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FASTTRACK CLINICAL RESEARCH
Interventional cardiology

Duration of antiplatelet therapy after complex percutaneous coronary intervention in patients at high bleeding risk: a MASTER DAPT trial sub-analysis

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Abstract

Aim To assess the effects of 1- or ≥3-month dual antiplatelet therapy (DAPT) in high bleeding risk (HBR) patients who received biodegradable-polymer sirolimus-eluting stents for complex percutaneous coronary intervention (PCI) and/or acute coronary syndrome (ACS).

Methods and results In the MASTER DAPT trial, 3383 patients underwent non-complex (abbreviated DAPT, $n = 1707$; standard DAPT, $n = 1676$) and 1196 complex (abbreviated DAPT, $n = 588$; standard DAPT, $n = 608$) PCI. Co-primary outcomes at 335 days were net adverse clinical events [NACE; composite of all-cause death, myocardial infarction, stroke, and bleeding academic research consortium (BARC) 3 or 5 bleeding events]; major adverse cardiac or cerebral events (MACCE; all-cause death, myocardial infarction, and stroke); and Types 2, 3, or 5 BARC bleeding. Net adverse clinical events and MACCE did not differ with abbreviated vs. standard DAPT among patients with complex [hazard ratio (HR): 1.03, 95% confidence

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interval (CI): 0.69–1.52, and HR: 1.24, 95% CI: 0.79–1.92, respectively] and non-complex PCI (HR: 0.90, 95% CI: 0.71–1.15, and HR: 0.91, 95% CI: 0.69–1.21; $P_{interaction} = 0.60$ and 0.26, respectively). BARC 2, 3, or 5 was reduced with abbreviated DAPT in patients with and without complex PCI (HR: 0.64; 95% CI: 0.42–0.98, and HR: 0.70; 95% CI: 0.55–0.89; $P_{interaction} = 0.72$). Among the 2816 patients with complex PCI and/or ACS, NACE and MACCE did not differ and BARC 2, 3, or 5 was lower with abbreviated DAPT.

Conclusion In HBR patients free from recurrent ischaemic events at 1 month, DAPT discontinuation was associated with similar NACE and MACCE and lower bleeding rates compared with standard DAPT, regardless of PCI or patient complexity.

Clinical Trial Registration This trial is registered with ClinicalTrials.gov, number NCT03023020, and is closed to new participants, with follow-up completed.

Structured Graphical Abstract

Key Question

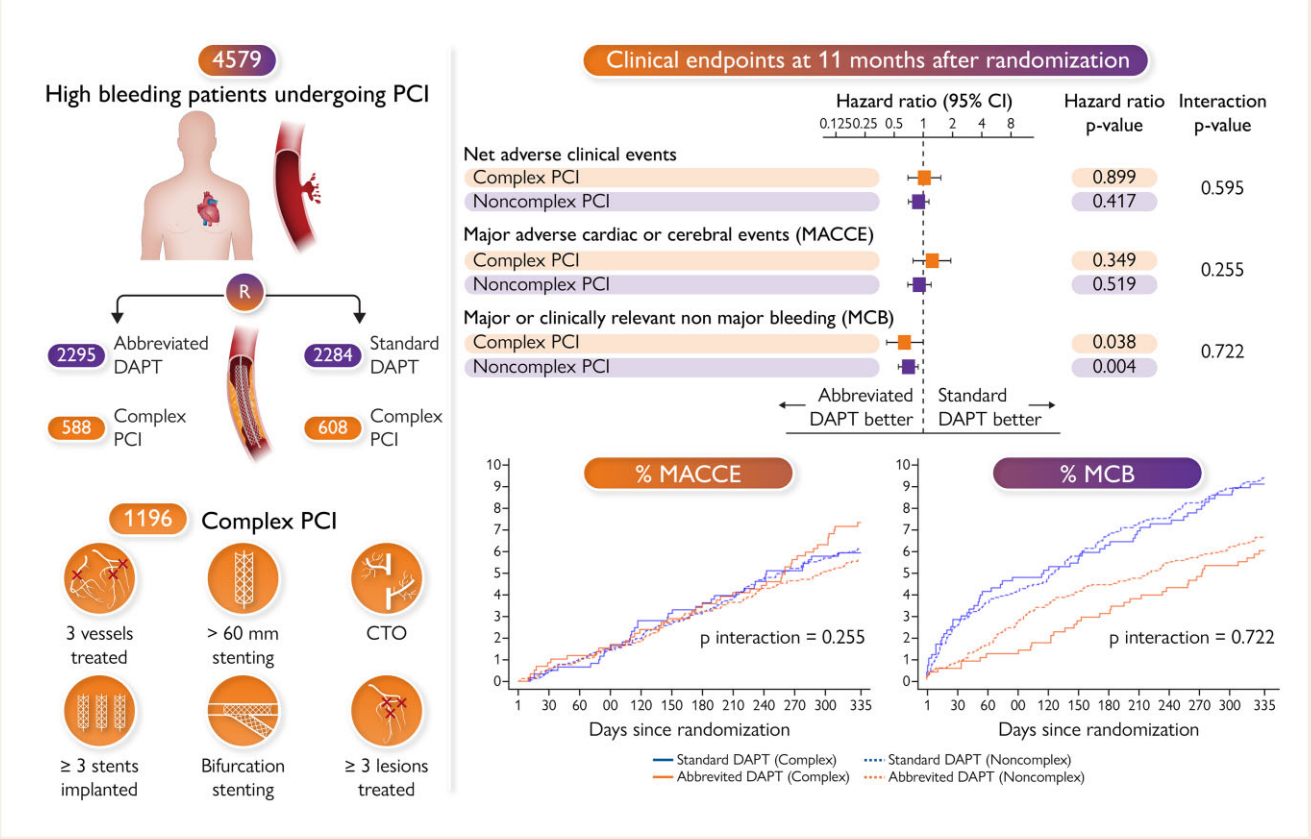
To assess the consistency of the treatment effects of 1- or ≥ 3-month dual antiplatelet therapy (DAPT) in high bleeding risk (HBR) patients with complex percutaneous coronary intervention (PCI) and/or acute coronary syndrome (ACS).

Key Finding

One-month DAPT after PCI with biodegradable-polymer sirolimus-eluting stent in HBR patients was associated with similar net adverse clinical events (NACE) and major adverse cardiac or cerebral events (MACCE) and lower bleeding rates compared with standard DAPT, regardless of PCI complexity and/or ACS.

Take Home Message

In HBR patients undergoing PCI without recurrent ischemic events in the first 30 days after coronary intervention, PCI complexity and/or ACS does not justify a DAPT regimen longer than one month.



One-month DAPT after PCI with biodegradable-polymer sirolimus-eluting stent in HBR patients was associated with similar NACE and MACCE and lower bleedingrates compared with standard DAPT, regardless of PCI complexity and/or ACS.

Keywords Percutaneous coronary intervention • High bleeding risk • Dual antiplatelet therapy • Complex intervention

Introduction

Patients undergoing percutaneous coronary intervention (PCI) with severe coronary artery disease (CAD) and challenging lesion subsets require complex procedures and remain at increased risk of short- and long-term adverse ischaemic events.[1–5]

A prior retrospective analysis of six randomized controlled trials, including 9577 patients, showed that among 1,680 unselected complex PCI patients, the risk of major adverse cardiac events was lower with a 12-month compared with a 3–6-month dual antiplatelet therapy (DAPT) regimen, with significant treatment duration by PCI complexity interaction testing.[2] A subsequent analysis which gathered individual patient data from eight randomized controlled trials and 14 963 patients, suggested that the bleeding risk might be an additional treatment modifier, based on the observation that an ischaemic benefit with prolonged treatment was observed only in patients not at high bleeding risk (HBR) who underwent complex PCI and/or were intervened upon with acute coronary syndrome (ACS) (complex patient group).[1] No benefit in terms of ischaemic endpoints was noted with prolonged DAPT in HBR patients, irrespective of PCI or patient complexity.[1] On the other hand, and regardless of PCI or patient complexity, extended DAPT duration remains associated with an increased risk of major bleeding,[1,2] especially among HBR patients.[1,6,7]

The aforementioned evidence informed the design of the MASTER DAPT (The Management of High Bleeding Risk Patients Post Bioresorbable Polymer-Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial, which randomized HBR patients to 1- or at least 3-month DAPT, irrespective of PCI complexity and/or ACS at presentation.[8] The primary results showed that 1 month of DAPT was non-inferior to treatment continuation for at least 2 additional months for the occurrence of net and major adverse clinical events and reduced major or clinically relevant non-major bleeding in the overall HBR population.[9] In this study, we conducted a pre-specified analysis to assess the consistency of the treatment effects of 1-month vs. a more prolonged DAPT duration based on PCI and patient (i.e. complex PCI and/or ACS) complexity.

Methods

Study design

The design and the primary endpoint results of the MASTER DAPT (ClinicalTrials.gov number, NCT03023020) investigator-initiated, randomized, open-label, non-inferiority trial with sequential superiority testing in largely unselected patients at HBR following implantation of a biodegradable-polymer-coated Ultimaster™ (Terumo Corporation, Tokyo, Japan) sirolimus-eluting stent, were reported previously.[8,9] Ethics approval was obtained in each country and centre. 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.

Study 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 uneventful until the time of randomization. Patients were considered at HBR if at least one of the following criteria applied: oral anticoagulant (OAC) 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, age ≥75 years, systemic conditions associated with an increased bleeding risk (e.g. haematological disorders or any known coagulation disorder associated with increased bleeding risk), documented anaemia (defined as repeated haemoglobin levels <11 g/dL or transfusion within 4 weeks before randomization), need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs, diagnosed malignancy (other than skin), stroke at any time or transient ischaemic attack in the previous 6 months, and PRECISE-DAPT score ≥25.[8–10]

Exclusion criteria were minimal and limited to implantation of a non-study 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.

Complex PCI was primarily defined as a procedure with at least one of the following angiographic characteristics: three vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with two stents implanted, total stent length >60 mm, or chronic total occlusion as target lesion.[1,2] An alternative and more comprehensive complex PCI definition which includes, in addition to all previous complex PCI criteria, also left main or graft intervention has also been used as sensitivity analysis.[11] Complex patients were defined as those fulfilling the primary complex PCI definition and/or with ACS, including ST-segment elevation or non-ST-segment elevation myocardial infarction or unstable angina.

Randomization and follow-up

Patients were centrally randomized (1:1 ratio) to an open-label abbreviated or non-abbreviated antiplatelet therapy regimen 30–44 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 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, and at 335 ± 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. All data were stored at a central database (CTU, Bern, Switzerland).

Randomized treatment

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 descriptions of the two treatment regimens are provided in the Supplementary material online, Appendix.

Outcomes

The three ranked primary outcomes were net adverse clinical events (NACE) (a composite of death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (MACCE) (a composite of death from any cause, myocardial infarction, or stroke), and major or clinically relevant non-major bleeding [composite of

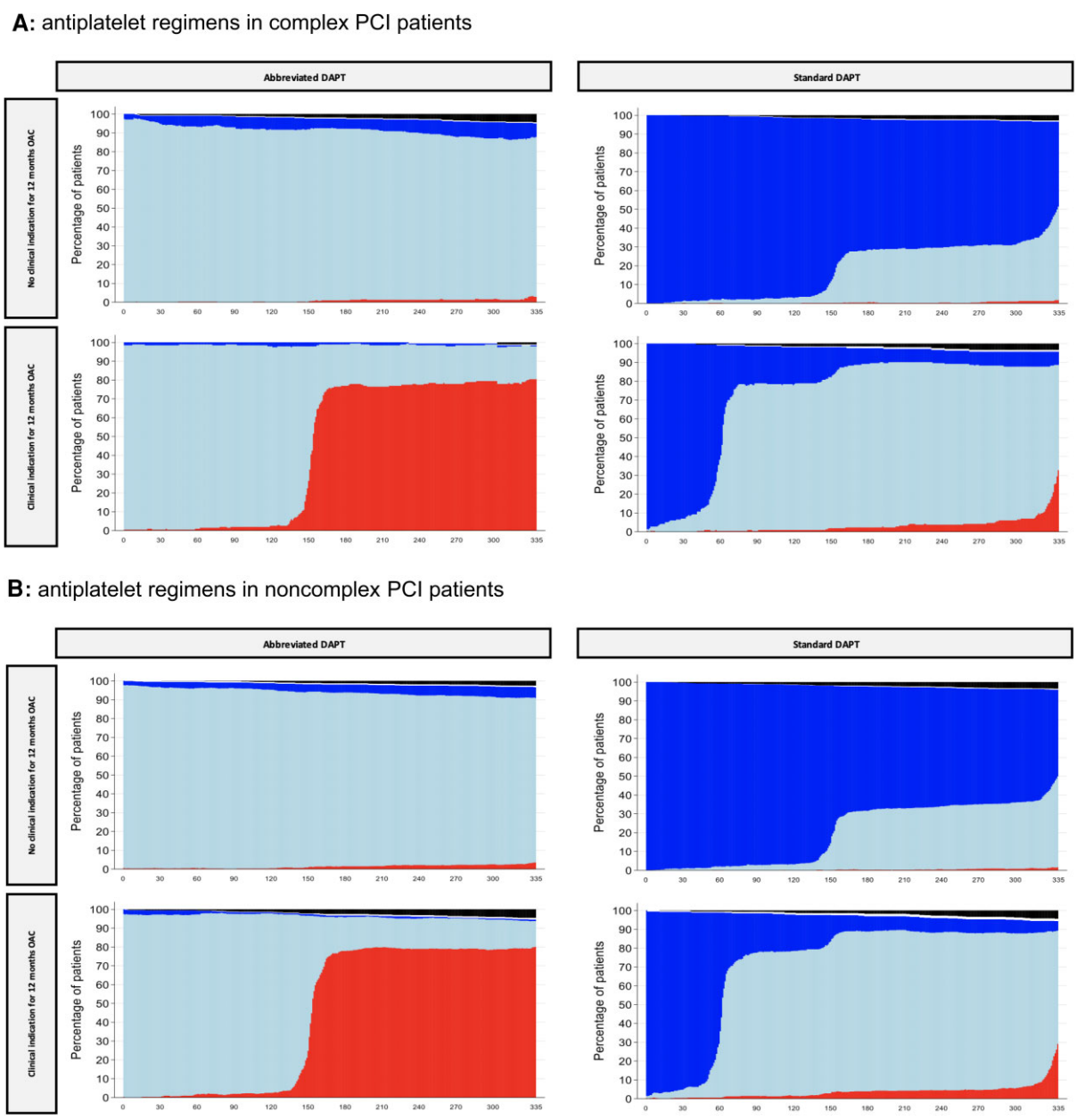


Figure 1 Antiplatelet regimens in complex (*A*) and non-complex (*B*) percutaneous coronary intervention patients. Dark blue denotes dual antiplatelet therapy, light blue denotes single antiplatelet therapy (see Supplementary material online, *Table S7* for type therefore and see Supplementary material online, *Table S8* for cross-overs), red denotes no antiplatelet therapy, black denotes deceased patients, white denotes no information. DAPT, dual antiplatelet therapy; OAC, oral anticoagulation.

Types 2, 3, or 5 Bleeding Academic Research Consortium (BARC) bleeding]; cumulative incidences were assessed at 335 days.

The secondary outcomes included the individual components of the three co-primary outcomes; the composite of cardiovascular death, myocardial infarction, and stroke; the composite of cardiovascular death, myocardial infarction, definite or probable stent thrombosis, the composite of stroke, and transient ischaemic attack; and all bleeding events, adjudicated according to the BARC classifications.

All outcomes were pre-specified.[8,9] All analyses evaluated the occurrence of the adjudicated outcomes between randomization and 335 days.

Statistical analysis

The data were analysed according to the intention-to-treat principle. Outcomes were assessed separately for patients with or without complex PCI procedure, by calculating hazard ratios (HR) with 95% confidence intervals (CI).

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 incomplete clinical follow-up, time to censoring was defined as the difference between the dates of last known clinical status and randomization plus

Table 1 Baseline characteristics

	Abbreviated DAPT		Standard DAPT		Complex	Non-complex
	Complex PCI N = 588	Non-complex PCI N = 1707	Complex PCI N = 608	Non-complex PCI N = 1676	P-value	P-value
Age, years (mean ± SD)	n = 588, 76.51 ± 8.17	n = 1707, 75.98 ± 8.88	n = 608, 76.78 ± 8.30	n = 1676, 75.66 ± 8.92	0.570	0.298
Male sex [n (%)]	n = 588, 419 (71.3%)	n = 1707, 1171 (68.6%)	n = 608, 428 (70.4%)	n = 1676, 1153 (68.8%)	0.751	0.911
Body mass index, kg/m^2 (mean ± SD)	n = 588, 27.56 ± 4.61	n = 1707, 27.15 ± 4.70	n = 608, 27.58 ± 4.62	n = 1676, 27.39 ± 4.79	0.943	0.136
Family history of coronary artery disease [n (%)]	n = 588, 162 (27.6%)	n = 1707, 394 (23.1%)	n = 608, 148 (24.3%)	n = 1676, 405 (24.2%)	0.210	0.466
Known arterial hypertension [n (%)]	n = 588, 473 (80.4%)	n = 1707, 1293 (75.7%)	n = 608, 468 (77.0%)	n = 1676, 1319 (78.7%)	0.158	0.045
Uncontrolled hypertension [n (%)]	n = 588, 23 (3.9%)	n = 1707, 96 (5.6%)	n = 608, 35 (5.8%)	n = 1676, 82 (4.9%)	0.141	0.356
Known Diabetes mellitus [n (%)]	n = 588, 202 (34.4%)	n = 1707, 552 (32.3%)	n = 608, 203 (33.4%)	n = 1676, 581 (34.7%)	0.760	0.155
Known hyperlipidaemia [n (%)]	n = 588, 420 (71.4%)	n = 1707, 1122 (65.7%)	n = 608, 403 (66.3%)	n = 1676, 1152 (68.7%)	0.061	0.067
Smoker [n (%)]	n = 588	n = 1702	n = 607	n = 1669	0.071	0.130
no—never smoked	287 (48.8%)	899 (52.8%)	336 (55.4%)	902 (54.0%)	0.024	0.490
yes—previous smoker	254 (43.2%)	620 (36.4%)	232 (38.2%)	622 (37.3%)	0.088	0.617
yes—current smoker	47 (8.0%)	183 (10.8%)	39 (6.4%)	145 (8.7%)	0.315	0.048
Known peripheral/vascular disease* [n (%)]	n = 588, 75 (12.8%)	n = 1707, 168 (9.8%)	n = 608, 62 (10.2%)	n = 1676, 180 (10.7%)	0.174	0.396
Known carotid artery disease [n (%)]	n = 588, 32 (5.4%)	n = 1707, 88 (5.2%)	n = 608, 38 (6.3%)	n = 1676, 106 (6.3%)	0.623	0.160
History of heart failure [n (%)]	n = 588, 116 (19.7%)	n = 1707, 313 (18.3%)	n = 608, 119 (19.6%)	n = 1676, 319 (19.0%)	1.000	0.628
Left ventricular ejection fraction, % (mean ± SD)	n = 559, 53.05 ± 11.29	n = 1610, 53.63 ± 11.49	n = 581, 52.27 ± 11.65	n = 1547, 53.22 ± 11.81	0.250	0.324
Prior myocardial infarction [n (%)]	n = 588, 124 (21.1%)	n = 1707, 310 (18.2%)	n = 608, 145 (23.8%)	n = 1676, 285 (17.0%)	0.268	0.391
Prior PCI [n (%)]	n = 588, 159 (27.0%)	n = 1707, 435 (25.5%)	n = 608, 153 (25.2%)	n = 1676, 441 (26.3%)	0.469	0.583
Prior cerebrovascular event reported [n (%)]	n = 588, 79 (13.4%)	n = 1707, 189 (11.1%)	n = 608, 76 (12.5%)	n = 1676, 226 (13.5%)	0.667	0.036
Stroke [n (%)]	n = 588, 58 (9.9%)	n = 1707, 135 (7.9%)	n = 608, 56 (9.2%)	n = 1676, 161 (9.6%)	0.768	0.088
TIA [n (%)]	n = 588, 27 (4.6%)	n = 1707, 59 (3.5%)	n = 608, 18 (3.0%)	n = 1676, 66 (3.9%)	0.171	0.467
Undetermined cerebrovascular event [n (%)]	n = 588, 3 (0.5%)	n = 1707, 8 (0.5%)	n = 608, 5 (0.8%)	n = 1676, 13 (0.8%)	0.726	0.281
Known history of arterial thrombo-embolism [n (%)]	n = 588, 14 (2.4%)	n = 1707, 17 (1.0%)	n = 608, 10 (1.6%)	n = 1676, 14 (0.8%)	0.413	0.719
Known history of venous thrombo-embolism [n (%)]	n = 588, 41 (7.0%)	n = 1707, 83 (4.9%)	n = 608, 34 (5.6%)	n = 1676, 81 (4.8%)	0.342	1.000
Prior CABG [n (%)]	n = 588, 46 (7.8%)	n = 1707, 124 (7.3%)	n = 608, 46 (7.6%)	n = 1676, 125 (7.5%)	0.914	0.844
Prior prosthetic mechanical heart valve [n (%)]	n = 588, 8 (1.4%)	n = 1707, 35 (2.1%)	n = 608, 11 (1.8%)	n = 1676, 47 (2.8%)	0.646	0.180
Known aortic valve stenosis [n (%)]	n = 518, 22 (4.2%)	n = 1551, 69 (4.4%)	n = 550, 31 (5.6%)	n = 1501, 73 (4.9%)	0.326	0.607
Prior bleeding before/after qualifying PCI [n (%)]	n = 588, 39 (6.6%)	n = 1707, 145 (8.5%)	n = 608, 34 (5.6%)	n = 1676, 141 (8.4%)	0.471	0.951
Known chronic pulmonary disease [n (%)]	n = 588, 72 (12.2%)	n = 1707, 183 (10.7%)	n = 608, 72 (11.8%)	n = 1676, 211 (12.6%)	0.859	0.097

Continued

Table 1 *Continued*

	Abbreviated DAPT		Standard DAPT		Complex	Non-complex
	Complex PCI N = 588	Non-complex PCI N = 1707	Complex PCI N = 608	Non-complex PCI N = 1676	P-value	P-value
Known chronic renal failure [n (%)]	n = 588, 131 (22.3%)	n = 1707, 287 (16.8%)	n = 608, 122 (20.1%)	n = 1676, 336 (20.0%)	0.358	0.017
Known liver disease [n (%)]	n = 588, 8 (1.4%)	n = 1707, 21 (1.2%)	n = 608, 8 (1.3%)	n = 1676, 24 (1.4%)	1.000	0.654
Atrial fibrillation [n (%)]	n = 588, 180 (30.6%)	n = 1707, 590 (34.6%)	n = 608, 181 (29.8%)	n = 1676, 539 (32.2%)	0.753	0.145
Known history of cancer [n (%)]	n = 588, 98 (16.7%)	n = 1707, 250 (14.6%)	n = 608, 98 (16.1%)	n = 1676, 253 (15.1%)	0.815	0.735
Known active cancer [n (%)]	n = 588, 41 (7.0%)	n = 1707, 69 (4.0%)	n = 608, 33 (5.4%)	n = 1676, 93 (5.5%)	0.282	0.044
Known haematological or coagulation disorders [n (%)]	n = 588, 86 (14.6%)	n = 1707, 204 (12.0%)	n = 608, 79 (13.0%)	n = 1676, 209 (12.5%)	0.451	0.674
Chronic treatment with steroids or NSAIDs [n (%)]	n = 588, 60 (10.2%)	n = 1707, 142 (8.3%)	n = 608, 68 (11.2%)	n = 1676, 171 (10.2%)	0.640	0.066
Prior VKA [n (%)]	n = 588, 67 (11.4%)	n = 1707, 260 (15.2%)	n = 608, 64 (10.5%)	n = 1676, 235 (14.0%)	0.644	0.331
Need for current treatment with OAC [n (%)]	n = 588, 200 (34.0%)	n = 1707, 649 (38.0%)	n = 608, 215 (35.4%)	n = 1676, 605 (36.1%)	0.628	0.255
Clinical indication for 12 months OAC [n (%)]	n = 588, 200 (34.0%)	n = 1707, 648 (38.0%)	n = 608, 214 (35.2%)	n = 1676, 604 (36.0%)	0.671	0.255
OAC treatment at randomization [n (%)]	n = 200, 199 (99.5%)	n = 648, 643 (99.2%)	n = 214, 213 (99.5%)	n = 604, 601 (99.5%)	1.000	0.727
PRECISE-DAPT score[a] (mean ± SD)	n = 588, 27.13 ± 11.54	n = 1707, 26.70 ± 10.69	n = 608, 26.91 ± 10.59	n = 1676, 26.64 ± 11.22	0.732	0.865
Prior bleeding [n (%)]	n = 588, 37 (6.3%)	n = 1707, 128 (7.5%)	n = 608, 29 (4.8%)	n = 1676, 126 (7.5%)	0.257	1.000
Haemoglobin, g/L (mean ± SD)	n = 588,13.08 ± 1.80	n = 1707, 13.29 ± 1.77	n = 608, 13.07 ± 1.81	n = 1676, 13.24 ± 1.79	0.951	0.439
White blood cell count[a], 109/L (mean ± SD)	n = 588, 8.73 ± 21.50	n = 1707, 8.13 ± 4.09	n = 607, 8.05 ± 4.07	n = 1676, 8.06 ± 3.12	0.440	0.542
Creatinine clearance eGFR (MDRD), mL/min/1.73 m^2 (mean ± SD)	n = 588, 69.77 ± 24.20	n = 1707, 71.05 ± 23.91	n = 608, 69.68 ± 24.33	n = 1676, 71.48 ± 24.00	0.947	0.595

Reported are means with standard deviations (±SD), counts (% of patients).

TIA, transient ischaemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulation (vitamin K-antagonist VKA or NOAC).

*Peripheral vascular disease was defined as intermittent claudicatio, peripheral-artery bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (≥ 6cm in diameter), an ankle-brachial index of no more than 0.90, aortic plaque.

[a]Calculated at screening visit. n = 1 PRECISE Score calculated without risk due to white blood cell count.

1. Kaplan–Meier calculations included all (first) adjudicated outcome events that occurred between randomization and 335 days thereafter according to the randomized treatment assignment, irrespective of the DAPT regimen received at the time of the outcome event. Hazard ratio and 95% CI were generated for primary and secondary outcomes with the use of Cox proportional hazards regression analysis with censoring at end of the study and at the time of death. Competing risk of death (subdistribution HR with 95% CI) and the Aalen–Johansen cumulative incidences (with 95% CI) were computed for BARC bleeding endpoints following the Fine and Gray methodology.[12] Absolute risk differences are shown as percentage points. Numbers needed to treat for harm (NNTH) or benefit (NNTB) were calculated dividing 1 by absolute risk difference for various endpoints between randomized groups.

P-values for testing homogeneity of the HR in subgroups of patients were derived in Cox proportional hazards models with the interaction term for the treatment group (abbreviated vs. standard) and complex PCI (yes vs. no) tested using one degree of freedom. The 95% CI and *P*-values for interaction were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

Details on the statistical analysis have been published.[8,9,13]

Results

From February 28, 2017 through December 5, 2019, 5204 patients (at 140 sites in 30 countries) were consented, of whom 1359 (26.1%) patients with and 3845 (73.9%) without complex PCI; a total of 1196

Table 2 **Clinical endpoints at 11 months post-randomization**

	Complex PCI					Non-complex PCI					Interaction *P*-value
	Abbreviated DAPT *N* = 588	Standard DAPT *N* = 608	Hazard ratio (95% CI)	*P*-value	Absolute risk difference (95% CI)	Abbreviated DAPT *N* = 1707	Standard DAPT *N* = 1676	Hazard ratio (95% CI)	*P*-value	Absolute risk difference (95% CI)	
Net adverse clinical events (NACE)	49 (8.35)	49 (8.08)	1.03 (0.69–1.52)	0.899	0.27 (−2.85 to 3.39)	123 (7.24)	133 (7.98)	0.90 (0.71–1.15)	0.418	−0.74 (−2.53 to 1.06)	0.595
Major adverse cardiac or cerebral events (MACCE)	43 (7.33)	36 (5.94)	1.24 (0.79–1.92)	0.349	1.39 (−1.43 to 4.22)	95 (5.59)	102 (6.12)	0.91(0.69–1.21)	0.520	−0.53 (−2.11 to 1.06)	0.256
Major or clinically relevant non-major bleeding (MCB)	35 (6.03)	55 (9.15)	0.64 (0.42–0.98)	0.038	−3.11 (−6.13 to −0.10)	113 (6.71)	156 (9.44)	0.70 (0.55–0.89)	0.004	−2.72 (−4.57 to −0.87)	0.723
Death	19 (3.24)	18 (2.97)	1.09 (0.57–2.07)	0.797	0.27 (−1.70 to 2.24)	56 (3.30)	63 (3.78)	0.87 (0.61–1.25)	0.449	−0.48 (−1.73 to 0.77)	0.553
Cardiovascular death	9 (1.55)	10 (1.66)	0.93 (0.38–2.28)	0.870	−0.11 (−1.54 to 1.32)	28 (1.66)	34 (2.06)	0.81 (0.49–1.33)	0.398	−0.40 (−1.31 to 0.52)	0.790
Non-cardiovascular death	6 (1.03)	7 (1.17)	0.88 (0.30–2.63)	0.825	−0.13 (−1.32 to 1.05)	23 (1.37)	21 (1.28)	1.07 (0.59–1.94)	0.818	0.09 (−0.68 to 0.87)	0.759
Undetermined death	4 (0.69)	1 (0.17)	4.12 (0.46–36.86)	0.205	0.52 (−0.23 to 1.28)	5 (0.30)	8 (0.49)	0.61 (0.20–1.87)	0.390	−0.19 (−0.61 to 0.24)	0.128
Cardiovascular or undetermined death	13 (2.23)	11 (1.83)	1.22 (0.55–2.72)	0.630	0.41 (−1.20 to 2.01)	33 (1.95)	42 (2.53)	0.77 (0.49–1.21)	0.260	−0.58 (−1.59 to 0.42)	0.329
Cerebrovascular accident	4 (0.70)	5 (0.84)	0.82 (0.22–3.07)	0.773	−0.14 (−1.14 to 0.86)	13 (0.78)	27 (1.64)	0.47 (0.24–0.91)	0.025	−0.87 (−1.61 to −0.12)	0.452
Stroke[a]	3 (0.52)	4 (0.67)	0.77 (0.17–3.45)	0.736	−0.15 (−1.03 to 0.73)	9 (0.53)	19 (1.16)	0.46 (0.21–1.02)	0.057	−0.62 (−1.25 to 0.00)	0.552
Ischaemic stroke	3 (0.52)	3 (0.50)	1.03 (0.21–5.10)	0.971	0.01 (−0.80 to 0.83)	8 (0.47)	15 (0.91)	0.52 (0.22–1.23)	0.138	−0.44 (−1.00 to 0.13)	0.461
Haemorhagic Stroke	0 (0.00)	1 (0.17)	0.34 (0.01–8.33)	1.000	−0.17 (−0.49 to 0.16)	1 (0.06)	4 (0.25)	0.24 (0.03–2.19)	0.208	−0.18 (−0.45 to 0.08)	1.000
TIA	1 (0.18)	1 (0.17)	1.03 (0.06–16.45)	0.984	0.01 (−0.47 to 0.48)	4 (0.24)	8 (0.49)	0.49 (0.15–1.62)	0.242	−0.25 (−0.66 to 0.17)	0.628
Myocardial infarction	23 (3.97)	19 (3.17)	1.25 (0.68–2.30)	0.471	0.80 (−1.32 to 2.92)	37 (2.21)	30 (1.83)	1.21 (0.75–1.96)	0.436	0.38 (−0.58 to 1.34)	0.935
Definite or probable stent thrombosis	4 (0.69)	6 (1.00)	0.69 (0.19–2.44)	0.562	−0.31 (−1.35 to 0.73)	10 (0.60)	3 (0.18)	3.27 (0.90–11.89)	0.071	0.41 (−0.01 to 0.84)	0.090
Definite stent thrombosis	4 (0.69)	4 (0.67)	1.03 (0.26–4.12)	0.965	0.02 (−0.92 to 0.96)	7 (0.42)	3 (0.18)	2.29 (0.59–8.85)	0.230	0.24 (−0.14 to 0.61)	0.419
Probable stent thrombosis	0 (0.00)	2 (0.33)	0.21 (0.01–4.36)	0.500	−0.33 (−0.79 to 0.13)	3 (0.18)	0 (0.00)	6.87 (0.36–132.90)	0.250	0.18 (−0.02 to 0.38)	1.000
Bleeding BARC classification											
Type 1	19 (3.28)	32 (5.34)	0.61 (0.34–1.07)	0.083	−2.06 (−4.37 to 0.25)	46 (2.73)	77 (4.65)	0.58 (0.40–0.83)	0.003	−1.93 (−3.21 to −0.65)	0.891
Type 2	26 (4.49)	42 (7.00)	0.63 (0.38–1.02)	0.060	−2.51 (−5.16 to 0.14)	76 (4.52)	110 (6.67)	0.67 (0.50–0.90)	0.007	−2.16 (−3.72 to −0.59)	0.824
Type 3	11 (1.90)	16 (2.67)	0.70 (0.33–1.52)	0.369	−0.77 (−2.47 to 0.93)	42 (2.50)	43 (2.61)	0.95 (0.62–1.46)	0.830	−0.10 (−1.17 to 0.97)	0.494
Type 3a	9 (1.55)	10 (1.67)	0.92 (0.38–2.27)	0.861	−0.12 (−1.55 to 1.32)	17 (1.01)	20 (1.21)	0.83 (0.44–1.59)	0.576	−0.20 (−0.91 to 0.52)	0.854
Type 3b	2 (0.35)	4 (0.67)	0.52 (0.09–2.82)	0.444	−0.32 (−1.13 to 0.49)	19 (1.13)	16 (0.97)	1.16 (0.60–2.26)	0.657	0.16 (−0.53 to 0.86)	0.381
Type 3c	1 (0.17)	2 (0.34)	0.52 (0.05–5.68)	0.588	−0.16 (−0.74 to 0.42)	6 (0.36)	7 (0.42)	0.84 (0.28–2.50)	0.754	−0.07 (−0.49 to 0.36)	0.717

Continued

Table 2 *Continued*

	Complex PCI					Non-complex PCI					Interaction P-value
	Abbreviated DAPT N = 588	Standard DAPT N = 608	Hazard ratio (95% CI)	P-value	Absolute risk difference (95% CI)	Abbreviated DAPT N = 1707	Standard DAPT N = 1676	Hazard ratio (95% CI)	P-value	Absolute risk difference (95% CI)	
Type 4	0 (0.00)	0 (0.00)				0 (0.00)	0 (0.00)				
Type 5	0 (0.00)	2 (0.34)	0.21 (0.01–4.36)	0.500	−0.34 (−0.80 to 0.13)	2 (0.12)	6 (0.37)	0.33 (0.07–1.62)	0.170	−0.25 (−0.58 to 0.09)	
Type 5a	0 (0.00)	0 (0.00)				0 (0.00)	2 (0.12)	0.20 (0.01–4.16)	0.245	−0.12 (−0.29 to 0.05)	1.000
Type 5b	0 (0.00)	2 (0.34)	0.21 (0.01–4.36)	0.500	−0.34 (−0.80 to 0.13)	2 (0.12)	4 (0.24)	0.49 (0.09–2.67)	0.409	−0.12 (−0.42 to 0.17)	
Type 3 or 5	11 (1.90)	18 (3.00)	0.63 (0.30–1.32)	0.220	−1.10 (−2.86 to 0.66)	44 (2.62)	49 (2.97)	0.88 (0.58–1.32)	0.529	−0.34 (−1.46 to 0.78)	0.435

Hazard ratio (95% CI) from Cox's time-to-first event analyses in ITT population. Continuity corrected risk ratios (95% CI) in case of zero events with Fisher's exact test *P*-value. Interaction *P*-value testing for modifying effect of Complex PCI (yes or no) on the hazard ratio scale. Absolute risk differences are shown as percentage points. MACCE, co-primary composite endpoint of all-cause death, myocardial infarction, stroke; MCB, co-primary composite endpoint of bleeding BARC 2, 3, or 5; NACE, co-primary composite endpoint of all-cause death, myocardial infarction, stroke, and bleeding BARC 3 or 5.
[a]Includes undetermined strokes.

(88%) patients with complex and 3383 (88%) without complex PCI were randomized (median 34 days post-stenting, interquartile range: 32–39) to an abbreviated ($n = 2295$ patients; complex PCI, $n = 588$; non-complex PCI, $n = 1707$) or a standard ($n = 2284$ patients complex PCI, $n = 608$; non-complex PCI, $n = 1676$) DAPT regimen. Clinical and procedural characteristics of the patients who did not undergo randomization are shown in the Supplementary material online, Appendix and were consistent across complex PCI strata (see Supplementary material online, *Tables S1 and S2*). More patients in the non-complex PCI group withdrew after consent due to medical reasons, whereas more patients in the complex PCI group died before randomization (see Supplementary material online, *Table S3*). Complex PCI criteria distribution is shown in Supplementary material online, *Table S4*.

Patients with complex PCI were more likely to be older, have a history of prior myocardial infarction, arterial thrombo-embolism, chronic renal failure, or non-ST-segment elevation ACS, but less likely to have prior bleeding or unstable angina, compared with the non-complex PCI group (see Supplementary material online, *Tables S5 and S6*). Procedural characteristics were largely imbalanced between complex and non-complex PCI patients (see Supplementary material online, *Tables S6*). Antiplatelet therapies in complex and non-complex PCI patients as stratified by study group are shown in *Figure 1* and Supplementary material online, *Table S7*. Type of antiplatelet therapy before and after randomization in patients with or without complex PCI in the abbreviated arm is shown in Supplementary material online, *Table S8*. Complex PCI patients incurred more myocardial infarctions compared with non-complex PCI patients (3.6 vs. 2.0%; HR: 1.78, 95% CI:1.21–2.61, $P = 0.004$), which was only marginally explained by a numerical difference in definite or probable stent thrombosis between groups (0.9 vs. 0.4%; HR: 2.17, 95% CI:0.95–4.94, $P = 0.066$, Supplementary material online, *Table S9*).

Baseline, angiographic, and procedural characteristics stratified by PCI complexity were well balanced between the two antiplatelet regimens (*Table 1* and Supplementary material online, *Table S10*).

Primary outcomes

Net adverse clinical events and MACCE did not differ with abbreviated vs. standard DAPT regimens among patients with complex [HR: 1.03, 95% CI: 0.69–1.52, $P = 0.90$, risk difference 0.27 (−2.85 to 3.39) and HR: 1.24, 95% CI: 0.79–1.92, $P = 0.349$, risk difference 1.39 (−1.43 to 4.22), respectively] and non-complex PCI [HR: 0.90, 95% CI: 0.71–1.15, $P = 0.418$, risk difference −0.74 (−2.53 to 1.06), and HR: 0.91, 95% CI: 0.69–1.21, risk difference −0.53 (−2.11 to 1.06), $P = 0.520$; $P_{interaction} = 0.60$ and 0.26, respectively]. BARC 2, 3, or 5 bleeding was significantly and consistently reduced in patients with and without complex PCI [HR: 0.64; 95% CI: 0.42–0.98, $P = 0.038$, risk difference −3.11 (−6.13 to −0.10) and HR: 0.70; 95% CI: 0.55–0.89, risk difference −2.72 (−4.57 to −0.87), $P = 0.004$; $P_{interaction} = 0.72$] (*Table 2* and *Figures 1 and 2*). The primary bleeding endpoint remained reduced with abbreviated DAPT in patients with or without complex PCI at competing risk of death analyses (see Supplementary material online, *Table S11*). The results remained entirely consistent when an alternative and more comprehensive complex PCI definition was explored at *post hoc* analysis (see Supplementary material online, *Table S12*).

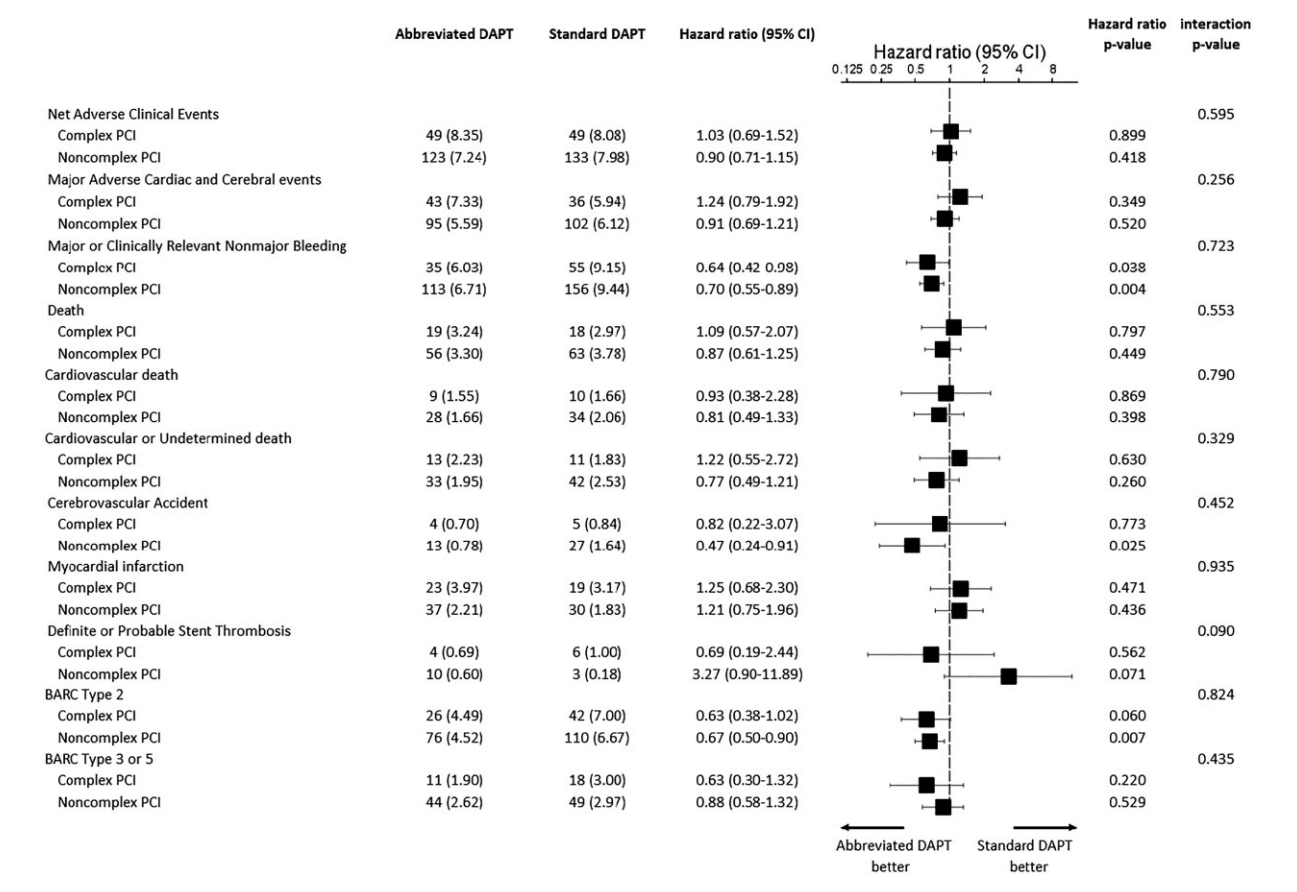


Figure 2 Clinical endpoints stratified by complexity of percutaneous coronary intervention. CI, confidence interval; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; BARC, bleeding academic research consortium.

Secondary outcomes

There was no overall evidence of heterogeneity of the treatment effects in relation to PCI complexity and none of the secondary endpoints differed between abbreviated and standard DAPT regimens in complex or non-complex PCI groups, with the only exceptions for BARC 1 and BARC 2 bleeding, which were lower (HR: 0.58, 95% CI: 0.40–0.83, $P = 0.003$; HR: 0.67, 95% CI: 0.50–0.90, $P = 0.007$, respectively) or trended lower (HR: 0.61, 95% CI: 0.34–1.07, $P = 0.08$; HR: 0.63, 95% CI: 0.38–1.02, $P = 0.06$, respectively) with abbreviated compared with standard DAPT in non-complex and complex PCI groups, respectively (*Table 2* and *Figure 1*). The results remained entirely consistent when an alternative and more comprehensive complex PCI definition as explored in *post hoc* analysis (see Supplementary material online, *Table S12*).

Complex percutaneous coronary intervention and/or acute coronary syndrome

Net adverse clinical events and MACCE did not differ with abbreviated vs. standard DAPT regimens among patients with complex PCI and/or ACS ($n = 2,816$; HR: 0.94, 95% CI: 0.73–1.21, $P = 0.62$ and HR: 1.00, 95% CI: 0.76–1.33, $P = 0.97$, respectively) and non-complex PCI without ACS ($n = 1743$; HR: 0.92, 95% CI: 0.64–1.32, $P = 0.66$ and HR: 0.95, 95% CI: 0.61–1.48, $P = 0.816$; $P_{interaction} = 0.94$ and 0.83, respectively) (*Table 3*). BARC 2, 3, or 5 bleeding was significantly and consistently reduced in patients with or without complex PCI and/or ACS (HR: 0.70; 95% CI: 0.53–0.93, $P = 0.013$ and HR: 0.66; 95% CI: 0.48–0.91, $P = 0.012$; $P_{interaction} = 0.78$). The primary bleeding endpoint remained reduced with abbreviated DAPT in patients with or without complex PCI and/or ACS at competing risk analyses (see Supplementary material online, *Table S13*). The results remained entirely consistent with abbreviated vs. standard DAPT regimens among ACS patients who underwent complex PCI ($n = 571$) and ACS patients who underwent non-complex PCI ($n = 1640$, *Table 4* and *Figure 3*).

Risk/benefit tradeoff of abbreviated dual antiplatelet therapy regimen

The NNTH for myocardial infarction and definite or probable stent thrombosis, calculated from between-group non-significant differences, were consistently higher than the NNTB for BARC 2, 3, or 5 and BARC 3 or 5, calculated from between-group significant or non-significant differences, in all complex PCI, complex PCI, and/or ACS and complex PCI ACS patients with abbreviated compared with standard treatment (*Figure 4*).

Table 3 Clinical endpoints at 11 months post-randomization with complex PCI and/or acute coronary syndrome

	Complex PCI or ACS					Non-complex PCI and no ACS					
	Abbreviated DAPT N = 1433	Standard DAPT N = 1403	Hazard ratio (95% CI)	P-value	Absolute risk difference (95% CI)	Abbreviated DAPT N = 862	Standard DAPT N = 881	Hazard ratio (95% CI)	P-value	Absolute risk difference (95% CI)	Interaction P-value
Net adverse clinical events (NACE)	117 (8.19)	121 (8.66)	0.94 (0.73–1.21)	0.622	−0.47 (−2.52 to 1.58)	55 (6.42)	61 (6.95)	0.92 (0.64–1.32)	0.655	−0.54 (−2.89 to 1.82)	0.935
Major adverse cardiac or cerebral events (MACCE)	100 (7.00)	97 (6.95)	1.00 (0.76–1.33)	0.974	0.06 (−1.82 to 1.93)	38 (4.44)	41 (4.68)	0.95 (0.61–1.48)	0.816	−0.24 (−2.20 to 1.72)	0.833
Major or clinically relevant non-major bleeding (MCB)	86 (6.10)	117 (8.46)	0.70 (0.53–0.93)	0.013	−2.36 (−4.29 to −0.44)	62 (7.27)	94 (10.78)	0.66 (0.48–0.91)	0.012	−3.51 (−6.21 to −0.81)	0.781
Death	52 (3.64)	55 (3.94)	0.92 (0.63–1.35)	0.670	−0.30 (−1.71 to 1.11)	23 (2.69)	26 (2.97)	0.91 (0.52–1.59)	0.727	−0.28 (−1.84 to 1.28)	0.960
Cardiovascular death	24 (1.70)	27 (1.95)	0.87 (0.50–1.50)	0.609	−0.26 (−1.25 to 0.74)	13 (1.53)	17 (1.95)	0.78 (0.38–1.61)	0.505	−0.42 (−1.65 to 0.81)	0.827
Non-cardiovascular death	20 (1.42)	20 (1.45)	0.97 (0.52–1.81)	0.933	−0.03 (−0.92 to 0.85)	9 (1.06)	8 (0.92)	1.15 (0.44–2.98)	0.772	0.14 (−0.80 to 1.07)	0.772
Undetermined death	8 (0.57)	8 (0.58)	0.97 (0.37–2.59)	0.957	−0.02 (−0.58 to 0.55)	1 (0.12)	1 (0.11)	1.02 (0.06–16.38)	0.986	0.00 (−0.32 to 0.32)	0.974
Cardiovascular or undetermined death	32 (2.25)	35 (2.52)	0.89 (0.55–1.44)	0.636	−0.27 (−1.40 to 0.86)	14 (1.64)	18 (2.06)	0.80 (0.40–1.60)	0.521	−0.42 (−1.69 to 0.85)	0.794
Cerebrovascular accident	10 (0.72)	20 (1.46)	0.49 (0.23–1.04)	0.062	−0.74 (−1.52 to 0.03)	7 (0.82)	12 (1.38)	0.60 (0.23–1.51)	0.277	−0.56 (−1.54 to 0.43)	0.741
Stroke[a]	8 (0.57)	13 (0.95)	0.60 (0.25–1.44)	0.254	−0.38 (−1.03 to 0.27)	4 (0.47)	10 (1.15)	0.41 (0.13–1.31)	0.131	−0.68 (−1.53 to 0.16)	0.607
Ischaemic stroke	7 (0.50)	10 (0.73)	0.68 (0.26–1.79)	0.436	−0.23 (−0.81 to 0.35)	4 (0.47)	8 (0.92)	0.51 (0.15–1.70)	0.274	−0.45 (−1.24 to 0.33)	0.714
Haemorrhagic stroke	1 (0.07)	3 (0.22)	0.32 (0.03–3.12)	0.330	−0.15 (−0.43 to 0.14)	0 (0.00)	2 (0.23)	0.20 (0.01–4.16)	0.500	−0.23 (−0.55 to 0.09)	
TIA	2 (0.15)	7 (0.51)	0.28 (0.06–1.34)	0.110	−0.37 (−0.80 to 0.06)	3 (0.36)	2 (0.23)	1.53 (0.26–9.18)	0.639	0.13 (−0.38 to 0.64)	0.160
Myocardial infarction	47 (3.34)	41 (2.99)	1.12 (0.74–1.70)	0.601	0.36 (−0.94 to 1.66)	13 (1.53)	8 (0.92)	1.67 (0.69–4.02)	0.256	0.61 (−0.43 to 1.66)	0.422
Definite or probable stent thrombosis	12 (0.85)	8 (0.58)	1.47 (0.60–3.58)	0.403	0.27 (−0.36 to 0.90)	2 (0.24)	1 (0.11)	2.04 (0.19–22.54)	0.559	0.12 (−0.27 to 0.52)	0.798
Definite stent thrombosis	9 (0.64)	6 (0.44)	1.46 (0.52–4.11)	0.469	0.20 (−0.34 to 0.75)	2 (0.24)	1 (0.11)	2.04 (0.19–22.54)	0.559	0.12 (−0.27 to 0.52)	0.802
Probable stent thrombosis	3 (0.21)	2 (0.15)	1.46 (0.24–8.76)	0.677	0.07 (−0.25 to 0.38)	0 (0.00)	0 (0.00)				
Bleeding BARC classification											
Type 1	40 (2.83)	72 (5.22)	0.53 (0.36–0.79)	0.002	−2.38 (−3.84 to −0.93)	25 (2.93)	37 (4.24)	0.69 (0.41–1.14)	0.146	−1.31 (−3.06 to 0.44)	0.447
Type 2	59 (4.19)	84 (6.10)	0.67 (0.48–0.94)	0.020	−1.91 (−3.55 to −0.26)	43 (5.05)	68 (7.81)	0.64 (0.44–0.93)	0.021	−2.76 (−5.07 to −0.45)	0.825
Type 3	30 (2.13)	34 (2.46)	0.86 (0.52–1.40)	0.535	−0.33 (−1.44 to 0.78)	23 (2.71)	25 (2.87)	0.94 (0.53–1.65)	0.824	−0.16 (−1.72 to 1.40)	0.811
Type 3a	16 (1.14)	23 (1.67)	0.68 (0.36–1.28)	0.228	−0.53 (−1.40 to 0.34)	10 (1.18)	7 (0.80)	1.46 (0.56–3.84)	0.440	0.38 (−0.56 to 1.32)	0.190
Type 3b	12 (0.85)	8 (0.58)	1.46 (0.60–3.58)	0.406	0.27 (−0.35 to 0.90)	9 (1.06)	12 (1.38)	0.77 (0.32–1.82)	0.544	−0.32 (−1.36 to 0.72)	0.308
Type 3c	3 (0.21)	3 (0.22)	0.98 (0.20–4.83)	0.975	0.00 (−0.35 to 0.34)	4 (0.47)	6 (0.69)	0.68 (0.19–2.42)	0.553	−0.22 (−0.94 to 0.50)	0.731

Continued

Table 3 *Continued*

	Complex PCI or ACS				Non-complex PCI and no ACS				Interaction P-value
	Abbreviated DAPT N = 1433	Standard DAPT N = 1403	Hazard ratio (95% CI)	P-value	Abbreviated DAPT N = 862	Standard DAPT N = 881	Hazard ratio (95% CI)	P-value	
Type 4	0 (0.00)	0 (0.00)			0 (0.00)	0 (0.00)			
Type 5	2 (0.14)	5 (0.36)	0.39 (0.08–2.01)	0.260	0 (0.00)	3 (0.35)	0.15 (0.01–2.90)	0.250	−0.35 (−0.74 to 0.05)
Type 5a	0 (0.00)	1 (0.07)	0.33 (0.01–8.09)	0.495	0 (0.00)	1 (0.12)	0.34 (0.01–8.33)	1.000	−0.12 (−0.35 to 0.11)
Type 5b	2 (0.14)	4 (0.29)	0.49 (0.09–2.65)	0.405	0 (0.00)	2 (0.23)	0.20 (0.01–4.16)	0.500	−0.23 (−0.55 to 0.09)
Type 3 or 5	32 (2.27)	39 (2.82)	0.80 (0.50–1.27)	0.339	23 (2.71)	28 (3.22)	0.84 (0.48–1.45)	0.527	−0.51 (−2.11 to 1.10)

Hazard ratio (95% CI) from Cox's time-to-first event analyses in ITT population. Continuity corrected risk ratios (95% CI) in case of zero events with Fisher's exact test *P*-value. Interaction *P*-value testing for modifying effect of Complex PCI or ACS vs. none of these on the hazard ratio scale. Absolute risk differences are shown as percentage points. NACE = co-primary composite endpoint of all-cause death, myocardial infarction, stroke, and bleeding BARC 3 or 5; MACCE, co-primary composite endpoint of all-cause death, myocardial infarction, stroke; MCB, co-primary composite endpoint of bleeding BARC 2, 3, or 5; ACS, STEMI, NSTEMI, and unstable angina.
[a]Includes undetermined strokes.

Discussion

The main findings of the current analysis from the international, multicentre, randomized MASTER DAPT trial, in which we examined the efficacy and safety of a 1 month vs. standard DAPT regimen in HBR patients after PCI, in relation to procedural or patient complexities, can be summarized as follows: (i) complex PCI or complex PCI and/or ACS at presentation did not affect the comparative efficacy and safety of an abbreviated vs. a more prolonged DAPT regimen in HBR patients. This observation is supported by negative interaction testing for the three ranked primary or major secondary endpoints; (ii) an abbreviated DAPT regimen was not associated with significantly higher risk of composite or individual ischaemic events compared with standard DAPT among HBR patients with complex PCI or complex PCI and/or ACS at presentation; and (iii) an abbreviated DAPT regimen resulted in significantly lower major or clinically relevant non-major bleeding complications compared with a non-abbreviated DAPT regimen, which was consistent across complex PCI and complex PCI and/or ACS strata (*Structured Graphical Abstract*).

MASTER DAPT, by design, enrolled HBR patients who underwent PCI of all intended *de novo* lesions with biodegradable-polymer-coated sirolimus-eluting stent(s), without restrictions based on number, type or location of the treated stenosis, or clinical presentation.[8] This drove a large proportion of study patients fulfilling complex PCI criteria ($N = 1196$ or 26%) and/or presented with ACS ($N = 2211$ or 48.3%) or presented both ($N = 571$ or 12.5%) characteristics. To the best of our knowledge, the current analysis represents the largest study investigating 1- vs. ≥3-month DAPT after complex PCI in HBR patients.

The analysis of consented vs. included patients showed no discernable bias from PCI to 1-month randomization in relation to the presence or absence of complex PCI criteria; an identical proportion of patients (88%) with or without complex PCI entered the trial after being consented. Notably, 30-day mortality was higher in patients with one or more complex PCI criteria compared with the non-complex PCI group, whereas from randomization to 335 days, complex PCI patients incurred more myocardial infarctions than non-complex PCI patients, largely due to non-stent related occurrences. In the complex PCI group, definite or definite or probable stent thrombosis explained only 19 and 24% of the overall myocardial infarction cases, respectively. The corresponding figures in the non-complex PCI group were 15 and 19%, respectively. These findings indicate that, even in the context of complex PCI patients with or without ACS, undergoing a relatively short (6 months) or very short (1 month) DAPT regimen, the majority of myocardial infarctions derives from non-stented coronary segments.[14] Bleeding risk was not higher in complex compared with non-complex PCI patients, which is also a consistent finding with previous studies.[15–17] Therefore, the consistency of the treatment effects of an abbreviated compared with a more prolonged DAPT regimen across the spectrum of PCI complexities remains critical to assess. More specifically, whether an abbreviated course of treatment mitigates bleeding without increasing ischaemic risks in selected patients who underwent complex PCI.

Net adverse clinical events or MACCE did not differ with abbreviated compared with standard DAPT in patients with or without complex PCI criteria with no signal of treatment-by-subgroup interaction. BARC 2, 3, or 5 bleeding was significantly and consistently reduced in patients with and without complex PCI. These findings

Table 4 Clinical endpoints at 11 months post-randomization with acute coronary syndrome

	Complex PCI				Non-complex PCI				
	Abbreviated DAPT *N* = 283	Standard DAPT *N* = 288	Hazard ratio (95% CI)	*P*-value	Abbreviated DAPT *N* = 845	Standard DAPT *N* = 795	Hazard ratio (95% CI)	*P*-value	interaction *P*-value
Net adverse clinical events (NACE)	28 (9.89)	28 (9.77)	1.00 (0.59–1.69)	0.998	68 (8.08)	72 (9.11)	0.88 (0.63–1.23)	0.450	0.683
Major adverse cardiac or cerebral events (MACCE)	25 (8.83)	23 (8.02)	1.09 (0.62–1.93)	0.757	57 (6.77)	61 (7.72)	0.87 (0.61–1.25)	0.457	0.508
Major or clinically relevant non-major bleeding (MCB)	18 (6.46)	30 (10.68)	0.58 (0.33–1.05)	0.071	51 (6.14)	62 (7.93)	0.76 (0.52–1.10)	0.146	0.464
Death	12 (4.24)	12 (4.18)	1.00 (0.45–2.23)	0.994	33 (3.92)	37 (4.68)	0.83 (0.52–1.33)	0.446	0.695
Cardiovascular death	6 (2.15)	8 (2.82)	0.75 (0.26–2.17)	0.598	15 (1.80)	17 (2.18)	0.83 (0.41–1.65)	0.587	0.888
Non-cardiovascular death	4 (1.43)	4 (1.41)	1.00 (0.25–4.01)	0.996	14 (1.69)	13 (1.67)	1.01 (0.47–2.14)	0.989	0.997
Undetermined death	2 (0.72)	0 (0.00)	5.09 (0.25–105.55)	0.245	4 (0.48)	7 (0.91)	0.53 (0.16–1.82)	0.317	
Cardiovascular or undetermined death	8 (2.85)	8 (2.82)	1.00 (0.38–2.67)	0.996	19 (2.27)	24 (3.06)	0.74 (0.41–1.35)	0.327	0.603
Cerebrovascular accident	1 (0.37)	3 (1.08)	0.33 (0.03–3.20)	0.341	6 (0.73)	15 (1.94)	0.37 (0.14–0.96)	0.040	0.931
Stroke[a]	0 (0.00)	2 (0.72)	0.20 (0.01–4.15)	0.499	5 (0.61)	9 (1.16)	0.52 (0.17–1.55)	0.239	
Ischaemic stroke	0 (0.00)	1 (0.36)	0.34 (0.01–8.31)	1.000	4 (0.48)	7 (0.90)	0.53 (0.16–1.82)	0.316	
Haemorhagic stroke	0 (0.00)	1 (0.36)	0.34 (0.01–8.31)	1.000	1 (0.12)	2 (0.26)	0.47 (0.04–5.14)	0.533	1.000
TIA	1 (0.37)	1 (0.36)	1.00 (0.06–15.93)	0.998	1 (0.12)	6 (0.78)	0.16 (0.02–1.29)	0.084	0.295
Myocardial infarction	15 (5.39)	12 (4.27)	1.26 (0.59–2.69)	0.552	24 (2.90)	22 (2.85)	1.02 (0.57–1.82)	0.946	0.667
Definite or probable stent thrombosis	3 (1.08)	5 (1.79)	0.60 (0.14–2.51)	0.485	8 (0.97)	2 (0.26)	3.75 (0.80–17.67)	0.094	0.089
Definite stent thrombosis	3 (1.08)	3 (1.08)	1.00 (0.20–4.95)	0.999	5 (0.61)	2 (0.26)	2.34 (0.45–12.08)	0.309	0.467
Probable stent thrombosis	0 (0.00)	2 (0.71)	0.20 (0.01–4.15)	0.499	3 (0.36)	0 (0.00)	6.59 (0.34–127.38)	0.250	1.000
Bleeding BARC classification									
Type 1	9 (3.25)	16 (5.68)	0.56 (0.25–1.26)	0.159	21 (2.52)	40 (5.12)	0.49 (0.29–0.82)	0.007	0.773
Type 2	13 (4.69)	22 (7.88)	0.58 (0.29–1.15)	0.117	33 (3.98)	42 (5.40)	0.73 (0.46–1.15)	0.170	0.594
Type 3	6 (2.15)	8 (2.85)	0.75 (0.26–2.16)	0.592	19 (2.29)	18 (2.30)	0.99 (0.52–1.88)	0.964	0.665
Type 3a	5 (1.79)	5 (1.79)	1.00 (0.29–3.46)	0.999	7 (0.84)	13 (1.67)	0.50 (0.20–1.26)	0.142	0.379
Type 3b	1 (0.36)	2 (0.70)	0.50 (0.05–5.56)	0.576	10 (1.21)	4 (0.51)	2.34 (0.73–7.46)	0.151	0.257

Continued

Table 4 *Continued*

	Complex PCI				Non-complex PCI				
	Abbreviated DAPT $N = 283$	Standard DAPT $N = 288$	Hazard ratio (95% CI)	*P*-value	Abbreviated DAPT $N = 845$	Standard DAPT $N = 795$	Hazard ratio (95% CI)	*P*-value	interaction *P*-value
Type 3c	0 (0.00)	1 (0.37)	0.34 (0.01–8.31)	1.000	2 (0.24)	1 (0.13)	1.87 (0.17–20.67)	0.608	
Type 4	0 (0.00)	0 (0.00)			0 (0.00)	0 (0.00)			
Type 5	0 (0.00)	2 (0.72)	0.20 (0.01–4.15)	0.499	2 (0.25)	3 (0.39)	0.62 (0.10–3.73)	0.604	1.000
Type 5a	0 (0.00)	0 (0.00)			0 (0.00)	1 (0.13)	0.31 (0.01–7.60)	0.485	1.000
Type 5b	0 (0.00)	2 (0.72)	0.20 (0.01–4.15)	0.499	2 (0.25)	2 (0.26)	0.93 (0.13–6.61)	0.944	
Type 3 or 5	6 (2.15)	10 (3.56)	0.60 (0.22–1.65)	0.321	21 (2.54)	21 (2.69)	0.93 (0.51–1.71)	0.823	0.461

Hazard ratio (95% CI) from Cox's time-to-first event analyses in ITT population. Continuity corrected risk ratios (95% CI) in case of zero events with Fisher's exact test *P*-value. Interaction *P*-value testing for modifying effect of Complex PCI (yes or no) on the hazard ratio scale. NACE, co-primary composite endpoint of all-cause death, myocardial infarction, stroke, and bleeding BARC 3 or 5; MACCE, co-primary composite endpoint of all-cause death, myocardial infarction, stroke; MCB, co-primary composite endpoint of bleeding BARC 2, 3, or 5; ACS, STEMI, NSTEMI, and unstable angina.
[a]Includes undetermined strokes.

suggest that PCI complexity does not justify *per se* a more prolonged course of DAPT, in excess of 1 month, in HBR patients who did not encounter recurrent ischaemic events in the first 30 days after intervention. Our findings remained entirely consistent when the intersection between complex PCI and ACS at presentation (complex patients) was further investigated, therefore replicating prospectively, with an even shorted DAPT regimen, the previously published retrospective observations arising from a combined dataset of eight trials that investigated 3–6 months vs. DAPT vs. 12 months or more of treatment duration.[1] Based on these prior findings, the control group of the present trial set DAPT duration at a minimum of 3 months, with a median duration of 193 days (interquartile range, 102–366).[8] The results of this analysis supports the use of a further shortened DAPT duration (median 34 days; interquartile range, 31–39) in HBR patients with or without complex PCI and irrespective of concomitant ACS. Our study was powered for assessing the non-inferiority of NACE and MACCE in the overall study population based on absolute risk differences expected to represent 30% of the corresponding event rates. No non-inferiority claim is obviously possible when interpreting subgroup analyses, to which this study is by definition underpowered. Therefore, similar to all subgroup analyses, our study is hypothesis-generating with respect to the risks and benefits of an abbreviated compared with a standard DAPT regimen in patients who underwent complex PCI and/or with ACS. Our results are consistent with prior studies which assessed the consistency of the treatment effects of a shortened DAPT regimen of either 1[4] or 3[11] month(s), followed by ticagrelor monotherapy compared with 12-month DAPT in patients who were not selected based on HBR criteria and underwent complex PCI.[18]

When the secondary endpoints were separately appraised, the results observed in the over trial population were consistently replicated in patients with or without complex PCI, suggesting no significant excess of myocardial infarction, stent thrombosis, or stroke with an abbreviated DAPT regimen, nor a significant difference of major bleeding. As observed in the overall trial population, there were numerical imbalances of myocardial infarction in disfavour, and of major bleeding in favour, of the abbreviated DAPT group in both complex and non-complex PCI patients. The rate of definite or probable stent thrombosis was numerical lower with abbreviated compared with standard DAPT in the complex PCI group, which therefore did not explain the insignificant small excess of myocardial infarction observed with abbreviated DAPT in this patient subgroup. In the complex PCI patients, ticagrelor, rather than aspirin monotherapy, was more frequently selected after DAPT discontinuation in the abbreviated arm compared with non-complex PCI patients. Ticagrelor monotherapy was shown more effective for myocardial infarction and stent thrombosis prevention compared with aspirin monotherapy.[19,20] However, in both complex and non-complex PCI patients, clopidogrel remained the most frequently used antiplatelet therapy after DAPT in the abbreviated arm.

In the non-complex PCI group, there was a small excess of stent thrombosis with abbreviated compared with standard DAPT, which explained 27 and 10% of the overall myocardial infarction events in the abbreviated and standard groups, respectively. Our study was clearly underpowered for relatively rarer endpoints such as myocardial infarction or major bleeding and even more for stent thrombosis. As a result, despite non-significant, these observations may indicate

the existence of a small risk of coronary ischaemic events and a small benefit in terms of major bleeding with abbreviated DAPT, in both patients with or without complex PCI. The appraisal of the tradeoff between possible risks and possible benefit is essential as they have been shown to exert similar prognostic implications for mortality.[21]

The computation of NNTH for myocardial infarction or stent thrombosis and NNTB for major or major and clinically relevant minor bleeding showed that the former were lower than the latter in complex PCI, complex PCI and/or ACS as well as complex PCI and ACS. Therefore, even assuming the existence of a tradeoff between risks and benefits in HBR patients in relation to DAPT duration, our analysis support the hypothesis that 1-month DAPT remains the preferrable treatment option in HBR patients who underwent complex PCI and did not experience ischaemic recurrences in the first 1 month after treatment.

The present results need to be interpreted in light of the several imitations.

The absence of a universally accepted definition for complex PCI is notable. We used the criteria proposed by Giustino *et al.*[2] because this approach integrated, by consensus, features of procedural complexity which were associated with higher risks in prior studies, have been adopted since then by multiple investigators[1,4,15–17] and this definition was used to generate the hypothesis, tested in the MASTER DAPT trial, that presence of HBR is a treatment modifier for DAPT duration, irrespective of PCI or patient complexity. However, results remained entirely consistent when an alternative and more comprehensive complex PCI definition was implemented, suggesting robust findings.

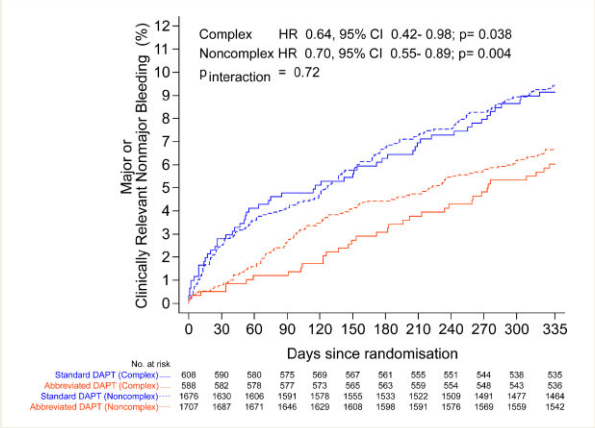


Figure 3 Kaplan–Meier curve for major or clinically relevant nonmajor bleeding stratified by complexity of percutaneous coronary intervention. CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio.

	Abbreviated DAPT	Standard DAPT	Hazard ratio (95% CI)	Hazard ratio p-value	interaction p-value
Net Adverse Clinical Events					0.683
Complex PCI	28 (9.89)	28 (9.77)	1.00 (0.59-1.69)	0.998	
Noncomplex PCI	68 (8.08)	72 (9.11)	0.88 (0.63-1.23)	0.450	
Major Adverse Cardiac and Cerebral events					0.508
Complex PCI	25 (8.83)	23 (8.02)	1.09 (0.62-1.93)	0.757	
Noncomplex PCI	57 (6.77)	61 (7.72)	0.87 (0.61-1.25)	0.457	
Major or Clinically Relevant Nonmajor Bleeding					0.464
Complex PCI	18 (6.46)	30 (10.68)	0.58 (0.33-1.05)	0.071	
Noncomplex PCI	51 (6.14)	62 (7.93)	0.76 (0.52-1.10)	0.146	
Death					0.695
Complex PCI	12 (4.24)	12 (4.18)	1.00 (0.45-2.23)	0.994	
Noncomplex PCI	33 (3.92)	37 (4.68)	0.83 (0.52-1.33)	0.446	
Cardiovascular death					0.888
Complex PCI	6 (2.15)	8 (2.82)	0.75 (0.26-2.17)	0.598	
Noncomplex PCI	15 (1.80)	17 (2.18)	0.83 (0.41-1.65)	0.587	
Cardiovascular or Undetermined death					0.603
Complex PCI	8 (2.85)	8 (2.82)	1.00 (0.38-2.67)	0.996	
Noncomplex PCI	19 (2.27)	24 (3.06)	0.74 (0.41-1.35)	0.327	
Cerebrovascular Accident					0.931
Complex PCI	1 (0.37)	3 (1.08)	0.33 (0.03-3.20)	0.341	
Noncomplex PCI	6 (0.73)	15 (1.94)	0.37 (0.14-0.96)	0.040	
Myocardial infarction					0.667
Complex PCI	15 (5.39)	12 (4.27)	1.26 (0.59-2.69)	0.552	
Noncomplex PCI	24 (2.90)	22 (2.85)	1.02 (0.57-1.82)	0.946	
Definite or Probable Stent Thrombosis					0.089
Complex PCI	3 (1.08)	5 (1.79)	0.60 (0.14-2.51)	0.485	
Noncomplex PCI	8 (0.97)	2 (0.26)	3.75 (0.80-17.67)	0.094	
BARC Type 2					0.594
Complex PCI	13 (4.69)	22 (7.88)	0.58 (0.29-1.15)	0.117	
Noncomplex PCI	33 (3.98)	42 (5.40)	0.73 (0.46-1.15)	0.170	
BARC Type 3 or 5					0.461
Complex PCI	6 (2.15)	10 (3.56)	0.60 (0.22-1.65)	0.321	
Noncomplex PCI	21 (2.54)	21 (2.69)	0.93 (0.51-1.71)	0.823	

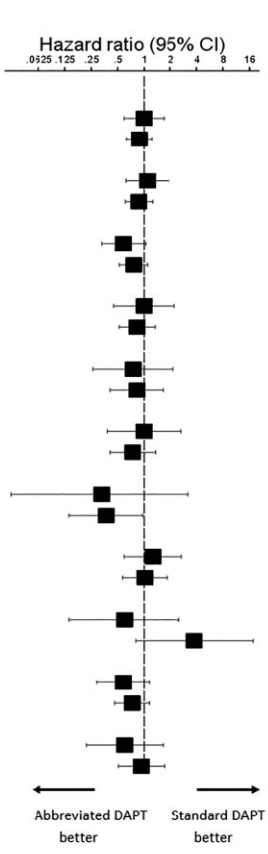


Figure 4 Clinical endpoints in acute coronary syndrome patients stratified by complexity of percutaneous coronary intervention. CI, confidence interval; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; BARC, bleeding academic research consortium.

In the overall trial, as well as in the current sub-analysis, an abbreviated DAPT regimen was associated with lower BARC 2 but not BARC 3 or 5 bleeding events. Randomization was not stratified based on PCI complexity. However, we stratified based on the history of acute myocardial infarction within the past 12 months, which almost exclusively comprised patients with ACS at presentation, as stenting within 6 months before randomization was an exclusion criterion. Our trial included HBR patients who underwent biodegradable-polymer sirolimus-eluting stent implantation; consequently, our results may not extend to non-HBR patients or who receive other stent types. Patients with in-stent restenosis or stent thrombosis were ineligible. The type of monotherapy after discontinuing DAPT was at discretion of the treating physicians and our results should be interpreted taking into account that ticagrelor was more and aspirin was less frequently preferred as monotherapy options in complex compared with non-complex PCI groups in the abbreviated arm. The type of monotherapy after DAPT discontinuation in the abbreviated arm may have influenced the treatment effects and its role cannot be easily addressed in the current analysis due to the large number of factors that may have influenced the choice.

In conclusion, in HBR patients who underwent complex or non-complex PCI with biodegradable-polymer sirolimus-eluting stent implantation and did not encounter early recurrent ischaemic events, the discontinuation of DAPT a median of 34 days after PCI, compared with continuation of treatment for a median duration of 193 days, was consistently associated with similar rates of NACE and MACCE and a lower rate of major or clinically relevant non-major bleeding.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: M.V. received an institutional grant from Terumo and consulting fees from Astra Zeneca, Terumo, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Bayer, CoreFLOW, DORSIA Pharmaceuticals LTD, Vifor, Bristol Myers Squib SA, Biotronik, Boston scientific, Medtronic, Vesalio, Novartis, Chiesi, PhaseBio, ECRI. P.C.S. received institutional grants from Microport, SMT, Daichy Sankyo, and Abbott Vascular; consulting fees from Cavis and Abbott Vascular; honoraria from Abiomed, Terumo, and Abbott Vascular; participated on advisory board of Terumo, Abbott Vascular, and SMI. B.M. received grants from Medtronic and Boston Scientific; Speaker fee from Biotronik, Abbott, Astra Zeneca, Boehringer Ingelheim, and Novartis. T.C. received consulting fees from Medtronic, Abbott vascular, Terumo, and Boston Scientific; honoraria from Medtronic, Abbott vascular, Terumo, and Boston Scientific. F.T.N.M. received consulting fees from Terumo. K.R. received honoraria from Boston Scientific, Terumo, and Astra Zeneca. P.V. received consulting fees from Daiichi Sankyo, Novartis, CSL Behring, and Bayer AG; honoraria from Daiichi Sankyo and Servier; participated on advisory board for Daiichi Sankyo. All other authors declared no conflict of interest.

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