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Title: Abbreviated Antiplatelet Therapy in Patients at High Bleeding Risk With or Without Oral Anticoagulant Therapy After Coronary Stenting An Open-Label, Randomized, Controlled Trial

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Abbreviated Antiplatelet Therapy in Patients at High Bleeding Risk With or Without Oral Anticoagulant Therapy After Coronary Stenting

An Open-Label, Randomized, Controlled Trial

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Running Title: **DAPT duration in high bleeding risk PCI patients**

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Summary A 1-month dual antiplatelet therapy compared to a 3 months or longer dual antiplatelet therapy in high bleeding risk patients results in similar ischemic but lower bleeding risk for patients with or without a clinical indication for oral anticoagulant therapy.

Twitter: @FelixMahfoud, @GoranEBC, @vlgmrc

Clinical Perspective

What is New?

- The MASTER DAPT trial investigated an abbreviated versus a nonabbreviated antiplatelet therapy (APT) strategy after coronary stenting with a sirolimus-eluting stent in an all-comer high-bleeding risk population. Patients with or without oral anticoagulation (OAC) indication were stratified at randomization (1 month after coronary stenting). Patients with OAC indication stopped triple therapy and continued dual therapy for 5 months in the abbreviated arm or continued triple therapy for at least 2 months followed by dual therapy for the remaining period in the nonabbreviated arm. Patients without OAC indication stopped dual APT (DAPT) after 1 month and continued with single APT in the abbreviated arm or continued DAPT for at least 5 months in the nonabbreviated arm.
- At 12-month follow-up, ischemic and net risk were not increased in the abbreviated antiplatelet arms of both subgroups, although significantly fewer clinically relevant bleeding events occurred in the group without OAC indication, whereas only numerically fewer bleeding events occurred in the group with OAC indication. However, after correction for nonadherence, significantly fewer bleeding events were also observed in the abbreviated APT arm of the OAC subgroup.
- Furthermore, the 6-month landmark censor weight analysis of the OAC subgroup showed that stopping APT at 6 months in the OAC therapy group significantly reduced bleeding events without additional ischemic risk.

What Are the Clinical Implications?

- The MASTER DAPT trial provides additional evidence that in patients with indication for OAC, triple therapy beyond 1 month after coronary stenting is harmful with respect to bleeding events, and that APT can be safely stopped at 6 months.
- In patients at high bleeding risk without indication for OAC, 1 month of DAPT followed by single APT results in fewer clinically relevant bleeding events with no additional ischemic risk.

ABSTRACT

BACKGROUND: The optimal duration of antiplatelet therapy (APT) in high bleeding risk patients with or without oral anticoagulation (OAC) after coronary stenting remains unclear.

METHODS: We randomized 4579 high bleeding risk patients who received 1-month of dual APT (DAPT) after coronary stenting to an abbreviated APT regimen (immediate transition to single APT for 5 months in patients with an OAC indication or for 11 months in patients without an OAC indication) or nonabbreviated APT regimen (≥2 months of DAPT and single APT thereafter in patients with an OAC indication or ≥5 months of DAPT in patients without an OAC indication and single APT thereafter). Coprimary outcomes at 335 days after randomization were: net adverse clinical outcomes (NACE; composite of all-cause death, myocardial infarction, stroke, and Bleeding Academic Research Consortium [BARC] 3 or 5 bleeding events); major adverse cardiac and cerebral events (MACCE; all-cause death, myocardial infarction, and stroke); and type 2, 3, or 5 BARC bleeding. Randomization was stratified by concomitant OAC indication. Censor-weights analyses were performed to correct for nonadherence to the allocated regimens.

RESULTS: NACE or MACE did not differ with abbreviated versus nonabbreviated APT regimens in patients with OAC indication (n=1666; HR, 0.83; 95% CI, 0.60 to 1.15, HR, 0.88; 95% CI, 0.60 to 1.30; respectively) or without OAC indication (n=2913; HR, 1.01; 95% CI, 0.77 to 1.33; HR, 1.06; 95% CI, 0.79 to 1.44; $P_{interaction}$=0.35 and 0.45, respectively). BARC 2,3 or 5 bleeding did not differ in patients with OAC indication (HR, 0.83; 95% CI, 0.62 to 1.12) but was lower with abbreviated APT in patents without OAC indication (HR, 0.55; 95% CI, 0.41 to 0.74; $P_{interaction}$=0.057). Results for NACE and MACCE remained consistent in censor-weights analyses, but bleeding was reduced with abbreviated APT in patients with (HR, 0.67, 0.48 to 0.93) and without (HR, 0.40, 0.23 to 0.69, $P_{interaction}$=0.11) OAC indication.

CONCLUSIONS: Abbreviated APT was associated with similar NACE and MACE rates but with lower bleeding rates versus nonabbreviated APT in high bleeding risk patients with or without OAC.

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Nonstandard Abbreviations And Nonstandard Acronyms

APT, antiplatelet therapy

BARC, Bleeding Academic Research Consortium

CI, confidence interval

DAPT, dual antiplatelet therapy

HR, hazard ratio

MACCE, major adverse cardiac and cerebral events

MASTER DAPT, Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen

NACE, net adverse clinical outcomes

NARC, nonadherence Academic Research Consortium

NOAC, nonvitamin K antagonist oral anticoagulant

NSAID, nonsteroidal anti-inflammatory drug

OAC, oral anticoagulation

VKA, vitamin K antagonist

Introduction

Patients undergoing coronary stenting for obstructive coronary artery disease require dual antiplatelet therapy (DAPT), comprising aspirin and a $P2Y_{12}$ receptor blocker, for a certain period to reduce the risk of ischemic events such as stent thrombosis. The optimal duration of antiplatelet therapy (APT) after implantation of drug-eluting coronary stents remains a matter of debate, especially in patients at high risk for bleeding, which is associated with a three- to fivefold increased risk of death.[1, 2] Approximately 10% of patients undergoing coronary stent implantation have an indication for oral anticoagulation (OAC), mainly because of concomitant atrial fibrillation.[3] These patients present with a clinical dilemma because of the need to combine APT with OAC therapy. OAC therapy *per se* is associated with increased risk of bleeding and adding APT further amplifies that risk.[4] Patients without OAC therapy but aged ≥75 years and/or with renal insufficiency, active cancer, blood disorders, bleeding history, need for surgery, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids, and cerebral infarcts constitute another large group at high risk of bleeding post coronary stenting.[5]

Little evidence exists on the optimal combination and duration of APT in patients at high bleeding risk with and without OAC therapy after coronary artery stenting. Only two relatively small-sized, randomized, controlled trials have investigated the combination of a vitamin K antagonist (VKA) and APT, with discordant results.[6, 7] With the advent of more potent $P2Y_{12}$ inhibitors and nonvitamin K antagonist oral anticoagulants (NOACs), finding the optimal antithrombotic therapy post coronary stenting has become more complex. Four randomized trials with different NOACs in patients with atrial fibrillation undergoing coronary stenting or treatment for acute coronary syndrome focused primarily on dual therapy with a NOAC and a $P2Y_{12}$ inhibitor (mainly clopidogrel) versus triple therapy with VKA and dual APT (DAPT).[8-11] Meta-analyses of these four trials show that dual therapy, after up to 1 week of triple therapy, significantly reduced the risk of bleeding compared with prolonged (i.e. mainly 6 months or more) triple therapy, at the cost of a significant increase in stent thrombosis and a borderline higher risk of myocardial infarction.[12-14] Therefore, the optimal duration of APT remains to be determined.

The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT) trial was designed to investigate the safety of abbreviated versus nonabbreviated APT in high-bleeding risk

patients undergoing coronary stenting. The trial protocol provided differential APT recommendations for patients at high bleeding risk with or without an indication for OAC therapy and stratified randomization accordingly. In this prespecified analysis, we assessed the treatment effects of abbreviated versus nonabbreviated APT regimens in patients with or without a concomitant indication for OAC.

Methods

Study design

The MASTER DAPT trial (ClinicalTrials.gov number, NCT03023020) was an investigator-initiated, randomized, open-label, noninferiority trial with sequential superiority testing in largely unselected patients at high bleeding risk who underwent implantation with a biodegradable polymer-coated Ultimaster™ (Terumo Corporation, Tokyo, Japan) sirolimus-eluting stent.[15] The trial was performed at 140 sites in 30 countries across Europe, South America, the Middle East, Asia, and Australia. Ethics approval was obtained in each country and center. All patients gave written informed consent. An independent data safety monitoring board regularly reviewed the conduct of the trial and the safety of the patients. Trial organization and participating sites are mentioned in Data Supplement I .

Patients

Patients at high risk for bleeding who underwent treatment of all planned coronary artery stenoses with Ultimaster stent implantation for acute or chronic coronary syndromes were eligible if they remained event-free until the time of randomization at 1 month after the index procedure. Patients were considered at high bleeding risk if at least one of the following criteria applied: OAC (VKA or NOAC) therapy for at least 12 months, recent (<12 months) nonaccess site bleeding episode(s) that required medical attention, previous bleeding episode(s) that required hospitalization if the underlying cause had not been definitively treated, age ≥75 years, systemic conditions associated with an increased bleeding risk (e.g. hematological 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 NSAIDs, diagnosed malignancy (other than skin), stroke at any time or transient ischemic attack in the previous 6 months, and PRECISE DAPT score ≥25.[16] Exclusion criteria were minimal and limited to

implantation of a nonstudy stent within the previous 6 months or a bioresorbable scaffold at any time before the index procedure, or if they underwent treatment because of an in-stent restenosis or stent thrombosis. Detailed inclusion and exclusion criteria are provided in the Data Supplement II.

Randomization, masking, and procedures

Patients were centrally randomized (1:1 ratio) to an open-label abbreviated or nonabbreviated 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 block sizes of 2, 4, or 6, and were stratified by site, history of acute myocardial infarction within 12 months, and indication for at least 12 months of OAC therapy.

Patients with an indication for OAC therapy who were randomly allocated to receive abbreviated treatment immediately discontinued DAPT and continued single APT for 6 months after the index procedure, and continued thereafter with OAC monotherapy. Patients on OAC therapy who were randomly allocated to receive nonabbreviated treatment continued DAPT until at least 3 months after the index stent procedure (i.e. at least 2 months after randomization) and continued thereafter with single APT until 12 months after the index procedure. Patients without an indication for OAC who were randomly allocated to the abbreviated group immediately discontinued DAPT and continued with single APT until 12 months after the index procedure. Patients without an indication for OAC who were randomly allocated to the nonabbreviated group continued DAPT for at least 6 months post index procedure (i.e. ≥5 months after randomization), after which single APT with aspirin was continued. All antiplatelet and OAC treatment options were dosed according to the corresponding authorization for use and locally approved regimens.

Follow-up visits occurred at 60±14 and 150±14 days after randomization, preferably as on-site visits, and at 335±14 days after randomization, exclusively as an on-site visit. Two independent clinical research organizations (CERC, Massy, France and Cardialysis, Rotterdam, the Netherlands) 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. All data was stored at a central database (CTU, Bern, Switzerland).

Outcomes

Coprimary outcomes were net adverse clinical outcomes (NACE), defined as the composite of all-cause death, myocardial infarction, stroke, and Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding events[17]; major adverse cardiac and cerebral events (MACCE), expressed as a composite of all-cause death, myocardial infarction, and stroke; and major or clinically relevant nonmajor bleeding, defined as a composite of type 2, 3, or 5 BARC bleeding events.

The secondary outcomes include the individual components of the three coprimary outcomes; the composite of cardiovascular death, myocardial infarction, and stroke; the composite of cardiovascular death, myocardial infarction, definite or probable stent thrombosis, and any revascularization; the composite of stroke and transient ischemic attack; and all bleeding events, adjudicated according to the BARC classifications.[17] All outcomes were prespecified.[15] All analyses evaluated the occurrence of the adjudicated outcomes between randomization and 335 days.

Statistical analysis

The data were analyzed according to the intention-to-treat principle. Outcomes were assessed separately for patients with and without indication for OAC therapy by calculating hazard ratios (HR) with 95% confidence intervals (CI).

The Com-Nougue method[18] was used to analyze time to event and calculate event rates and *P* values. Censor-weights analyses were performed to correct for nonadherence to the allocated treatment regimen. To derive censor-weighted estimates, patients were censored after the first major nonadherence (nonadherence Academic Research Consortium [NARC] 2 or 3[19]) and "replaced" by adherent patients for each day *t* using censor weights from four models (one model for each randomization arm in the two subgroups). Censor-weighted estimates were then derived from patient identifier cluster-robust logistic regressions for the first occurrence of the outcome at each day *t* (with *t*≤day of first occurrence of NARC 2 or 3; or if not applicable, *t*≤day of death; or if not applicable *t*≤last information on adherence; patients were removed from the risk set after the first occurrence of the outcome). See the Data Supplement II and Tables I and II in the online-only Data Supplement for more details.

Role of the funding source

The study was sponsored by the European Cardiovascular Research Institute (ECRI), a nonprofit organization, and received grant support from Terumo. The sponsor and funder had no role in the study design, data collection, data monitoring, analysis, interpretation, or writing of the report.

Results

From 28 February 2017 to 5 December 2019, 5204 patients were screened and 4579 (88.1%) were randomized a median of 34 days (interquartile range, 32 to 39) post stenting, of which 1666 (36.4%) patients had an indication for OAC and 2913 (63.6%) had no indication for OAC. Of the 1666 patients with OAC therapy, 848 were assigned to the abbreviated APT group and 818 to the nonabbreviated APT group (Figure 1). Of the 2913 patients without OAC, 1447 were assigned to the abbreviated APT group and 1466 to the nonabbreviated APT group. Complete follow-up in the OAC subgroup was 99.3% for the abbreviated APT arm and 98.8% for the nonabbreviated APT arm, and 99.4% and 99.5%, respectively, in the subgroup without OAC.

Baseline and procedural characteristics are described in Tables 1 and 2 and Table III in the online-only Data Supplement. The overall mean±SD age was 76.0±8.7 years. On average, 33.6% of patients received treatment for diabetes. The indication for coronary stenting was acute coronary syndrome for 48.3% of patients. Atrial fibrillation was present in 84.2% of patients in the OAC group.

In the OAC group, 64.9% of the patients received a NOAC and 33.5% a VKA (Table IV in the online-only Data Supplement), largely in combination with clopidogrel (98.8%) in the abbreviated group or aspirin plus clopidogrel (97.4%) in the nonabbreviated group. In the non-OAC group, aspirin plus clopidogrel (67.8%) was the most frequently implemented regimen, followed by aspirin and ticagrelor (28.4%) (Table V in the online-only Data Supplement). Median durations of DAPT since coronary stenting were 33 days (IQR, 30 to 39) in patients with OAC and 34 days (IQR, 31 to 40) in patients without OAC in the abbreviated arm; and 96 days (IQR, 90 to 114) and 364 days (IQR, 190 to 369), respectively, in the nonabbreviated group. Detailed information on antiplatelet use is shown in Figure 2.

Adherence to the allocated antiplatelet regimen decreased over time and was lower in the abbreviated versus nonabbreviated group at 12 months in the OAC subgroup (82.7% vs 95.8%; *P*<0.001, respectively). Detailed information on adherence is depicted in Figure I and Tables V and VI

in the online-only Data Supplement, with 16.1% of the patients with an OAC indication who still used APT at the 11 months visit post randomization in the abbreviated arm.

Outcomes among patients with OAC indication

Clinical outcomes at 12 months in OAC patients are shown in Table 3. NACE occurred in 68 (8.0%) patients in the abbreviated arm versus 78 (9.6%) patients in the nonabbreviated arm (HR, 0.83; 95% CI, 0.60 to 1.15; *P*=0.26) (Figure 3A). MACCE did not differ, occurring in 50 (5.9%) patients in the abbreviated arm versus 54 (6.7%) patients in the nonabbreviated arm (HR, 0.88; 95% CI, 0.60 to 1.30; *P*=0.53) (Figure 3B). BARC 2, 3, or 5 bleeding occurred in 83 (9.9%) patients in the abbreviated arm versus 94 (11.7%) patients in the nonabbreviated arm (HR, 0.83; 95% CI, 0.62 to 1.12; *P*=0.25) (Figure 3C). Fewer cerebrovascular events occurred in the abbreviated arm (*P*=0.01). Other outcomes did not differ between groups.

Subgroup analyses showed a significant benefit in terms of NACE for patients with chronic kidney disease on abbreviated APT ($P_{interaction}$=0.02) (Figure IIA in the online-only Data Supplement). No other differences in terms of MACCE or BARC 2, 3, or 5 bleeding were noted (Figures IIIA and IVA in the online-only Data Supplement).

Landmark analyses at 150 days after randomization showed consistent treatment effects for the coprimary and secondary endpoints with respect to time among patients with an indication for OAC (Table VII in the online-only Data Supplement).

Outcomes among patients without an OAC indication

Clinical outcomes at 12 months in patients without an OAC indication are shown in Table 3. NACE did not differ between the abbreviated and nonabbreviated APT groups (104 [7.2%] vs 104 [7.1%], respectively; HR, 1.01; 95% CI, 0.77 to 1.33; *P*=0.91) (Figure 3A). MACCE also did not differ between the treatment groups (88 [6.1%] vs 84 [5.7%]; HR, 1.06; 95% CI, 0.79 to 1.44; *P*=0.67) (Figure 3B). BARC 2, 3, and 5 bleeding occurred less frequently in the abbreviated arm (65 [4.6%] vs 117 [8.1%]; HR, 0.55; 95% CI, 0.41 to 0.74; *P*<0.001) (Figure 3C). Fewer BARC 1 and BARC 2 bleedings occurred in the abbreviated APT arm (*P*=0.001 and *P*<0.001, respectively).

Subgroup analyses showed no differences in terms of NACE, MACCE, or BARC 2, 3 or 5 bleeding events, although a borderline treatment effect was noted in favor of female sex for MACCE ($P_{interaction}$=0.05; Figures IIB, IIIB and IVB in the online-only Data Supplement).

Landmark analyses at 150 days after randomization showed consistent treatment effects with respect to time for the coprimary and secondary endpoints among patients without an indication for OAC (Table VII in the online-only Data Supplement).

Consistency of treatment effects between OAC and non-OAC patients

The treatment effects between abbreviated and nonabbreviated APT were consistent in patients with or without an OAC indication, except for the coprimary endpoint of BARC 2, 3, or 5 bleeding and the secondary endpoint of BARC 2 bleeding. Both were lower in patients with an OAC indication, with a borderline ($P_{interaction}$=0.057) and significant ($P_{interaction}$=0.021) interaction test, respectively.

The coprimary endpoint of BARC 2, 3, or 5 bleedings was twofold higher in the OAC versus non-OAC therapy subgroup, whereas first ischemic events occurred at similar rates in both subgroups (Figures 3B and 3C).

Censor-weight model and per-protocol population

In censor-weighted analyses, the differences in NACE and MACCE remained nonsignificant between antiplatelet regimens in patients with or without OAC. Significantly fewer BARC 2, 3, or 5 bleedings occurred in the abbreviated versus nonabbreviated arm in patients on OAC therapy (HR, 0.67; 95% CI, 0.48 to 0.93; *P*=0.018) and not on OAC therapy (HR, 0.40; 95% CI, 0.23 to 0.69; *P*<0.001; $P_{interaction}$=0.11) (Table 4, Figure V in the online-only Data Supplement). The unadjusted (Table VIII in the online-only Data Supplement) and adjusted (Table 4) coprimary findings remained unchanged in the per-protocol population. An overview of protocol violations used to define the per-protocol population are summarized in Table IX in the online-only Data Supplement.

Censor-weighted landmark analyses showed consistent treatment effects with respect to time for the coprimary and secondary endpoints in patients with or without an OAC indication, with no greater risk of NACE or MACE before or after 150 days since randomization and consistently fewer bleeding events (Table X in the online-only Data Supplement).

Discussion

The main findings of this subgroup analysis from the MASTER DAPT trial are threefold. First, an abbreviated APT strategy, stopping DAPT at 1 month post coronary stenting with a biodegradable

polymer coated sirolimus-eluting stent, has a consistent and similar effect on the occurrence of ischemic and net events in patients with or without OAC therapy. Second, stopping DAPT at 1 month and continuing with single APT significantly reduces clinically relevant bleeding risk in high bleeding risk patients without an indication for OAC, as well as in patients with indication for OAC after adjustment for nonadherence. Third, stopping single APT 6 months after coronary stenting significantly reduces clinically relevant bleeding events in patients with an indication for OAC. These findings have the following implications: our results show that it is safe and beneficial to stop DAPT after 1 month in patients at high bleeding risk with or without an indication for OAC, and that it is safe and beneficial to stop all APT after 6 months in patients on OAC.

Patients at high bleeding risk constitute a considerable proportion of those undergoing coronary stenting.[20] This high-bleeding-risk population comprises a heterogenous group in which two large subgroups can be identified based on the need, or not, for concomitant OAC therapy. The need for APT in combination with OAC therapy increases bleeding risk,[3, 21] whereas OAC therapy alone post stenting is insufficient in preventing ischemic complications such as stent thrombosis.[22, 23] Therefore, guidelines[24-26] recommend different APT strategies for patients at high bleeding risk after coronary stenting depending on whether they receive APT or OAC therapy. Based on these recommendations, the MASTER DAPT trial was designed as an all-comer high-bleeding-risk trial with two APT strategies for each stratified subgroup: patients without an indication for OAC who were allocated to the nonabbreviated APT regimen received DAPT for a minimum of 6 months, consistent with the guidelines. Patients allocated to the experimental abbreviated APT therapy arm received 1 month of DAPT, similar to other recent high-bleeding-risk trials investigating an abbreviated DAPT regimen.[20, 27, 28] However, in the OAC subgroup, the duration of therapy in the nonabbreviated APT arm (with a minimum of 3 months of DAPT) is longer than recommended in the current North-American guidelines[24] and European non−ST-segment elevation myocardial infarction[25] and atrial fibrillation guidelines,[26] which recommend DAPT for 1 week to 1 month in patients on OAC. No previous trial has investigated the value of 1 month versus 3 months of DAPT in the OAC population. The ISAR-TRIPLE compared 6 weeks of clopidogrel with 6 months of clopidogrel in 614 patients receiving aspirin and OAC after drug-eluting stent implantation; the authors found no difference between treatment strategies for the composite of death, myocardial infarction, stroke, stent thrombosis, or major bleeding.[6] Therefore, the recommendation of a very short (i.e. 1 week) duration

of DAPT in OAC patients after percutaneous coronary intervention or an acute coronary syndrome in the current NOAC era is supported by the findings of four studies.[8-11] Three of these studies[8, 9, 11] tested a very short duration of triple therapy consisting of aspirin, NOAC, and a $P2Y_{12}$ inhibitor, followed by continuation of the latter two drugs, versus a very long duration of triple therapy comprising aspirin, VKA, and a $P2Y_{12}$ inhibitor for mainly 6 months or longer. The AUGUSTUS trial is the largest among the four and the only study that disentangled the effect of OAC type from duration of aspirin treatment.[8] When data from these studies are pooled, they show a major reduction in bleeding events with a very short duration of triple therapy. However, they also show higher rates of stent thrombosis, likely clustered in the first few weeks after aspirin discontinuation,[29] which are consistently observed in patients with or without an acute coronary syndrome.[12] Our findings are in concert with observational data,[30] showing no rebound of ischemic events after 1 month of DAPT in OAC patients. Furthermore, no previous trial has investigated the value of no APT versus single APT after 6 months in an OAC population. Our present study shows that stopping APT after 6 months is safe and beneficial and supports the current recommendation (level of evidence C) in the European guidelines[25, 26] to consider stopping APT after 6 months.

In our trial of an all-comer population at high bleeding risk, we observed a twofold higher bleeding rate in the OAC subgroup compared with the non-OAC subgroup. This can be explained in part by the relative long DAPT regimens in the nonabbreviated APT arm of this subgroup but not for the abbreviated APT arm. Furthermore, most patients on OAC were treated with a NOAC (64.9%) and no outcome differences were noted between patients on VKA or NOAC medications (data not shown). The increased bleeding risk of patients on OAC versus not on OAC emphasizes the importance of defining the optimal APT duration and combination in this subgroup who are already categorized as at high bleeding risk.

An interesting finding is the reduced risk of ischemic stroke in the abbreviated APT arm of the OAC subgroup (P=0.03). A similar observation was noted in the WOEST trial (P=0.056).[7] Whether this paradoxical finding relates to lower dosing of VKA or NOAC in the nonabbreviated DAPT arm or is a result of chance of this low frequent event remains to be determined.

In this study, we used inverse-cumulative probability censor-weights to correct for nonadherence to the allocated medication. Nonadherence often occurs in randomized trials and can have important implications for the results. In general, nonadherence of <20% is considerate

acceptable; however, the cut-off of 20% is arbitrary and encompasses several reasons as to why nonadherence occurred. Nonadherence due to medical reasons (e.g. changing medication after an event at the end of the follow-up period) has a different implication than not adhering to the allocated regimen without medical reasons at the start of the study (e.g. misunderstanding the study protocol by the doctor or the instructions by the patient). Consequently, nonadherence is classified on four levels (type of nonadherence, person who took the decision, reason for nonadherence, and timing).[19] In the MASTER DAPT trial, nonadherence was carefully monitored and classified. A significant drop in adherence was observed in the abbreviated APT arm of the OAC subgroup. A considerable number of patients continued APT after 6 months, whereas the protocol stipulated stopping at 6 months. In both subgroups the temporary (NARC 2) and permanent discontinuation (NARC 3) types of nonadherence were evaluated and classified. Patients with NARC 2 or NARC 3 nonadherence without medical reasons were corrected in the censor-weights model by replacing those patients with similar patients who were adherent. Censor-weighted correction is a validated tool to attenuate the potential bias of nonadherence. For the specific abbreviated APT arm in the OAC subgroup, this correction retrieved the population of patients that should have discontinued APT after 6 months. After this censor-weights correction, stopping APT after 6 months resulted in fewer bleedings without compromising ischemic risk. In all other arm much fewer NARC2 or 3 nonadherences were observed, and accordingly censor-weighted model corrections did not affect the results.

Limitations

Several limitations must be acknowledged. This was a subgroup analysis (albeit the investigated subgroups were prespecified and stratified at randomization). The subgroups were not powered for the coprimary outcomes and the results should therefore be interpreted with caution. Treatment allocation was open label, which reflects a treatment-strategy trial and the impossibility of masking treatment for three oral $P2Y_{12}$ inhibitors and aspirin. Nonadherence to the allocated APT regimen occurred more often in the abbreviated DAPT arm of the OAC subgroup, for which a censor-weighted correction was implemented. Our trial included patients at high risk for bleeding who underwent biodegradable polymer sirolimus-eluting stent implantation; consequently, our results may not extend to patients who are not at high bleeding risk or received other stent types.

Conclusions

In an all-comer high bleeding risk population with minimal angiographic restrictions, stopping DAPT 1 month after coronary stenting was associated with lower bleeding risk without additional ischemic risk in patients with or without OAC. Stopping APT after 6 months in patients on OAC was also associated with lower bleeding risk and without additional ischemic risk.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement I: MASTER DAPT trial: committees and investigators

Data Supplement II: Additional information on the methods

Data Supplement Tables I to X

Data Supplement Figures I to V

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Figure legends

Figure 1. Patient Flow

M1=1 month after index coronary stent procedure, meaning the last intended coronary stent implantation. *Did not start within 14 days of randomization, or nonpermitted alternative regimen due to event within 14 days from randomization. †At day 335 or on allowed alternative regimen due to, for example, prior events; if not recorded on exactly day 335, the last information on adherence is used.

Figure 2. Antiplatelet Use Per Day Since Randomization for Patients With and Without Oral Anticoagulation Therapy

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

Figure 3. Kaplan-Meier Curves of the three coprimary outcomes at 11 months post-randomization (12-month follow-up): (A) net adverse clinical events; (B) Major Cardiovascular Events; and (C) Major or Clinically Relevant Nonmajor Bleeding

Figure 4. Forest Plot of the 6-month Landmark Analysis Using Censor-Weights for Net Adverse Clinical Events; Major Adverse Cardiac and Cerebral Events; and Major or Clinically Relevant Nonmajor Bleeding at 11 Months Post-Randomization (12-Month Follow-Up)

$P_{interaction}$ values from intention-to-treat population.

Table 1. **Baseline Characteristics According to Presence or Absence of Clinical Indication for OAC**

Characteristic	Indication for OAC		No indication for OAC		*P* value
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	(OAC vs APT subgroup)
Age, years	73.5 (8.8)	73.3 (9.5)	77.7 (8.3)	77.5 (8.0)	<0.001
Male sex	636 (75.0%)	612 (74.8%)	954 (65.9%)	969 (66.1%)	<0.001
Body mass index, kg/m²	28.6 (4.9)	28.5 (4.8)	26.5 (4.4)	26.8 (4.6)	<0.001
Family history of coronary artery disease	244 (28.8%)	217 (26.5%)	312 (21.6%)	336 (22.9%)	<0.001
Arterial hypertension	669 (78.9%)	652 (79.7%)	1097 (75.8%)	1135 (77.4%)	0.04
Uncontrolled hypertension	50 (5.9%)	36 (4.4%)	69 (4.8%)	81 (5.5%)	1.00
Diabetes mellitus	279 (32.9%)	283 (34.6%)	475 (32.8%)	501 (34.2%)	0.90
Hyperlipidemia	581 (68.5%)	559 (68.3%)	961 (66.4%)	996 (67.9%)	0.39
Smoking status					<0.001
Never	405 (47.8%)	395/817 (48.3%)	781/1442 (54.2%)	843/1459 (57.8%)	<0.001
Previous	344 (40.6%)	348/817 (42.6%)	530/1442 (36.8%)	506/1459 (34.7%)	<0.001
Current	99 (11.7%)	74/817 (9.1%)	131/1442 (9.1%)	110/1459 (7.5%)	0.02
Left ventricular ejection fraction, %	51.2 (12.3) (n=805)	50.2 (12.4) (n=779)	54.8 (10.7) (n=1364)	54.6 (11.1) (n=1349)	<0.001
Medical history					
Peripheral vascular disease*	117 (13.8%)	81 (9.9%)	126 (8.7%)	161 (11.0%)	0.04

Characteristic	Indication for OAC		No indication for OAC		*P* value (OAC vs APT subgroup)
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	
Carotid artery disease	56 (6.6%)	39 (4.8%)	64 (4.4%)	105 (7.2%)	0.04
Heart failure	222 (26.2%)	233 (28.5%)	207 (14.3%)	205 (14.0%)	0.04
Myocardial infarction	172 (20.3%)	169 (20.7%)	262 (18.1%)	261 (17.8%)	0.04
PCI	241 (28.4%)	197 (24.1%)	353 (24.4%)	397 (27.1%)	0.70
Cerebrovascular event	124 (14.6%)	105 (12.8%)	144 (10.0%)	197 (13.4%)	0.05
Stroke	88 (10.4%)	76 (9.3%)	105 (7.3%)	141 (9.6%)	0.12
Transient ischemic attack	42 (5.0%)	31 (3.8%)	44 (3.0%)	53 (3.6%)	0.07
Undetermined cerebrovascular event	5 (0.6%)	5 (0.6%)	6 (0.4%)	13 (0.9%)	1.00
Arterial thromboembolism	15 (1.8%)	9 (1.1%)	16 (1.1%)	15 (1.0%)	0.26
Venous thromboembolism	83 (9.8%)	83 (10.1%)	41 (2.8%)	32 (2.2%)	<0.001
Coronary artery bypass graft surgery	85 (10.0%)	74 (9.0%)	85 (5.9%)	97 (6.6%)	<0.001
Prosthetic mechanical heart valve	33 (3.9%)	47 (5.7%)	10 (0.7%)	11 (0.8%)	<0.001
Aortic valve stenosis	36/763 (4.7%)	48/735 (6.5%)	55/1306 (4.2%)	56/1316 (4.3%)	0.05
Bleeding before/after qualifying PCI	76 (9.0%)	72 (8.8%)	108 (7.5%)	103 (7.0%)	0.05
Chronic pulmonary disease	101 (11.9%)	102 (12.5%)	154 (10.6%)	181 (12.3%)	0.50
Chronic kidney disease[†]	156 (18.4%)	156 (19.1%)	262 (18.1%)	302 (20.6%)	0.61

Characteristic	Indication for OAC		No indication for OAC		*P* value (OAC vs APT subgroup)
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	
Liver disease	12 (1.4%)	14 (1.7%)	17 (1.2%)	18 (1.2%)	0.35
Atrial fibrillation	726 (85.6%)	677 (82.8%)	44 (3.0%)	43 (2.9%)	<0.001
History of cancer	96 (11.3%)	101 (12.3%)	252 (17.4%)	250 (17.1%)	<0.001
Active cancer	24 (2.8%)	24 (2.9%)	86 (5.9%)	102 (7.0%)	<0.001
Hematological or coagulation disorder	77 (9.1%)	80 (9.8%)	213 (14.7%)	208 (14.2%)	<0.001
Chronic treatment with steroids or NSAIDs	65 (7.7%)	76 (9.3%)	137 (9.5%)	163 (11.1%)	0.05
Prior VKA treatment	317 (37.4%)	290 (35.5%)	10 (0.7%)	9 (0.6%)	<0.001
PRECISE-DAPT score‡	24.9 (11.2)	24.7 (11.3)	28.0 (10.6)	27.8 (10.7)	<0.001
Prior bleeding	61 (7.2%)	57 (7.0%)	104 (7.2%)	98 (6.7%)	0.86
Hemoglobin, g/L	13.6 (1.8)	13.6 (1.7)	13.0 (1.8)	13.0 (1.8)	<0.001
White blood cell count,‡ $\times 10^9$/L	8.6 (18.0)	8.0 (2.7)	8.1 (4.3)	8.1 (3.7) (n=1465)	0.49
Creatinine clearance,§ mL/min/1.73 m²	71.8 (23.3)	71.9 (23.1)	70.1 (24.4)	70.5 (24.7)	0.04

Data are mean (SD), n (%), or n/n (%) in case of missing data.

Abbrev indicates abbreviated; DAPT=dual antiplatelet therapy; NSAID=nonsteroidal anti-inflammatory drug; OAC=oral anticoagulation medication; PCI=percutaneous coronary intervention; PRECISE-DAPT=predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy; SD=standard deviation; VKA=vitamin K antagonist.

*Defined as intermittent claudication, peripheral artery bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (≥6 cm), ankle brachial index ≤0.90, and aortic plaque.

†Defined as kidney damage (pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or estimated glomerular filtration rate <60 mL/min/1.73 m² for ≥3 months. ‡Calculated at screening visit; n=1 PRECISE Score calculated without risk due to white blood cell. §Modification of Diet in Renal Disease.

Table 2. Procedural Characteristics According to Presence or Absence of Clinical Indication for OAC

Characteristic	Indication for OAC		No indication for OAC		*P* value
	Abbreviated DAPT (n=848)	Nonabbreviated DAPT (n=818)	Abbreviated DAPT (n=1447)	Nonabbreviated DAPT (n=1466)	
Clinical presentation*					<0.001
Stable angina	364 (42.9%)	367 (44.9%)	558 (38.6%)	560 (38.2%)	
Silent ischemia	101 (11.9%)	131 (16.0%)	144 (10.0%)	143 (9.8%)	
NSTEMI	207 (24.4%)	168 (20.5%)	388 (26.8%)	390 (26.6%)	
STEMI	67 (7.9%)	72 (8.8%)	206 (14.2%)	193 (13.2%)	
Unstable angina	109 (12.9%)	80 (9.8%)	151 (10.4%)	180 (12.3%)	
Clinical status*					
Killip class II, III, or IV	89 (10.5%)	90 (11.0%)	163 (11.3%)	164 (11.2%)	0.63
Cardiac arrest	9 (1.1%)	12 (1.5%)	17 (1.2%)	20 (1.4%)	1.00
Heart rate, bpm	76.1 (18.8)	76.5 (18.2)	72.0 (14.7) (n=1446)	72.3 (15.2) (n=1462)	<0.001
SBP, mmHg	134.7 (24.6) (n=846)	134.7 (24.4) (n=817)	139.0 (26.4) (n=1443)	138.1 (25.5) (n=1461)	<0.001
Procedural characteristics*					
Arterial access site					0.31
Femoral	122 (14.4%)	101 (12.3%)	238 (16.4%)	192 (13.1%)	
Radial	725 (85.5%)	715 (87.4%)	1205 (83.3%)	1269 (86.6%)	
Brachial	1 (0.1%)	2 (0.2%)	4 (0.3%)	5 (0.3%)	
IABP	8 (0.9%)	8 (1.0%)	16 (1.1%)	22 (1.5%)	0.32
LVAD	1 (0.1%)	2 (0.2%)	1 (0.1%)	4 (0.3%)	1.00
Total amount of contrast, mL	168.4 (78.5) (n=841)	171.0 (81.3) (n=810)	168.0 (81.5) (n=1434)	164.5 (78.3) (n=1452)	0.17

Characteristic	Indication for OAC		No indication for OAC		*P* value
	Abbreviated DAPT (n=848)	Nonabbreviated DAPT (n=818)	Abbreviated DAPT (n=1447)	Nonabbreviated DAPT (n=1466)	
Medications during the procedure*					
Unfractionated heparin	809 (95.4%)	782 (95.6%)	1375 (95.0%)	1390/1465 (94.9%)	0.43
Bivalirudin	3 (0.4%)	1 (0.1%)	2 (0.1%)	1/1465 (0.1%)	0.27
LMWH	27 (3.2%)	26 (3.2%)	36 (2.5%)	38/1465 (2.6%)	0.22
Cangrelor	5 (0.6%)	2 (0.2%)	3 (0.2%)	1/1465 (0.1%)	0.11
Glycoprotein II/IIIa inhibitor	28 (3.3%)	21 (2.6%)	58 (4.0%)	55/1465 (3.8%)	0.11
Total number of PCI†					0.002
1	789 (93.0%)	757 (92.5%)	1304 (90.1%)	1309 (89.3%)	
2	57 (6.7%)	60 (7.3%)	134 (9.3%)	154 (10.5%)	
3	2 (0.2%)	1 (0.1%)	9 (0.6%)	3 (0.2%)	
Number of vessels treated per patient*					0.09
1	648 (76.4%)	607 (74.2%)	1068 (73.8%)	1042 (71.1%)	
2	166 (19.6%)	177 (21.6%)	317 (21.9%)	364 (24.8%)	
3	34 (4.0%)	34 (4.2%)	62 (4.3%)	60 (4.1%)	
Treated vessel(s)					
Left main	50 (5.9%)	44 (5.4%)	76 (5.3%)	90 (6.1%)	1.00
LAD artery	449 (52.9%)	442 (54.0%)	791 (54.7%)	829 (56.5%)	0.17
Left circumflex artery	248 (29.2%)	246 (30.1%)	404 (27.9%)	443 (30.2%)	0.69
Right coronary artery	301 (35.5%)	284 (34.7%)	553 (38.2%)	522 (35.6%)	0.24
Bypass graft	15 (1.8%)	19 (2.3%)	23 (1.6%)	19 (1.3%)	0.15
Number of treated lesions					0.15

Characteristic	Indication for OAC		No indication for OAC		*P* value
	Abbreviated DAPT (n=848)	Nonabbreviated DAPT (n=818)	Abbreviated DAPT (n=1447)	Nonabbreviated DAPT (n=1466)	
per patient					
1	598 (70.5%)	561 (68.6%)	981 (67.8%)	975 (66.5%)	
2	182 (21.5%)	181 (22.1%)	321 (22.2%)	341 (23.3%)	
≥3	68 (8.0%)	76 (9.3%)	145 (10.0%)	150 (10.2%)	
Number stented lesions per patient					0.16
1	612 (72.2%)	568 (69.4%)	999 (69.0%)	997 (68.0%)	
2	173 (20.4%)	179 (21.9%)	313 (21.6%)	328 (22.4%)	
≥3	63 (7.4%)	71 (8.7%)	135 (9.3%)	141 (9.6%)	
At least one complex lesion B2 or C	543 (64.0%)	537 (65.6%)	1019 (70.4%)	1042 (71.1%)	<0.001
Number of stents per patient	1.7 (1.1)	1.7 (1.1)	1.8 (1.2)	1.8 (1.1)	0.12
Total stent length per patient, mm	37.5 (28.1)	38.7 (28.1)	40.3 (29.9)	40.3 (28.6)	0.01
Any overlapping stenting	172 (20.3%)	149 (18.2%)	316 (21.8%)	301 (20.5%)	0.13
Any bifurcation or trifurcation stenting‡	32 (3.8%)	41 (5.0%)	51 (3.5%)	60 (4.1%)	0.35

Data are mean (SD), n (%), or n/n (%) in case of missing data.

bpm indicates beats per minute; DAPT, dual antiplatelet treatment; IABP, intra-aortic balloon pump; LAD, left anterior descending; LMWH, low-molecular-weight heparin; LVAD, left-ventricular assist device; NSTEMI, non-ST-segment elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

*Data from first PCI only.

†One PCI and up to two staged PCIs. The last PCI was the qualifying PCI 1 month before randomization.

‡Left main counted as two vessels.

Table 3. **Clinical Outcomes at 11 Months Post-Randomization (12-Month Follow-Up) (Intention-To-Treat Population)**

	Clinical indication for OAC				No clinical indication for OAC				$P_{interaction}$ ‡
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	HR† (95% CI)	Com-Nogue *P* value	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	HR† (95% CI)	Com-Nogue *P* value	
Coprimary composite outcome of all-cause death, myocardial infarction, stroke, bleeding BARC 3 or 5 (NACE)	68 (8.0)	78 (9.6)	0.83 (0.60–1.15)	0.26	104 (7.2)	104 (7.1)	1.01 (0.77–1.33)	0.91	0.35
Coprimary composite outcome of all-cause death, myocardial infarction, stroke (MACCE)	50 (5.9)	54 (6.7)	0.88 (0.60–1.30)	0.53	88 (6.1)	84 (5.7)	1.06 (0.79–1.44)	0.67	0.45
Coprimary composite outcome of bleeding BARC 2, 3 or 5	83 (9.9)	94 (11.7)	0.83 (0.62–1.12)	0.25	65 (4.6)	117 (8.1)	0.55 (0.41–0.74)	<0.001	0.06
Death	31 (3.7)	33 (4.1)	0.90 (0.55–1.47)	0.67	44 (3.1)	48 (3.3)	0.93 (0.62–1.40)	0.73	0.93
Cardiovascular death	16 (1.9)	21 (2.6)	0.73 (0.38–1.40)	0.34	21 (1.5)	23 (1.6)	0.92 (0.51–1.67)	0.80	0.60
Noncardiovascular death	11 (1.3)	7 (0.9)	1.51 (0.58–3.88)	0.40	18 (1.3)	21 (1.5)	0.87 (0.46–1.63)	0.66	0.34
Cerebrovascular accident	3 (0.4)	13 (1.6)	0.22 (0.06–0.77)	0.01	14 (1.0)	19 (1.3)	0.75 (0.37–1.49)	0.40	0.10
Stroke§	2 (0.2)	10 (1.3)	0.19 (0.04–0.87)	0.02	10 (0.7)	13 (0.9)	0.78 (0.34–1.78)	0.54	0.11

	Clinical indication for OAC				No clinical indication for OAC				$P_{interaction}$ ‡
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	HR† (95% CI)	Com-Nogue *P* value	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	HR† (95% CI)	Com-Nogue *P* value	
Ischemic stroke	2 (0.2)	9 (1.1)	0.21 (0.05–0.99)	0.03	9 (0.6)	9 (0.6)	1.01 (0.40–2.55)	0.99	0.09
Hemorrhagic stroke	0 (0.0)	2 (0.3)	0.19 (0.01–3.95)	0.16	1 (0.1)	3 (0.2)	0.34 (0.04–3.24)	0.33	1.00
Transient ischemic attack	1 (0.1)	3 (0.4)	0.32 (0.03–3.06)	0.31	4 (0.3)	6 (0.4)	0.67 (0.19–2.39)	0.55	0.57
Myocardial infarction	19 (2.3)	17 (2.1)	1.07 (0.56–2.06)	0.83	41 (2.9)	32 (2.2)	1.30 (0.82–2.07)	0.26	0.64
Late definite or probable stent thrombosis	3 (0.4)	4 (0.5)	0.72 (0.16–3.21)	0.66	11 (0.8)	5 (0.3)	2.23 (0.78–6.43)	0.12	0.23
Late definite stent thrombosis	2 (0.2)	3 (0.4)	0.64 (0.11–3.82)	0.62	9 (0.6)	4 (0.3)	2.28 (0.70–7.41)	0.16	0.24
Late probable stent thrombosis	1 (0.1)	1 (0.1)	0.96 (0.06–15.32)	0.98	2 (0.1)	1 (0.1)	2.03 (0.18–22.37)	0.55	0.69
Bleeding BARC classification									
Type 1	34 (4.1)	47 (5.8)	0.69 (0.44–1.07)	0.10	31 (2.2)	62 (4.3)	0.50 (0.33–0.77)	0.001	0.32
Type 2	60 (7.2)	65 (8.1)	0.88 (0.62–1.24)	0.49	42 (3.0)	87 (6.0)	0.48 (0.33–0.69)	<0.001	0.02
Type 3	26 (3.1)	33 (4.1)	0.75 (0.45–1.26)	0.28	27 (1.9)	26 (1.8)	1.05 (0.61–1.80)	0.84	0.38
Type 3a	11 (1.3)	18 (2.2)	0.58 (0.28–1.24)	0.16	15 (1.1)	12 (0.8)	1.26 (0.59–2.70)	0.53	0.16
Type 3b	13 (1.6)	12 (1.5)	1.04 (0.47–2.27)	0.91	8 (0.6)	8 (0.6)	1.01 (0.38–2.70)	0.98	0.97

	Clinical indication for OAC				No clinical indication for OAC				$P_{interaction}$ ‡
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	HR† (95% CI)	Com-Nogue *P* value	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	HR† (95% CI)	Com-Nogue *P* value	
Type 3c	3 (0.4)	3 (0.4)	0.96 (0.19–4.75)	0.97	4 (0.3)	6 (0.4)	0.67 (0.19–2.39)	0.54	0.74
Type 4	0 (0.0)	0 (0.0)		−	0 (0.0)	0 (0.0)		−	
Type 5	1 (0.1)	3 (0.4)	0.32 (0.03–3.07)	0.30	1 (0.1)	5 (0.4)	0.20 (0.02–1.73)	0.11	0.77
Type 5a	0 (0.0)	1 (0.1)	0.32 (0.01–7.84)	0.32	0 (0.0)	1 (0.1)	0.34 (0.01–8.34)	0.32	1.00
Type 5b	1 (0.1)	2 (0.3)	0.48 (0.04–5.29)	0.55	1 (0.1)	4 (0.2)	0.25 (0.03–2.26)	0.19	0.70
Type 3 or 5	27 (3.2)	36 (4.5)	0.71 (0.43–1.18)	0.19	28 (2.0)	31 (2.1)	0.91 (0.55–1.52)	0.75	0.50
Revascularizations (any)	21 (2.5)	28 (3.5)	0.71 (0.41–1.26)	0.25	59 (4.2)	54 (3.8)	1.11 (0.76–1.60)	0.58	0.20

Data are n (%) unless otherwise specified.

Abbrev indicates abbreviated; BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet treatment; HR, hazard ratio; MACCE, major adverse cardiac and cerebral events; NACE, net adverse clinical outcomes; OAC, oral anticoagulant.

*HRs (95% CIs) from Cox's time-to-first event analyses.

†Continuity corrected risk ratios (95% CIs) in case of zero events.

‡Interaction p-value testing for modifying effect of clinical indication 12 months on the HR. §Includes undetermined strokes.

Table 4. **Censor-Weighted Estimates of the Primary and Secondary Outcomes 11 Months Post-Randomization (12-Month Follow-Up)**

	Clinical indication for OAC				No clinical indication for OAC				$P_{interaction}$
	Abbrev DAPT (n=848)	Nonabbrev DAPT (n=818)	HR† (95% CI)	*P* value	Abbrev DAPT (n=1447)	Nonabbrev DAPT (n=1466)	HR† (95% CI)	*P* value	
Intention-to-treat population									
Coprimary composite outcome of all-cause death, myocardial infarction, stroke, bleeding BARC 3 or 5	56/12	64/14	0.95 (0.66–1.37)	0.79	90/14	92/12	1.04 (0.77–1.40)	0.79	0.70
Coprimary composite outcome of all-cause death, myocardial infarction, stroke	42/8	43/11	1.05 (0.68–1.62)	0.83	75/13	73/11	1.09 (0.78–1.51)	0.62	0.90
Coprimary composite outcome of bleeding BARC 2, 3 or 5	61/22	91/3	0.67 (0.48–0.93)	0.02	50/15	109/8	0.40 (0.23–0.69)	<0.001	0.11
Bleeding BARC 3 or 5	19/8	33/3	0.59 (0.33–1.04)	0.07	21/7	27/4	0.86 (0.48–1.51)	0.59	0.36
All-cause death	25/6	26/7	0.96 (0.55–1.68)	0.90	37/7	42/6	0.92 (0.58–1.45)	0.72	0.90
Cerebrovascular accident	1/2	8/5	0.10 (0.01–0.84)	0.03	10/4	16/3	0.70 (0.32–1.54)	0.37	0.10

	Clinical indication for OAC				No clinical indication for OAC				$P_{interaction}$
	Abbrev DAPT (n=848)	**Nonabbrev DAPT (n=818)**	**HR† (95% CI)**	***P* value**	**Abbrev DAPT (n=1447)**	**Nonabbrev DAPT (n=1466)**	**HR† (95% CI)**	***P* value**	
Myocardial infarction	17/2	16/1	1.24 (0.61–2.51)	0.55	34/7	28/4	1.33 (0.80–2.20)	0.27	0.88
Per-protocol population									
Coprimary composite outcome of all-cause death, myocardial infarction, stroke, bleeding BARC 3 or 5	53/11	62/12	0.93 (0.64–1.36)	0.72	89/12	87/11	1.08 (0.80–1.46)	0.61	0.54
Coprimary composite outcome of all-cause death, myocardial infarction, stroke	40/7	42/10	1.03 (0.66–1.60)	0.91	74/12	70/10	1.11 (0.80–1.56)	0.53	0.78
Coprimary composite outcome of bleeding BARC 2, 3 or 5	60/21	87/2	0.70 (0.50–0.98)	0.04	49/10	106/8	0.40 (0.23–0.69)	0.001	0.09
bleeding BARC 3 or 5	18/8	31/2	0.60 (0.33–1.08)	0.09	20/5	24/4	0.91 (0.50–1.65)	0.76	0.32
All-cause death	24/6	26/6	0.92 (0.52–1.61)	0.77	36/6	41/6	0.91 (0.57–1.45)	0.69	0.98
Cerebrovascular accident	1/1	7/5	0.12 (0.01–0.98)	0.05	10/4	16/3	0.69 (0.31–1.53)	0.37	0.13

	Clinical indication for OAC				No clinical indication for OAC				$P_{interaction}$
	Abbrev DAPT (n=848)	**Nonabbrev DAPT (n=818)**	**HR† (95% CI)**	***P* value**	**Abbrev DAPT (n=1447)**	**Nonabbrev DAPT (n=1466)**	**HR† (95% CI)**	***P* value**	
Myocardial infarction	16/2	16/1	1.19 (0.58–2.43)	0.63	34/7	26/3	1.42 (0.85–2.38)	0.18	0.70

Data are number of events/number of events not used (events were not used when they occurred after the patient experienced NARC 2 or 3, as these patients were no longer in the risk set).

Abbrev indicates abbreviated; BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet treatment; HR, hazard ratio; NARC, non-adherence Academic Research Consortium; OAC, oral anticoagulant.

*****HRs (95% CIs) from cluster-robust daily estimates of event rates using logistic regression (at each day *t*; *t*=0 to 335 days post-randomization), but censoring patients 1 day after occurrence of NARC 2 or 3, which were compensated for with inverse-cumulative probability weighted patients not (yet) censored at that specific day *t.*

Figure 1

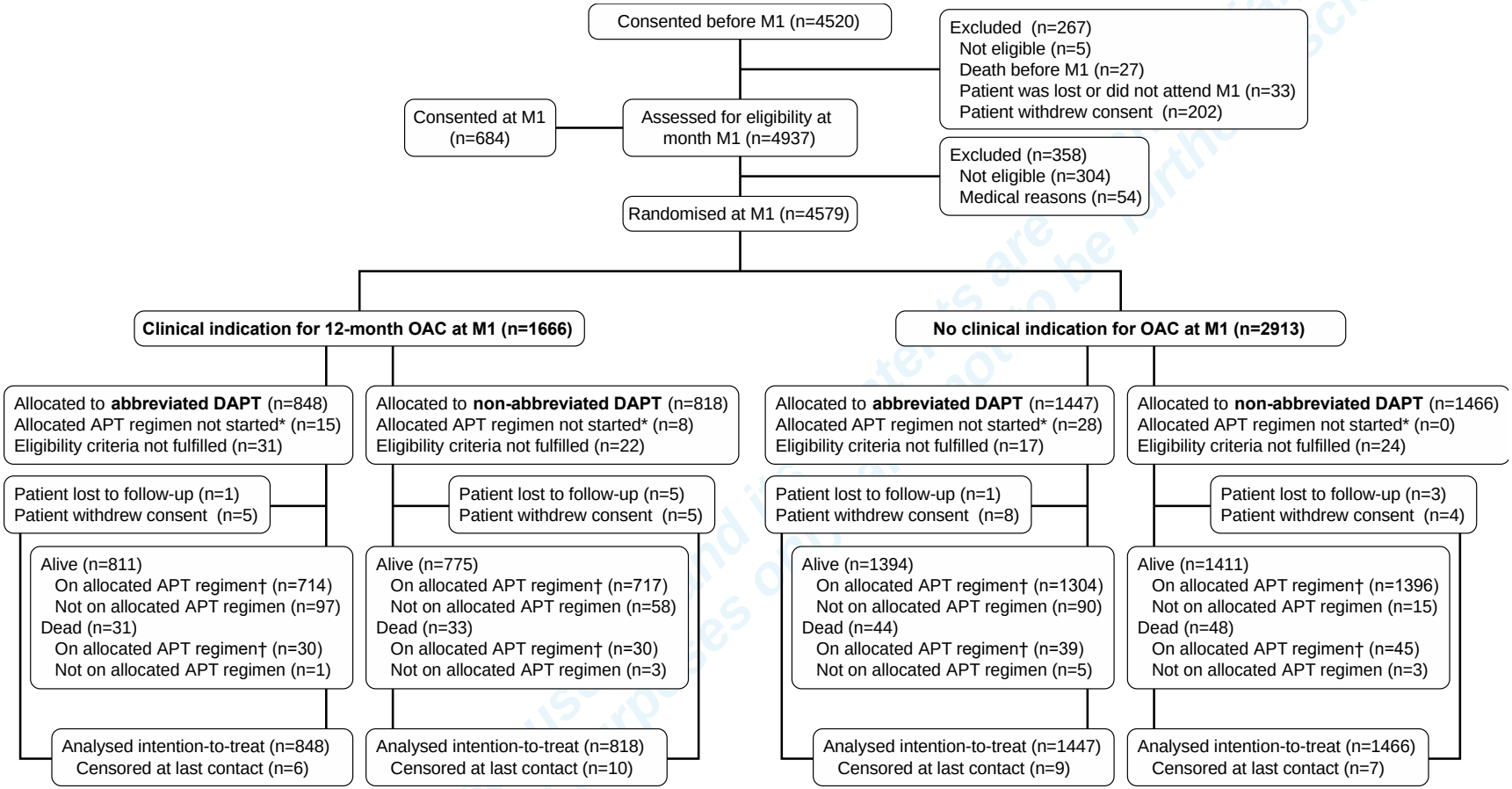


Figure 2

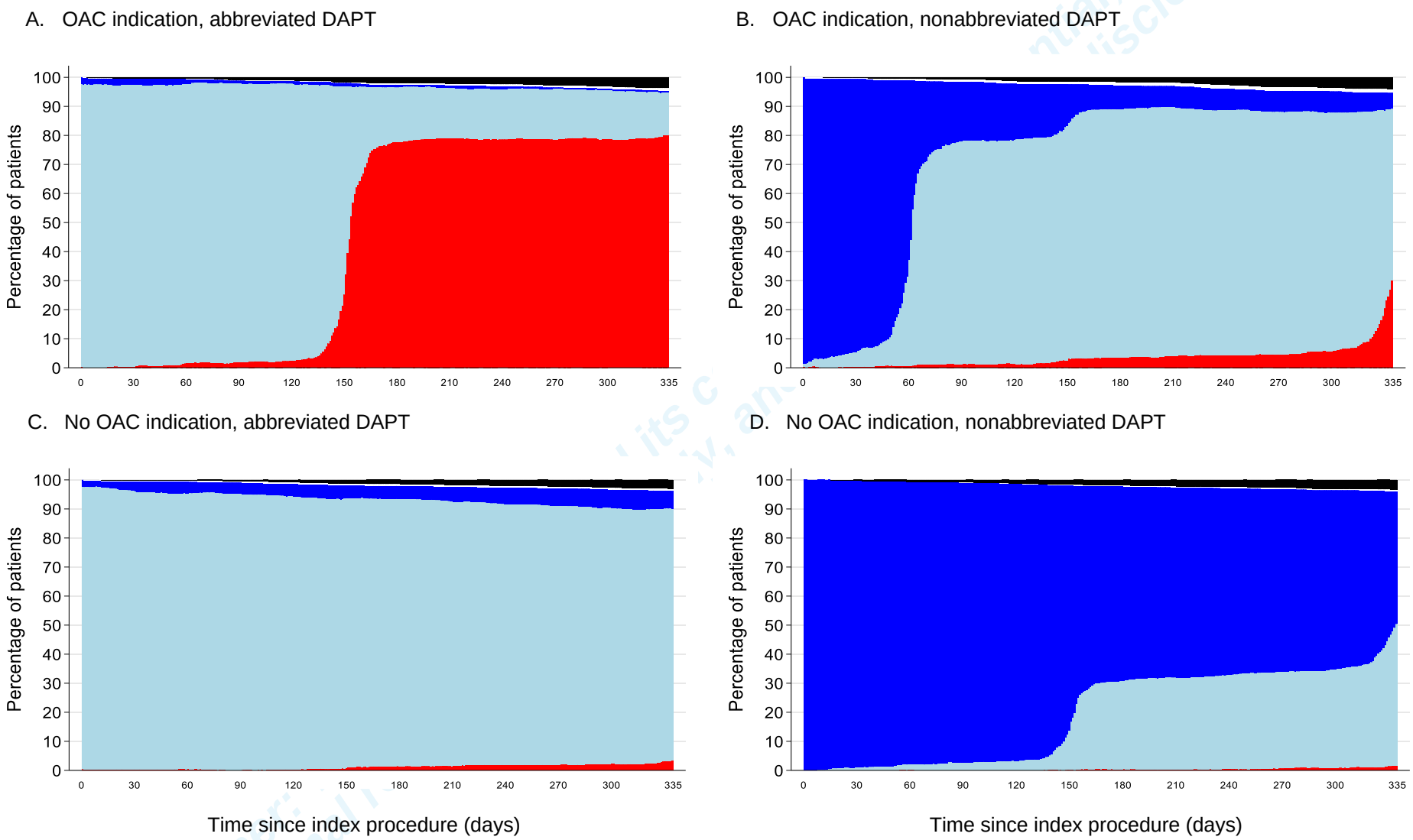
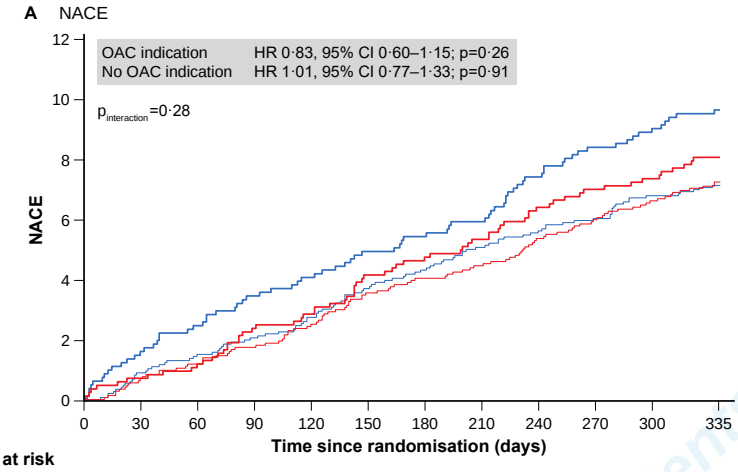
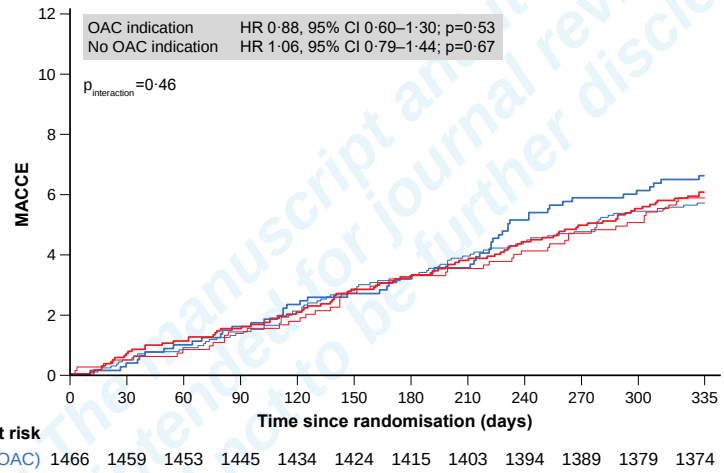


Figure 3



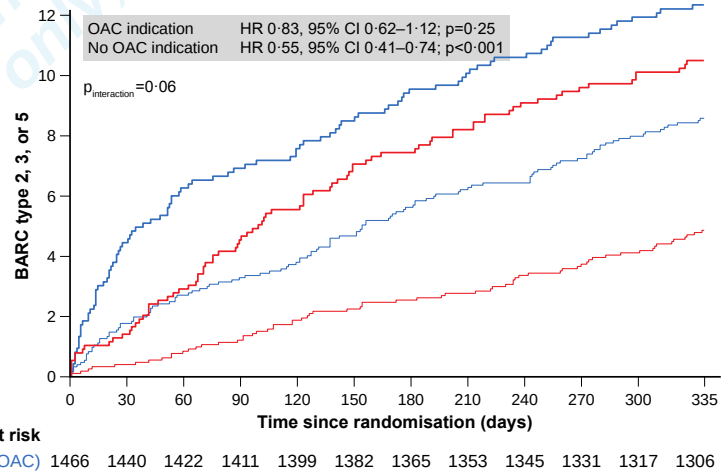
No. at risk

Non-abbrev. DAPT (no OAC)	1466	1453	1444	1435	1425	1411	1399	1387	1377	1371	1360	1354
Non-abbrev. DAPT (OAC)	818	802	794	784	779	772	765	761	749	740	735	730
Abbrev. DAPT (no OAC)	1447	1432	1425	1415	1404	1388	1381	1375	1362	1353	1344	1333
Abbrev. DAPT (OAC)	848	841	837	826	822	811	805	800	790	785	782	775



No. at risk

Non-abbrev. DAPT (no OAC)	1466	1459	1453	1445	1434	1424	1415	1403	1394	1389	1379	1374
Non-abbrev. DAPT (OAC)	818	812	806	799	793	790	783	780	767	760	758	754
Abbrev. DAPT (no OAC)	1447	1432	1426	1418	1410	1398	1392	1384	1375	1367	1359	1349
Abbrev. DAPT (OAC)	848	843	840	834	831	823	817	815	809	804	801	792



No. at risk

Non-abbrev. DAPT (no OAC)	1466	1440	1422	1411	1399	1382	1365	1353	1345	1331	1317	1306
Non-abbrev. DAPT (OAC)	818	780	764	755	748	740	729	724	715	704	698	693
Abbrev. DAPT (no OAC)	1447	1435	1428	1419	1406	1393	1387	1382	1371	1363	1354	1338
Abbrev. DAPT (OAC)	848	834	821	804	796	780	774	768	759	754	748	740

Figure 4

Endpoints	Abbreviated DAPT nr of events / nr of events not used*	Non-abbreviated DAPT nr of events / nr of events not used*	Hazard Ratio [Abbreviated/Non-abbreviated] (95%CI)	p-value	p-value for interaction
Net Adverse Clinical Events					
Clinical indication OAC					0,718
0 to 150 days	31/ 4	33/ 7	0.89 (0.54-1.45)	0,631	
151 to 335 days	25/ 8	31/ 7	1.01 (0.59-1.73)	0,959	
No clinical indication OAC					0,716
0 to 150 days	46/ 5	51/ 4	0.92 (0.62-1.38)	0,701	
151 to 335 days	44/ 9	41/ 8	1.18 (0.76-1.83)	0,455	
Major Adverse Cardiovascular Events					
Clinical indication OAC					0,942
0 to 150 days	21/ 2	18/ 4	1.03 (0.55-1.94)	0,929	
151 to 335 days	21/ 6	25/ 7	1.06 (0.59-1.92)	0,839	
No clinical indication OAC					0,941
0 to 150 days	36/ 5	38/ 4	0.96 (0.60-1.53)	0,864	
151 to 335 days	39/ 8	35/ 7	1.22 (0.76-1.96)	0,407	
Major or Clinically Relevant Nonmajor Bleeding					
Clinical indication OAC					0,249
0 to 150 days	51/ 5	63/ 3	0.77 (0.53-1.11)	0,161	
151 to 335 days	10/ 17	28/ 0	0.47 (0.22-0.99)	0,047	
No clinical indication OAC					0,249
0 to 150 days	25/ 5	61/ 3	0.44 (0.27-0.69)	<0.001	
151 to 335 days	25/ 10	48/ 5	0.37 (0.15-0.90)	0,028