%) patients in the abbreviated and 214 (9.5%) patients in the standard therapy group (HR 0.92, [95% CI, 0.76-1.12]; P= 0.399; **Figure 2A**), for a difference in risk of −0.75 percentage points (95% CI, −2.42 to 0.93). Major adverse cardiac and cerebral events occurred in 158 (6.9%) patients in the abbreviated arm versus 167 (7.4%) patients in the standard therapy arm (HR 0.94, [95% CI, 0.76-1.17]; P= 0.579; **Figure 2B**), for a difference in risk of −0.51 percentage points (95% CI, −2.01 to 1.00). Major or clinically relevant nonmajor bleeding remained lower in the abbreviated compared with the standard therapy arm (167 [7.4%] *versus* 239 [10.7%]; HR, 0.68 [95% CI, 0.56-0.83]; P= 0.0001; **Figure 2C**), for a difference in risk of −3.25 percentage points (95% CI, −4.93 to -1.58).

Fewer BARC 1 and BARC 2 bleedings occurred in the abbreviated APT arm (P=0.0027 and P=0.001, respectively), whereas the rates of BARC 3 or 5 bleeding were 2.8% and 3.5% in the abbreviated and standard treatment groups, respectively (HR, 0.79 [95% CI, 0.56-1.10]; P= 0.156). Fewer stroke occurred in the abbreviated compared with the standard APT arm (HR, 0.53 [95% CI, 0.28-0.99]; P= 0.048). Other outcomes did not differ between groups.

Clinical outcomes in patients with or without clinical indication for OAC showed consistent treatments effects with regards to net and major adverse cardiac or cerebral events whereas interaction test was positive for major or clinically relevant nonmajor bleeding, largely driven by BARC 2 bleeding and ischemic stroke (**Table S11**).

Clinical outcomes in the routine care period

Clinical outcomes in the routine care period are shown in **Table 2**. Net adverse clinical outcomes and major adverse cardiac and cerebral events did not differ between the abbreviated and standard therapy groups (NACE: 31 [1.4%] *versus* 38 [1.8%]; HR, 0.81 [95% CI, 0.50-1.30]; P= 0.387;

Figure 2D; MACCE: 23 [1.1%] *versus* 31 [1.5%]; HR, 0.74 [95% CI, 0.43-1.26]; P= 0.268; **Figure 2E**). Major or clinically relevant nonmajor bleeding did not differ between the treatment groups (26 [1.2%] *versus* 32 [1.5%]; HR, 0.81 [95% CI, 0.48–1.35]; P=0.414; **Figure 2F**). All-cause death was lower in the abbreviated compared with standard treatment groups (0.4% *versus* 1.0%, HR, 0.42 [95% CI, 0.18-0.95]; P= 0.038). Results remained consistent in patients with and without clinical indication for 12-month OAC (**Tables S12)**. Stratified outcomes in patients (SAPT versus no APT) and without (DAPT versus SAPT) OAC use at day 335 after randomization are shown in **Tables S13** and **S14**.

Landmark analyses

Landmark analyses at 335 days after randomization showed consistent treatment effects for the coprimary and secondary endpoints with respect to study phases (**Table 3**), including before and after routine care was allowed. Landmark analyses at 335 days among patients with or without clinical indication for OAC are displayed in **Table S15**.

The results of landmark analyses at 150 days (when the protocol allowed DAPT discontinuation in the standard treatment group) and at 335 days (when routine care was implemented) also showed consistent treatment effects for the coprimary and secondary endpoints with respect to time (**Figure 3)**. The results remained consistent when patients with or without OAC were separately appraised (**Figure S3).**

DISCUSSION

The main findings of this prespecified subanalysis from the MASTER DAPT trial are 4-fold:

1. A considerable proportion of patients in the routine care period received a more intensified than currently recommended APT regimen, either in terms of DAPT instead of SAPT

among patients without indication for OAC, or SAPT instead of no APT among patients with OAC.

2. Among the non-OAC patients who had been previously allocated to the abbreviated treatment group, DAPT instead of SAPT was largely implemented in patients with prior events, including MI, cerebrovascular accidents or revascularization, whereas only a minority of patients who continued DAPT beyond one-year experienced prior events in the standard treatment group. Conversely, prior events occurred only in a minority of OAC patients who continued SAPT beyond one year in both treatment groups, albeit more frequently in the abbreviated compared with standard treatment arms.
3. Irrespective of clinical indication for OAC, previous allocation to abbreviated treatment was associated with less intense antiplatelet treatment in the routine care period, suggesting the existence of a carry-over reflex, whereby prior treatment is likely to be continued. Bleeding risk or even prior bleeding did not affect the decision making for antiplatelet therapy intensity, with the only exception for age with regards to DAPT versus SAPT selection.
4. Clinical outcomes during the 3-month routine care period were consistent with the treatment effects observed during the protocol-mandated antithrombotic regimen. At 15 months, the cumulative rates of net and major adverse cardiac or cerebral events remained similar in the two study groups and major or clinically relevant nonmajor bleeding remained lower in patients who had been previously allocated to an abbreviated compared with a standard treatment.

International guidelines endorse DAPT for 1 to 6 month(s) in PCI-HBR patients without clinical indication for OAC and for 1 week to 1 month in patients on OAC, depending on thrombotic and bleeding risks (11–13). In the latter group, it is recommended to stop SAPT after 12 months, or even after 6 months in patients at high bleeding and low thrombotic risks.

However, we expected a large variability across sites in terms of DAPT and SAPT durations based on a site survey conducted before study initiation which revealed that the perceived standard of care was more than 6-month DAPT for non-OAC patients in a sizable proportion of sites and more than 6-month SAPT for OAC patients in almost all sites in HBR patients. Registry data and randomized trials have suggested the existence of a possible rebound effect, with a cluster of ischemic events in the 3 months following DAPT discontinuation (14–17). Therefore, the MASTER DAPT trial was designed to assess final clinical outcomes at 15 months after PCI, with the rational of collecting the cumulative treatment effects of an abbreviated versus standard APT when all non-OAC patients were supposed to discontinue DAPT and all OAC patients were supposed to discontinue SAPT, irrespective of prior randomization (if free from recurrent ischemic events or repeat interventions). We found that more than 15% of non-OAC patients were still on DAPT at 15 months in the standard DAPT arm, which was approximately three-times higher than the corresponding figure in the abbreviated treatment arm. In the OAC group, more than one fourth of patients were still on SAPT in the standard DAPT arm, whereas the corresponding figure was approximately 14% in the abbreviated treatment group. At multivariate modeling, prior allocation to the abbreviated treatment group was a strong independent predictor of preferential SAPT versus DAPT in non-OAC patients and no APT versus SAPT in OAC patients. These findings highlight the existence of a carry-over reflex, whereby prior treatment tends to be continued in routine practice despite non-supportive evidence and at variance with guidelines recommendations (12,13). This unexpected finding may explain the consistency of the treatment effects between the protocol-mandated and the routine care phases of our study. This observation carries relevant clinical implications and suggests the need for clearly defining treatment duration upfront to mitigate the carry-over reflex of potentially unnecessary treatment. We also observed that bleeding risk, as captured by PRECISE DAPT or other high bleeding risk features such as comorbidities or concomitant treatment, or even prior bleeding did not affect the decision-making for DAPT or SAPT duration, with the only exception

for age in respect to the former, but interestingly, not the latter treatment option for non-OAC and OAC patients, respectively. Conversely, clinical or procedural markers of ischemic risks drove clinicians to prolong DAPT beyond one year, despite the existence of non-supportive evidence in HBR patients.

The current 15-month outcome data of the MASTER DAPT trial confirms and extends prior findings at 12 months after PCI (5), showing no penalty with respect to ischemic or fatal events of an abbreviated compared with a standard treatment, with persistently lower risk of major or clinically relevant nonmajor bleeding in HBR-PCI patients. During the routine case phase, not only bleeding but also major cardiac or cerebral events were numerically lower in patients who were previously allocated to the abbreviated treatment group, which was largely driven by lower fatal events. Hence, our study reinforces the need for a timely identification of HBR patients undergoing PCI, allowing an upfront decision-making with respect to APT treatment and duration, in order to mitigate bleeding risk and optimize outcomes.

Study limitations

Some limitations of this study should be considered. The MASTER DAPT trial was an open-label study with inherent limitations related to that study design. Randomization was done at 1 month after PCI in patients free from ischemic and active bleeding events and who adhered to a DAPT regimen. Therefore, our study results cannot inform treatment in patients with a complicated 30-day course after PCI. The duration of DAPT was heterogeneous in the standard-therapy group and longer than currently recommended for patients at HBR. DAPT and SAPT durations in the two study groups was also longer than that currently recommended in patients with OAC. The type of SAPT after DAPT discontinuation in the abbreviated-therapy group also varied. Finally, the trial included HBR patients who underwent biodegradable polymer sirolimus-eluting stent implantation; consequently, our results may not extend to patients who are not at HBR or received other stent types.

In conclusion, at 15 months after PCI in HBR patients, prior allocation to standard antiplatelet treatment was associated with more frequent prolongation of DAPT and SAPT beyond 1 year during routine care. Abbreviated APT was associated with similar cumulative rates of 15-month net and major adverse events and lower risk of major or clinically relevant nonmajor bleeding compared with prior allocation to standard therapy. The final results of our study support the need for a greater awareness towards bleeding risk assessment in PCI patients and emphasize the importance of an upfront decision-making with respect to APT duration and intensity taking not only ischemic but also bleeding risks into account.

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SUPPLEMENTAL MATERIAL

MASTER DAPT trial: committees and investigators

ADDITIONAL INFORMATION ON THE METHODS

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Figure S3. Clinical outcomes at 425 days post-randomization (15-month post-index PCI) using two landmark analyses: at 150 days (6 months) and at 335 days (12 months) stratified by clinical indication for 12-month oral anticoagulation (OAC).

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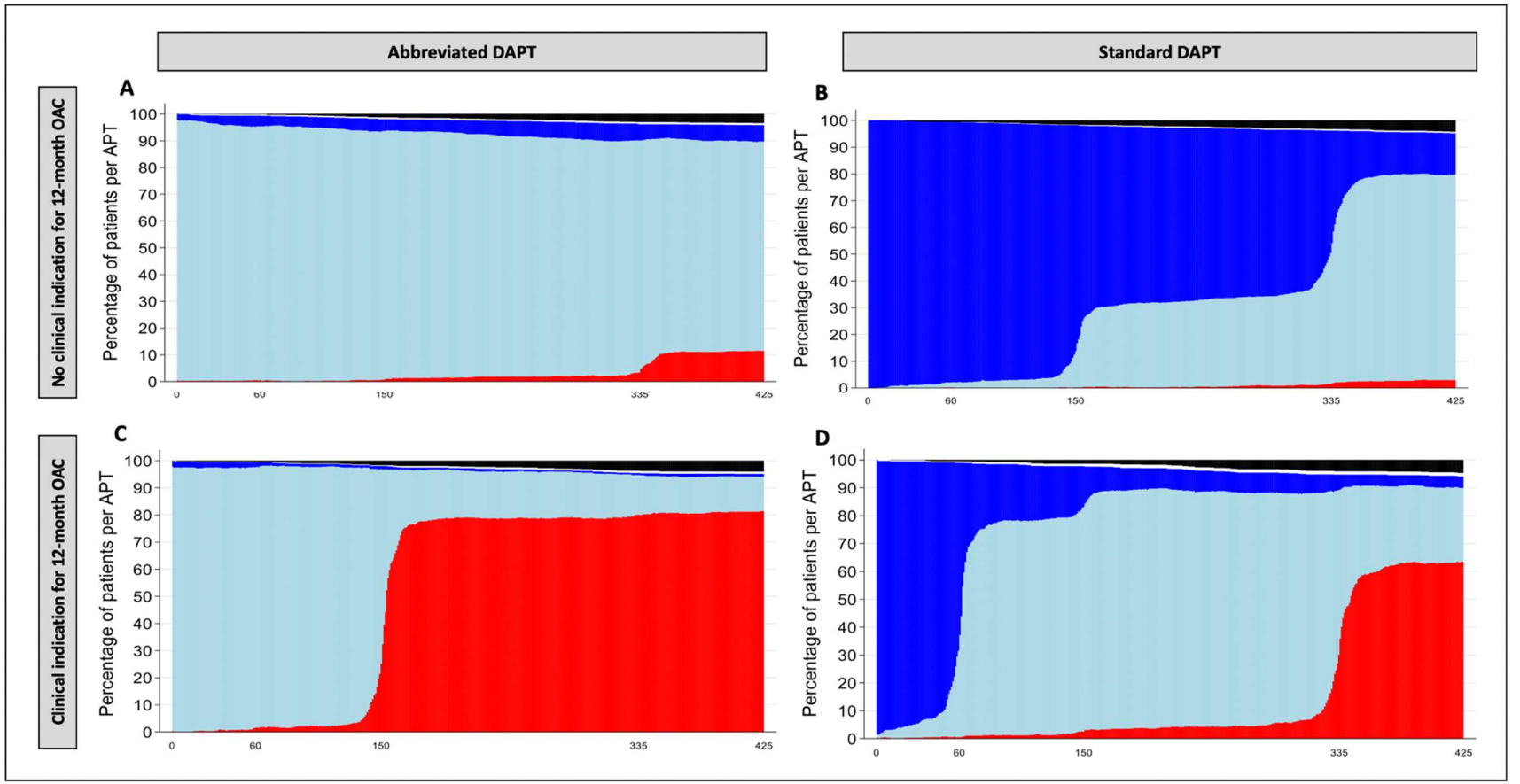
FIGURE LEGENDS

Figure 1. Antiplatelet use per day since randomization for patients with and without indication for 12-month oral anticoagulation (OAC) therapy. *Abbreviations: DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; APT, antiplatelet therapy.*



Dark blue = DAPT, light blue = SAPT, red = no APT, black = deceased, white = no information.

Figure 2. Kaplan-Meier curves of the 3 coprimary outcomes at 425 months after randomization (14-month follow- up, left panels) and during the routine care period. *Abbreviations: HR, hazard ratio; CI, confidence interval.*

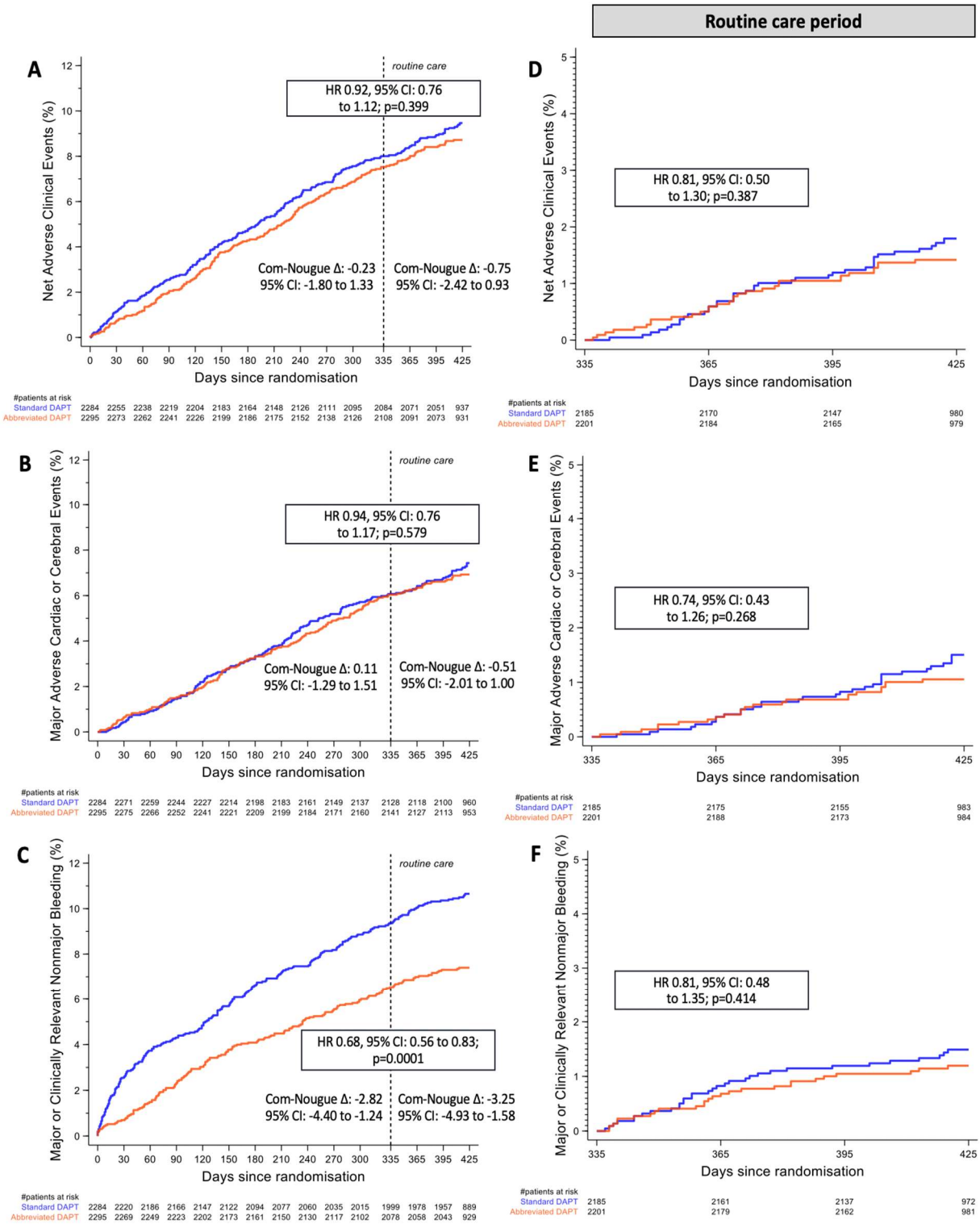
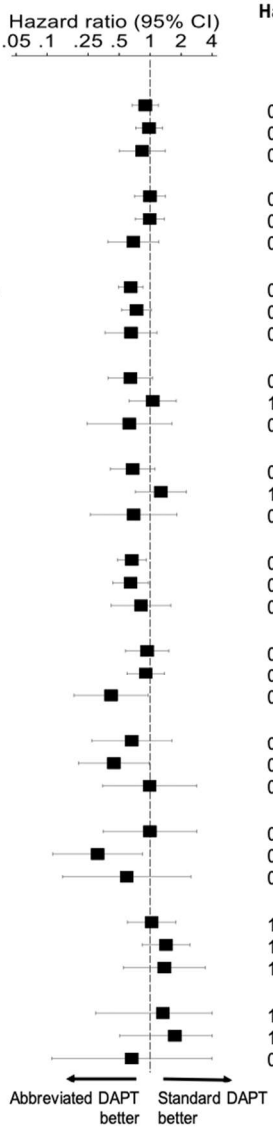


Figure 3. Clinical outcomes at 425 days post-randomization (15-month post-index PCI) using two landmark analyses: at 150 days (6-month follow-up) and at 335 days (12-month follow-up).
Abbreviations: DAPT, dual antiplatelet therapy; CI, confidence interval; BARC, Bleeding Academic Research Consortium.

	Abbreviated DAPT N = 2295	Standard DAPT N = 2284	Hazard ratio (95% CI)	p-value	Interaction p-value
Net Adverse Clinical Events					0.856
0 to 150 days	86/2295 (3.8%)	95/2284 (4.2%)	0.897 (0.670-1.201)	0.467	
151 to 335 days	86/2199 (3.9%)	87/2180 (4.0%)	0.976 (0.724-1.315)	0.873	
336 to 425 days	27/2106 (1.3%)	32/2084 (1.6%)	0.837 (0.501-1.396)	0.495	
Major Adverse Cardiovascular Events					0.504
0 to 150 days	64/2295 (2.8%)	64/2284 (2.8%)	0.996 (0.705-1.409)	0.983	
151 to 335 days	74/2221 (3.3%)	74/2211 (3.4%)	0.991 (0.718-1.368)	0.957	
336 to 425 days	20/2139 (0.9%)	29/2128 (1.4%)	0.687 (0.389-1.214)	0.196	
Major or Clinically Relevant Nonmajor Bleeding					0.824
0 to 150 days	86/2295 (3.8%)	130/2284 (5.7%)	0.648 (0.494-0.851)	0.002	
151 to 335 days	62/2173 (2.9%)	81/2119 (3.9%)	0.739 (0.531-1.028)	0.072	
336 to 425 days	19/2076 (0.9%)	28/1999 (1.4%)	0.652 (0.364-1.168)	0.151	
BARC type 3 or 5					0.349
0 to 150 days	26/2295 (1.1%)	40/2284 (1.8%)	0.643 (0.393-1.054)	0.08	
151 to 335 days	29/2230 (1.3%)	27/2207 (1.2%)	1.061 (0.628-1.792)	0.825	
336 to 425 days	7/2164 (0.3%)	11/2135 (0.5%)	0.628 (0.244-1.621)	0.337	
BARC type 3					0.238
0 to 150 days	26/2295 (1.1%)	38/2284 (1.7%)	0.677 (0.411-1.115)	0.125	
151 to 335 days	27/2230 (1.2%)	21/2207 (1.0%)	1.270 (0.718-2.246)	0.412	
336 to 425 days	7/2164 (0.3%)	10/2135 (0.5%)	0.691 (0.263-1.816)	0.454	
BARC type 2					0.835
0 to 150 days	62/2295 (2.7%)	92/2284 (4.0%)	0.664 (0.481-0.916)	0.013	
151 to 335 days	40/2194 (1.8%)	60/2151 (2.8%)	0.646 (0.433-0.964)	0.033	
336 to 425 days	16/2107 (0.8%)	19/2042 (0.9%)	0.815 (0.419-1.584)	0.546	
All-cause death					0.217
0 to 150 days	32/2295 (1.4%)	34/2284 (1.5%)	0.936 (0.577-1.516)	0.787	
151 to 335 days	43/2253 (1.9%)	47/2241 (2.1%)	0.907 (0.599-1.371)	0.642	
336 to 425 days	8/2201 (0.4%)	19/2185 (1.0%)	0.418 (0.183-0.955)	0.038	
Cerebrovascular Accident					0.479
0 to 150 days	8/2295 (0.4%)	12/2284 (0.5%)	0.663 (0.271-1.622)	0.368	
151 to 335 days	9/2246 (0.4%)	20/2230 (0.9%)	0.444 (0.202-0.976)	0.043	
336 to 425 days	7/2188 (0.3%)	7/2162 (0.3%)	0.988 (0.347-2.818)	0.983	
Stroke					0.286
0 to 150 days	7/2295 (0.3%)	7/2284 (0.3%)	0.995 (0.349-2.838)	0.993	
151 to 335 days	5/2247 (0.2%)	16/2235 (0.7%)	0.309 (0.113-0.844)	0.022	
336 to 425 days	3/2193 (0.1%)	5/2170 (0.2%)	0.593 (0.142-2.483)	0.475	
Myocardial infarction					0.688
0 to 150 days	27/2295 (1.2%)	26/2284 (1.2%)	1.034 (0.604-1.772)	0.902	
151 to 335 days	33/2227 (1.5%)	23/2217 (1.1%)	1.426 (0.837-2.428)	0.192	
336 to 425 days	11/2147 (0.5%)	8/2142 (0.4%)	1.374 (0.553-3.416)	0.494	
Definite stent thrombosis					0.685
0 to 150 days	4/2295 (0.2%)	3/2284 (0.1%)	1.329 (0.297-5.939)	0.709	
151 to 335 days	7/2249 (0.3%)	4/2238 (0.2%)	1.736 (0.508-5.929)	0.379	
336 to 425 days	2/2191 (0.1%)	3/2179 (0.1%)	0.663 (0.111-3.966)	0.652	



Depicted are: Number of events / Number of patients at risk (% from Kaplan-Meier estimate).
Hazard ratio (95% CI) from Cox's time-to-first event analyses. using two Landmarks: at 150 days and 335 days post-randomization. In the forrest plot CI above 4 or below 0.05 cut for clarity.
Interaction p-value for randomization (Abbreviated vs Standard DAPT) for three periods (0 to 150 vs 151 to 335 days vs 336 to 425 days) modifying effect with df=2.

TABLES

Table 1. Clinical outcomes at 14 months post-randomization (15-month follow-up). *Abbreviations: DAPT, dual antiplatelet therapy; CI, confidence interval; TIA, transient ischemic attack; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction; GUSTO, Global Use of Strategies To Open Occluded Coronary Arteries; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.*

	Abbreviated DAPT	**Standard DAPT**	**Hazard ratio (95% CI)**	**p-value**	**Com-Nougue difference (95% CI)**
	N = 2295	N = 2284			
Net Adverse Clinical Events (NACE)	199 (8.7)	214 (9.5)	0.92 (0.76-1.12)	0.399	-0.75 [-2.42 to 0.93]
Major Adverse Cardiac or Cerebral events (MACCE)	158 (6.9)	167 (7.4)	0.94 (0.76-1.17)	0.579	-0.51 [-2.01 to 1.00]
Major or Clinically Relevant Nonmajor Bleeding (MCB)	167 (7.4)	239 (10.7)	0.68 (0.56-0.83)	0.0001	-3.25 [-4.93 to -1.58]
Death	83 (3.6)	100 (4.5)	0.82 (0.62-1.10)	0.191	-0.84 [-2.00 to 0.32]
Cardiovascular death	41 (1.8)	47 (2.1)	0.87 (0.57-1.32)	0.500	-0.30 [-1.12 to 0.52]
Non-cardiovascular death	33 (1.5)	42 (1.9)	0.78 (0.49-1.23)	0.285	-0.43 [-1.19 to 0.32]
Undetermined death	9 (0.4)	11 (0.5)	0.81 (0.34-1.96)	0.642	-0.13 [-0.54 to 0.28]
Cardiovascular or Undetermined death	50 (2.2)	58 (2.6)	0.86 (0.59-1.25)	0.418	-0.42 [-1.33 to 0.48]
Cerebrovascular Accident	24 (1.1)	39 (1.8)	0.61 (0.37-1.01)	0.056	-0.68 [-1.37 to 0.01]
Stroke	15 (0.7)	28 (1.3)	0.53 (0.28-0.99)	0.048	-0.59 [-1.16 to -0.02]
Ischemic Stroke	14 (0.6)	23 (1.0)	0.60 (0.31-1.17)	0.137	-0.41 [-0.94 to 0.12]
Hemorrhagic Stroke	1 (0.0)	5 (0.2)	0.20 (0.02-1.70)	0.140	-0.18 [-0.39 to 0.04]
TIA	9 (0.4)	11 (0.5)	0.81 (0.34-1.96)	0.642	-0.09 [-0.49 to 0.31]
Myocardial infarction	71 (3.2)	57 (2.6)	1.24 (0.88-1.76)	0.227	0.61 [-0.36 to 1.59]
Definite or Probable Stent Thrombosis	16 (0.7)	13 (0.6)	1.22 (0.59-2.54)	0.589	0.13 [-0.34 to 0.60]
Definite Stent Thrombosis	13 (0.6)	10 (0.5)	1.29 (0.57-2.95)	0.542	0.13 [-0.29 to 0.55]
Probable Stent Thrombosis	3 (0.1)	3 (0.1)	0.99 (0.20-4.92)	0.994	0.00 [-0.22 to 0.21]

Bleeding BARC classification					
Type 1	80 (3.6)	121 (5.4)	0.65 (0.49-0.86)	0.0027	-1.80 [-3.02 to -0.59]
Type 2	118 (5.2)	171 (7.6)	0.67 (0.53-0.85)	0.0010	-2.39 [-3.83 to -0.96]
Type 3	60 (2.7)	69 (3.1)	0.86 (0.61-1.21)	0.391	-0.43 [-1.41 to 0.55]
Type 3a	32 (1.4)	37 (1.7)	0.86 (0.53-1.37)	0.522	-0.23 [-0.96 to 0.49]
Type 3b	22 (1.0)	24 (1.1)	0.91 (0.51-1.62)	0.747	-0.10 [-0.70 to 0.49]
Type 3c	7 (0.3)	9 (0.4)	0.77 (0.29-2.07)	0.607	-0.09 [-0.44 to 0.26]
Type 4	0 (0.0)	0 (0.0)			
Type 5	2 (0.1)	9 (0.4)	0.22 (0.05-1.02)	0.053	-0.31 [-0.61 to -0.02]
Type 5a	0 (0.0)	2 (0.1)	0.20 (0.01-4.16)		-0.09 [-0.21 to 0.03]
Type 5b	2 (0.1)	7 (0.3)	0.28 (0.06-1.36)	0.116	-0.22 [-0.49 to 0.04]
Type 3 or 5	62 (2.8)	78 (3.5)	0.79 (0.56-1.10)	0.156	-0.74 [-1.76 to 0.28]
Bleeding (any)	232 (10.3)	338 (15.0)	0.66 (0.56-0.78)	<0.001	-4.73 [-6.67 to -2.78]
TIMI major or minor bleeding	46 (2.0)	54 (2.4)	0.84 (0.57-1.25)	0.399	-0.36 [-1.22 to 0.50]
TIMI minor	21 (0.9)	24 (1.1)	0.87 (0.48-1.56)	0.635	-0.13 [-0.72 to 0.45]
TIMI major	25 (1.1)	31 (1.4)	0.80 (0.47-1.36)	0.407	-0.27 [-0.92 to 0.38]
GUSTO moderate or severe bleeding	52 (2.3)	61 (2.7)	0.84 (0.58-1.22)	0.369	-0.43 [-1.34 to 0.49]
GUSTO moderate	44 (2.0)	46 (2.1)	0.95 (0.63-1.43)	0.797	-0.11 [-0.93 to 0.71]
GUSTO severe	8 (0.4)	16 (0.7)	0.50 (0.21-1.16)	0.105	-0.36 [-0.79 to 0.07]

Number of events up to 425 days post-randomization (% from Kaplan-Meier estimate). Hazard ratio from Cox's time-to-first event analyses, patients censored at death if died within 425 days or last contact if before 425 days or else at 425 days post-randomization. Only one event per type or per subtype / patient is counted. Three patients died due to SARS-CoV-9 between 335 and 425 days post-randomization (n=2 standard DAPT and n=1 abbreviated DAPT arm). An additional abbreviated DAPT patient died on 427 days post-randomization due to SARS-CoV-9, not shown in this table.

Table 2. Clinical outcomes in the 3-month of routine care period. *Abbreviations: DAPT, dual antiplatelet therapy; CI, confidence interval; TIA, transient ischemic attack; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction; GUSTO, Global Use of Strategies To Open Occluded Coronary Arteries; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.*

	Abbreviated DAPT N = 2200	**Standard DAPT** N = 2185	**Hazard ratio (95% CI)**	**p-value**
Net Adverse Clinical Events (NACE)	31 (1.4)	38 (1.8)	0.81 (0.50-1.30)	0.387
Major Adverse Cardiac or Cerebral events (MACCE)	23 (1.1)	31 (1.5)	0.74 (0.43-1.26)	0.268
Major or Clinically Relevant Nonmajor Bleeding (MCB)	26 (1.2)	32 (1.5)	0.81 (0.48-1.35)	0.414
Death	8 (0.4)	19 (1.0)	0.42 (0.18-0.95)	0.038
Cardiovascular death	4 (0.2)	3 (0.2)	1.32 (0.30-5.91)	0.714
Non-cardiovascular death	4 (0.2)	14 (0.7)	0.28 (0.09-0.86)	0.026
Undetermined death	0 (0.0)	2 (0.1)	0.20 (0.01-4.16)	0.248
Cardiovascular or Undetermined death	4 (0.2)	5 (0.3)	0.79 (0.21-2.95)	0.729
Cerebrovascular Accident	7 (0.3)	8 (0.4)	0.87 (0.32-2.40)	0.786
Stroke	3 (0.1)	5 (0.2)	0.60 (0.14-2.49)	0.478
Ischemic Stroke	3 (0.1)	5 (0.2)	0.60 (0.14-2.49)	0.478
Hemorrhagic Stroke	0 (0.0)	0 (0.0)		
TIA	4 (0.2)	3 (0.1)	1.33 (0.30-5.92)	0.712
Myocardial infarction	13 (0.6)	8 (0.4)	1.62 (0.67-3.90)	0.285
Definite or Probable Stent Thrombosis	2 (0.1)	4 (0.2)	0.50 (0.09-2.71)	0.418
Definite Stent Thrombosis	2 (0.1)	3 (0.1)	0.66 (0.11-3.96)	0.651
Probable Stent Thrombosis	0 (0.0)	1 (0.0)	0.33 (0.01-8.10)	0.498

Bleeding BARC classification				
Type 1	17 (0.8)	16 (0.7)	1.06 (0.53-2.09)	0.876
Type 2	19 (0.9)	20 (0.9)	0.94 (0.50-1.77)	0.853
Type 3	8 (0.4)	11 (0.5)	0.72 (0.29-1.80)	0.484
Type 3a	7 (0.3)	7 (0.3)	0.99 (0.35-2.83)	0.992
Type 3b	1 (0.0)	4 (0.2)	0.25 (0.03-2.22)	0.212
Type 3c	0 (0.0)	0 (0.0)		
Type 4	0 (0.0)	0 (0.0)		
Type 5	0 (0.0)	1 (0.0)	0.33 (0.01-8.10)	0.498
Type 5a	0 (0.0)	0 (0.0)		
Type 5b	0 (0.0)	1 (0.0)	0.33 (0.01-8.10)	0.498
Type 3 or 5	8 (0.4)	12 (0.6)	0.66 (0.27-1.62)	0.367
Bleeding (any)	41 (1.9)	47 (2.2)	0.87 (0.57-1.32)	0.499
Bleeding TIMI major or minor	6 (0.3)	7 (0.3)	0.85 (0.29-2.53)	0.773
Bleeding TIMI minor	6 (0.3)	3 (0.1)	1.99 (0.50-7.95)	0.331
Bleeding TIMI major	0 (0.0)	4 (0.2)	0.11 (0.01-2.04)	0.062
Bleeding GUSTO moderate or severe	4 (0.2)	11 (0.5)	0.36 (0.11-1.13)	0.081
Bleeding GUSTO moderate	4 (0.2)	9 (0.4)	0.44 (0.14-1.43)	0.174
Bleeding GUSTO severe	0 (0.0)	2 (0.1)	0.20 (0.01-4.16)	0.248

Number of events during the routine care period of 90 days (% from Kaplan-Meier estimate), excluding patients which were already permanently lost to follow-up or had withdrawn consent (n=37) or had deceased (n=156) up to and including day 335. Hazard ratio from Cox's time-to-first event analyses, patients censored at death if died between 336 days and 425 days; else censored at last contact if before 425 days; else censored at 425 days post-randomization.
Three patients died due to SARS-CoV-9 between 335 and 425 days post-randomization (n=2 standard DAPT and n=1 abbreviated DAPT arm). And additional abbreviated DAPT patient on 427 days post-randomization, not shown in this table.
Fisher's exact test and continuity corrected risk ratios (95% CI) in case of zero events in one arm.

Table 3. Clinical outcomes using a landmark analysis at 335 days (12-month follow-up). *Abbreviations: DAPT, dual antiplatelet therapy; BARC, Bleeding Academic Research Consortium; CI, confidence interval.*

	Abbreviated DAPT	Standard DAPT	Hazard ratio (95% CI)*	P value	interaction P value §
	N = 2295	N = 2284			
Net Adverse Clinical Events					0.694
0 to 335 days	172/2295 (7.5%)	182/2284 (8.0%)	0.935 (0.759-1.152)	0.527	
336 to 425 days	27/2106 (1.3%)	32/2084 (1.6%)	0.837 (0.501-1.396)	0.495	
Major Adverse Cardiovascular Events					0.241
0 to 335 days	138/2295 (6.0%)	138/2284 (6.1%)	0.993 (0.785-1.258)	0.957	
336 to 425 days	20/2139 (0.9%)	29/2128 (1.4%)	0.687 (0.389-1.214)	0.196	
Major or Clinically Relevant Nonmajor Bleeding					0.883
0 to 335 days	148/2295 (6.5%)	211/2284 (9.4%)	0.683 (0.554-0.843)	<0.001	
336 to 425 days	19/2076 (0.9%)	28/1999 (1.4%)	0.652 (0.364-1.168)	0.151	
All-cause death					0.081
0 to 335 days	75/2295 (3.3%)	81/2284 (3.6%)	0.919 (0.671-1.258)	0.597	
336 to 425 days	8/2201 (0.4%)	19/2185 (1.0%)	0.418 (0.183-0.955)	0.038	
Cerebrovascular Accident					0.303
0 to 335 days	17/2295 (0.8%)	32/2284 (1.4%)	0.526 (0.292-0.947)	0.032	
336 to 425 days	7/2188 (0.3%)	7/2162 (0.3%)	0.988 (0.347-2.818)	0.983	
Stroke					0.867
0 to 335 days	12/2295 (0.5%)	23/2284 (1.0%)	0.518 (0.258-1.040)	0.064	
336 to 425 days	3/2193 (0.1%)	5/2170 (0.2%)	0.593 (0.142-2.483)	0.475	
Myocardial infarction					0.810
0 to 335 days	60/2295 (2.7%)	49/2284 (2.2%)	1.218 (0.835-1.777)	0.305	
336 to 425 days	11/2147 (0.5%)	8/2142 (0.4%)	1.374 (0.553-3.416)	0.494	
Definite stent thrombosis					0.407

0 to 335 days	11/2295 (0.5%)	7/2284 (0.3%)	1.562 (0.605-4.029)	0.357	
336 to 425 days	2/2191 (0.1%)	3/2179 (0.1%)	0.663 (0.111-3.966)	0.652	
BARC type 3 or 5					0.620
0 to 335 days	55/2295 (2.4%)	67/2284 (3.0%)	0.812 (0.568-1.159)	0.251	
336 to 425 days	7/2164 (0.3%)	11/2135 (0.5%)	0.628 (0.244-1.621)	0.337	
BARC type 3					0.634
0 to 335 days	53/2295 (2.4%)	59/2284 (2.6%)	0.888 (0.613-1.287)	0.531	
336 to 425 days	7/2164 (0.3%)	10/2135 (0.5%)	0.691 (0.263-1.816)	0.454	
BARC type 2					0.553
0 to 335 days	102/2295 (4.5%)	152/2284 (6.8%)	0.657 (0.511-0.844)	0.001	
336 to 425 days	16/2107 (0.8%)	19/2042 (0.9%)	0.815 (0.419-1.584)	0.546	

Dare are presented as number of events/number of patients at risk (% from Kaplan-Meier estimate). The landmark is at the moment patients are expected to switch to routine care.

* Hazard ratio (95% CI) from Cox's time-to-first event analyses. using a Landmark at 335 days post-randomization.

§ Interaction P value testing for the modifying effect of randomization (Abbreviated vs Standard DAPT) and period (0 to 335 days vs 336 to 425 days).