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Impact of Medication Nonadherence in a Clinical Trial of Dual Antiplatelet Therapy

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ABSTRACT

BACKGROUND Nonadherence to antiplatelet therapy after percutaneous coronary intervention (PCI) is common, even in clinical trials.

OBJECTIVES The purpose of this study was to investigate the impact of nonadherence to study protocol regimens in the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) trial.

METHODS At 1-month after PCI, 4,579 high bleeding risk patients were randomized to single antiplatelet therapy (SAPT) for 11 months (or 5 months in patients on oral anticoagulation [OAC]) or dual antiplatelet therapy (DAPT) for ≥2 months followed by SAPT. Coprimary outcomes included net adverse clinical events (NACE), major adverse cardiac and cerebral events (MACE), and major or clinically relevant nonmajor bleeding (MCB) at 335 days. Inverse probability-of-censoring weights were used to correct for nonadherence Academic Research Consortium type 2 or 3.

RESULTS In total, 464 (20.2%) patients in the abbreviated-treatment and 214 (9.4%) in the standard-treatment groups incurred nonadherence Academic Research Consortium type 2 or 3. At inverse probability-of-censoring weights analyses, NACE (HR: 1.01; 95% CI: 0.88-1.27) or MACE (HR: 1.07; 95% CI: 0.83-1.40) did not differ, and MCB was lower with abbreviated compared with standard treatment (HR: 0.51; 95% CI: 0.60-0.73) consistently across OAC subgroups; among OAC patients, SAPT discontinuation 6 months after PCI was associated with similar MACE and lower MCB (HR: 0.47; 95% CI: 0.22-0.99) compared with SAPT continuation.

CONCLUSIONS In the MASTER DAPT adherent population, 1-month compared with ≥3-month DAPT was associated with similar NACE or MACE and lower MCB. Among OAC patients, SAPT discontinuation after 6 months was associated with similar MACE and lower MCB than SAPT continuation (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen [MASTER DAPT]; NCT03023020) (J Am Coll Cardiol 2022;80:766-778) © 2022 by the American College of Cardiology Foundation.

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Superiority and, sometimes, noninferiority trials are analyzed according to the intention-to-treat (ITT) principle. According to this principle, patients allocated to a group, are analyzed as if they all had implemented the protocol-mandated treatment strategy foreseen in the study arm. This approach may lead to overestimation or underestimation of risks and benefits if the adherence rate to the allocated treatment is suboptimal or changes over time.[1] An unbiased estimation of the true effect measure that, unlike the intention-to-treat effect, is not influenced by the degree of adherence, remains highly desirable for clinicians and complements ITT analyses.[1]

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The traditional approach to adjust for incomplete adherence is to censor outcome data after the study participants deviated from their assigned treatment strategy, often called on-treatment analysis or naïve per-protocol analysis. However, this approach can also bias the results, because it does not consider whether nonadherence patterns were driven by clinical reasons (eg, a bleeding event occurring on dual antiplatelet therapy) and assumes that nonadherence occurs at random among participants, which is rarely the case.[1,2] More sophisticated approaches have been suggested for the per-protocol analysis of trials, integrating prerandomization and postrandomization factors, which are influenced by the allocated treatment.[1-3] However, this analysis is rarely performed because it requires prespecifying all clinical conditions in which deviations from the treatment mandated by the protocol is clinically justifiable.[1]

In the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial, 1 month duration of dual antiplatelet therapy (DAPT) was noninferior for net or major adverse cardiac or cerebral events (MACE) to a standard-treatment duration and was associated with lower bleeding.[4] In this trial, adherence to protocol-mandated regimens decreased over time, especially in patients with oral anticoagulation (OAC) who were allocated to the abbreviated-treatment group.[5] Therefore, the treatment effect on ischemic and bleeding risks of 1-month DAPT followed by single antiplatelet therapy (SAPT) for 5 months in patients with OAC or 11 months in patients without OAC in adherent patients remains unclear and may have been biased by nonadherence patterns in the primary study analyses.[5]

We report the results of the prespecified per-protocol analysis of the MASTER DAPT trial in the overall and stratified populations, according to clinical indication or no clinical indication for OAC.

ABBREVIATIONS AND ACRONYMS

DAPT = dual antiplatelet therapy

IPCW = Inverse probability-of-censoring weights

ITT = intention-to-treat

MACE = major adverse cardiac and cerebral events

MCB = major or clinically relevant nonmajor bleeding

NACE = net adverse clinical events

NARC = nonadherence Academic Research Consortium

OAC = oral anticoagulation

SAPT = single antiplatelet therapy

METHODS

PATIENTS. In the MASTER DAPT trial, patients were considered for participation in the trial if they had an acute or chronic coronary syndrome; had undergone successful percutaneous coronary intervention (PCI) for 1 or more coronary artery stenoses with implantation of a biodegradable-polymer sirolimus-eluting stent (Ultimaster, Terumo), and no further revascularization of additional coronary artery stenoses was planned; and met 1 or more of the criteria for high bleeding risk.[4-6] In addition, eligible patients were required to be free of adverse cardiovascular events (including a new acute coronary syndrome, symptomatic restenosis, stent thrombosis, stroke, or any revascularization requiring prolonged dual antiplatelet therapy) during the first month after the index PCI. Exclusion criteria included implantation of a stent other than the Ultimaster stent within 6 months

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics Stratified by Type 2 or 3 Nonadherence Academic Research Consortium

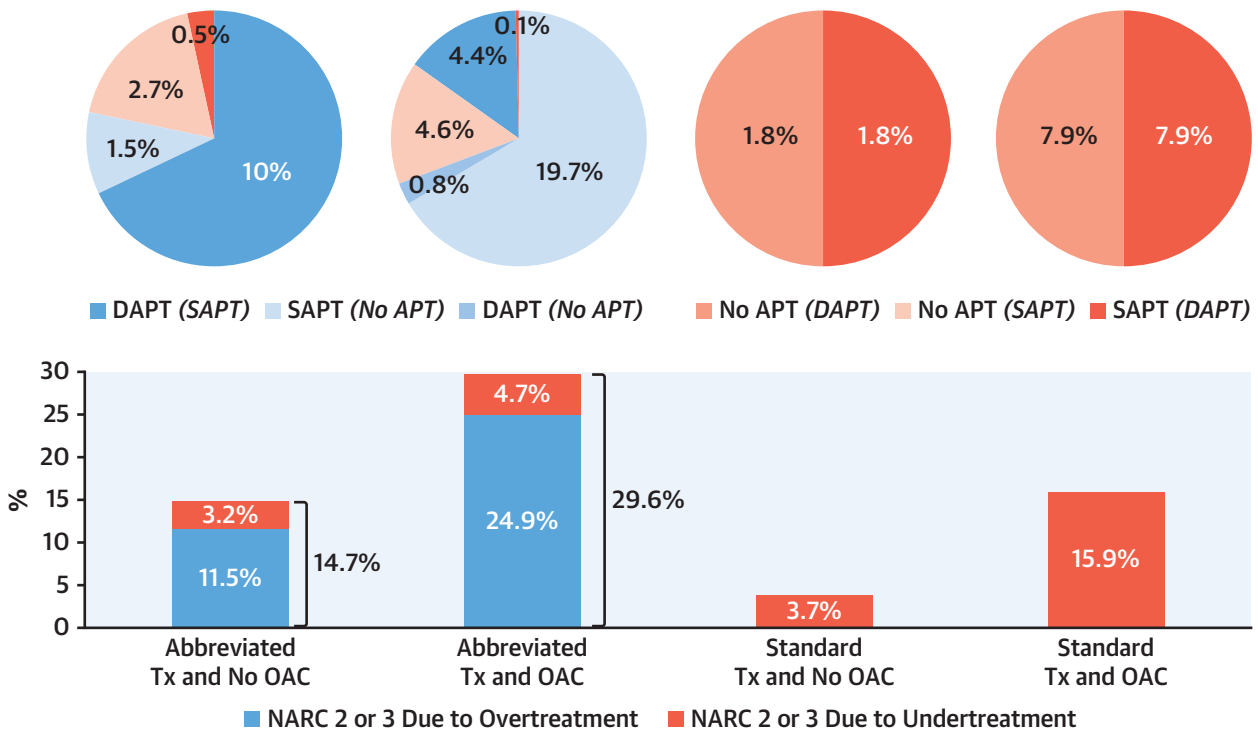
	Abbreviated Treatment Group			Standard Treatment Group		
	NARC 0 or 1 (n = 1,831)	NARC 2 or 3 (n = 464)	*P* Value (NARC 0/1 vs 2/3)	NARC 0 or 1 (n = 2,070)	NARC 2 or 3 (n = 214)	*P* Value (NARC 0/1 vs 2/3)
Age, y	76.2 ± 8.7	75·8 ± 8.8	0.36	75.91 ± 8.84	76.40 ± 8.05	0.441
Male	1,247 (68.1)	343 (73.9)	0.015	1,423 (68.7)	158 (73.8)	0.139
Body mass index, kg/m^2	27.15 ± 4.63	27.66 ± 4.85	0.038	27.40 ± 4.74	27.83 ± 4.77	0.207
Family history of coronary artery disease	432 (23.6)	124 (26.7)	0.163	493 (23.8)	60 (28.0)	0.180
Arterial hypertension	1,406 (76.8)	360 (77.6)	0.758	1,619 (78.2)	168 (78.5)	1.000
Uncontrolled hypertension	93 (5.1)	26 (5.6)	0.640	106 (5.1)	11 (5.1)	1.000
Diabetes mellitus	595 (32.5)	159 (34.3)	0.472	707 (34.2)	77 (36.0)	0.597
Hyperlipidemia	1,219 (66.6)	323 (69.6)	0.224	1,411 (68.2)	144 (67.3)	0.817
Smoking status						
Never	960 (52.6)	226 (48.7)	0.145	1,126 (54.6)	112 (52.6)	0.613
Previous	689 (37.7)	185 (39.9)	0.422	769 (37.3)	85 (39.9)	0.458
Current	177 (9.7)	53 (11.4)	0.262	168 (8.1)	16 (7.5)	0.895
Left ventricular ejection fraction, %	53.88 ± 11.27	51.89 ± 11.96	0.001	52.93 ± 11.84	53.24 ± 11.12	0.725
Medical history						
Peripheral vascular disease[a]	173 (9.4)	70 (15.1)	0.001	220 (10.6)	22 (10.3)	1.000
Carotid artery disease	85 (4.6)	35 (7.5)	0.019	133 (6.4)	11 (5.1)	0.555
Heart failure	319 (17.4)	110 (23.7)	0.003	402 (19.4)	36 (16.8)	0.412
Myocardial infarction	336 (18.4)	98 (21.1)	0.184	387 (18.7)	43 (20.1)	0.646
PCI	463 (25.3)	131 (28.2)	0.213	543 (26.2)	51 (23.8)	0.513
Cerebrovascular event	205 (11.2)	63 (13.6)	0.169	275 (13.3)	27 (12.6)	0.833
Stroke	154 (8.4)	39 (8.4)	1.000	197 (9.5)	20 (9.3)	1.000
Transient ischemic attack	60 (3.3)	26 (5.6)	0.027	76 (3.7)	8 (3.7)	0.851
Undetermined cerebrovascular event	10 (0.5)	1 (0.2)	0.705	17 (0.8)	1 (0.5)	1.000
Arterial thromboembolism	21 (1.1)	10 (2.2)	0.112	18 (0.9)	6 (2.8)	0,020
Venous thromboembolism	80 (4.4)	44 (9.5)	<0.001	96 (4.6)	19 (8.9)	0.013
Coronary artery bypass graft surgery	124 (6.8)	46 (9.9)	0.028	152 (7.3)	19 (8.9)	0.413
Prosthetic mechanical heart valve	33 (1.8)	10 (2.2)	0.570	48 (2.3)	10 (4.7)	0.062
Aortic valve stenosis	71 (4.3)	20 (4.9)	0.591	86 (4.6)	18 (9.3)	0.009
Bleeding before/after qualifying PCI	134 (7.3)	50 (10.8)	0.017	156 (7.5)	19 (8.9)	0.499
Chronic pulmonary disease	197 (10.8)	58 (12.5)	0.283	254 (12.3)	29 (13.6)	0.586
Chronic kidney disease[b]	333 (18.2)	85 (18.3)	0,946	414 (20.0)	44 (20.6)	0.858
Liver disease	27 (1.5)	2 (0.4)	0.100	29 (1.4)	3 (1.4)	1.000
Atrial fibrillation	549 (30.0)	221 (47.6)	<0.001	613 (29.6)	107 (50.0)	<0.001
History of cancer	260 (14.2)	88 (19.0)	0.014	313 (15.1)	38 (17.8)	0.319
Active cancer	87 (4.8)	23 (5.0)	0.809	111 (5.4)	15 (7.0)	0.343
Hematological or coagulation disorder	222 (12.1)	68 (14.7)	0.159	251 (12.1)	37 (17.3)	0.039
Chronic treatment with steroids or NSAIDs	156 (8.5)	46 (9.9)	0.359	214 (10.3)	25 (11.7)	0.557
Prior VKA treatment	215 (11.7)	112 (24.1)	<0.001	253 (12.2)	46 (21.5)	<0.001
Indication to 12-month oral anticoagulant	597 (32.6)	251 (54.1)	<0.001	688 (33.2)	130 (60.7)	<0.001
PRECISE-DAPT score[c]	26.57 ± 10.55	27.78 ± 12.20	0.033	26.70 ± 10.94	26.76 ± 12.16	0.942
Prior bleeding	116 (6.3)	49 (10.6)	0.002	141 (6.8)	14 (6.5)	1.000
Hemoglobin, g/L	13.26 ± 1.78	13.14 ± 1.78	0.182	13.21 ± 1.79	13.07 ± 1.79	0.287
White blood cell count,[c] × 10^9/L	8.32 ± 12.72	8.15 ± 2.87	0.778	8.08 ± 3.47	7.77 ± 2.65	0.192
Creatinine clearance,[d] mL/min/1.73 m^2	70.69 ± 23.94	70.82 ± 24.19	0.916	70.98 ± 24.13	71.22 ± 23.80	0.890

Values are mean ± SD or n (%). [a]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. [b]Defined as kidney damage (pathological 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 m^2 for ≥3 months. [c]Calculated at screening visit; n = 1 PRECISE score calculated without risk caused by white blood cell. [d]Modification of Diet in Renal Disease. *P* values comparing NARC 2, 3 vs NARC 0, 1 from Fisher exact tests (2 × 2 comparisons) or chi-square tests (3 or more × 2 comparisons), Student's *t*-tests for continuous variables.

DAPT = dual antiplatelet therapy; NARC = nonadherence Academic Research Consortium; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; VKA = vitamin K antagonist.

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. A full list of inclusion and exclusion criteria is provided in the Supplemental Appendix.[4-6] All patients gave written informed consent, and the protocol was approved by the Institutional Review Board of all participating sites.

FIGURE 1 Types of NARC 2 or 3 Nonadherence



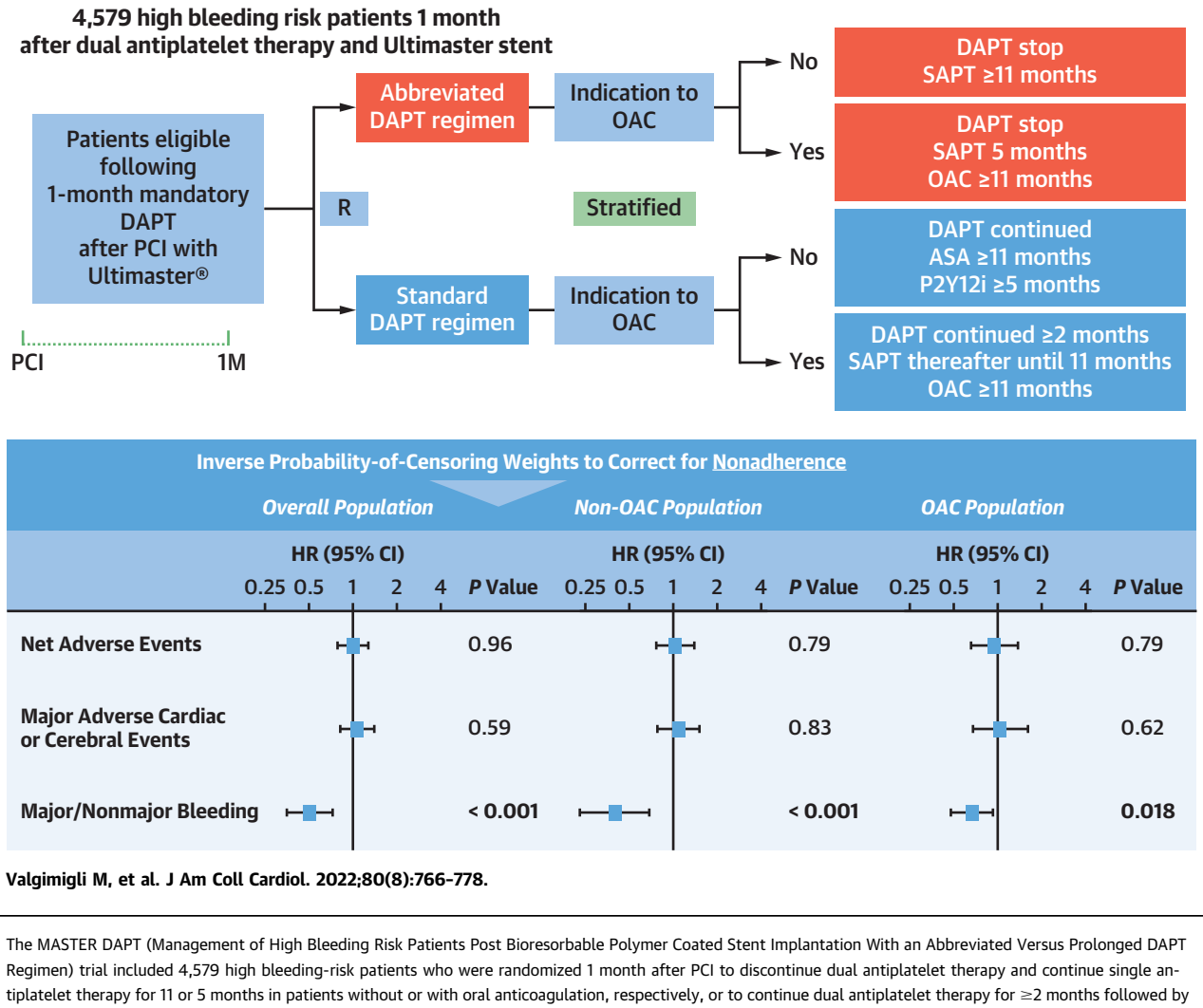
Rates of overtreatment or undertreatment stratified across randomization and indication to oral anticoagulation (OAC) groups. The observed antiplatelet regimen is shown first and the protocol recommended regimen is shown in **parentheses and italics**. In the abbreviated treatment groups, dual antiplatelet therapy (DAPT) was to be reinstituted in case of an unplanned percutaneous coronary intervention after randomization. Overtreatment or undertreatment was defined based on the protocol-mandated vs observed number of antiplatelet therapy medications (ie, 0, 1, or 2). The figure highlights that there were relatively higher rates of nonadherence Academic Research Consortium (NARC) 2 or 3 nonadherence in the abbreviated compared with standard treatment groups, mainly because of DAPT instead of SAPT in patients without OAC or single-antiplatelet therapy (SAPT) instead of no antiplatelet therapy (APT) in patients with OAC, both of which have been labeled as overtreatment. Tx = treatment.

RANDOMIZATION AND FOLLOW-UP. Patients free from ischemic and active (ie, not resolved) bleeding events and who had adhered to a dual antiplatelet therapy regimen were screened for inclusion 30-44 days after the index procedure (single procedure or last installment of a planned staged procedure). Patients were centrally randomized (1:1) to receive open-label abbreviated (abbreviated-treatment group) or standard dual antiplatelet therapy (standard-treatment group). Randomization was stratified, among others, by clinical indication for 12 months' OAC.[4-6] Follow-up visits occurred at 60 ± 14 days and 150 ± 14 days after randomization, preferably as on-site visits, and at 335 ± 14 days after randomization, exclusively as an on-site visit.

RANDOMIZED TREATMENT. Patients randomly allocated to the abbreviated-treatment group immediately discontinued DAPT and transitioned to SAPT until study completion, except for those receiving clinically indicated OAC, who continued SAPT up to 6 months after the index procedure and thereafter continued with OAC monotherapy. 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 clinically indicated OAC, for at least 2 additional months (3 months after the index procedure) and thereafter continued SAPT.[4-6] Antiplatelet and anticoagulant treatments were dosed according to authorizations for use and locally approved regimens.[4-6]

TRIAL OUTCOMES. The trial protocol prespecified 3 ranked coprimary outcomes, which included net adverse clinical events (NACE) (the composite of all-cause death, myocardial infarction, stroke, and major or clinically relevant nonmajor bleeding), MACE (the composite of all-cause death, myocardial infarction, and stroke), and major or clinically relevant nonmajor bleeding (MCB), occurring between

CENTRAL ILLUSTRATION **Per-Protocol Analysis of the MASTER DAPT Trial**



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The MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) trial included 4,579 high bleeding-risk patients who were randomized 1 month after PCI to discontinue dual antiplatelet therapy and continue single antiplatelet therapy for 11 or 5 months in patients without or with oral anticoagulation, respectively, or to continue dual antiplatelet therapy for ≥2 months followed by single antiplatelet therapy. Nonadherence rates to study regimens was low and exclusively caused by undertreatment (ie, premature dual antiplatelet therapy or single antiplatelet therapy discontinuation) in the standard treatment group. Nonadherence rates to study regimens was higher in the abbreviated treatment group and mainly caused by overtreatment, especially in the oral anticoagulation population, because of single antiplatelet therapy continuation beyond 5 months after randomization. After correcting for nonadherence with inverse probability-of-censoring weights, net and major adverse clinical events did not differ and major or clinically relevant nonmajor bleeding was lower at 335 days with abbreviated compared with standard treatment in patients with or without oral anticoagulation. ASA = aspirin; DAPT = dual antiplatelet therapy; OAC = oral anticoagulation; P2Y12i = $P2Y_{12}$ inhibitor; PCI = percutaneous coronary intervention; R = randomization; SAPT = single antiplatelet therapy.

randomization and 335 days.[4-6] MCB was defined as Bleeding Academic Research Consortium type 2, 3, or 5 bleeding.[7]

Secondary outcomes included the individual components of the 3 coprimary outcomes; the composite of cardiovascular death, myocardial infarction, and stroke; cardiovascular and noncardiovascular death; definite or probable stent thrombosis; and all bleeding events.[4-6] Outcome events were adjudicated according to the Academic Research Consortium[8] and Bleeding Academic Research Consortium definitions by a committee whose members were unaware of trial-group assignments (see the Supplemental Appendix for outcome definitions).

STATISTICAL ANALYSIS. The trial was designed to hierarchically test whether the abbreviated dual antiplatelet regimen, compared with the standard dual antiplatelet regimen, was noninferior for NACE, noninferior for MACE, and superior for MCB.[4-6] To derive inverse probability-of-censoring weights (IPCW),

TABLE 2 Primary and Secondary Outcomes at Inverse Probability-of-Censoring Weights Analysis

	Abbreviated DAPT (n = 2,295)	Standard DAPT (n = 2,284)	HR (95% CI)	*P* Value
Coprimary composite endpoint of all-cause death, myocardial infarction, stroke, and bleeding BARC 3 or 5 (NACE)	146/26	156/26	1.01 (0.80-1.27)	0.96
Coprimary composite endpoint of all-cause death, myocardial infarction, stroke (MACE)	117/21	116/22	1.07 (0.83-1.40)	0.59
Coprimary composite endpoint of bleeding BARC 2, 3, or 5	111/37	200/11	0.51 (0.36-0.73)	<0.001
All-cause death	62/13	68/13	0.94 (0.66-1.34)	0.73
Cerebrovascular accident	11/6	24/8	0.47 (0.23-0.97)	0.040
Myocardial infarction	51/9	44/5	1.30 (0.86-1.96)	0.22
Bleeding BARC 3 or 5	40/15	60/7	0.71 (0.47-1.06)	0.094
Bleeding BARC 2	76/26	146/6	0.48 (0.33-0.71)	<0.001

Values are number of overall events/number of events not used for the analysis because of their occurrence after a NARC 2 or 3 event.
BARC = bleeding academic research consortium; DAPT = dual antiplatelet therapy; MACE = major adverse cardiac and cerebral events; NACE = net adverse clinical events.

patients were first censored after the first major nonclinically justified nonadherence to protocol-mandated antiplatelet therapy/therapies (non-adherence Academic Research Consortium [NARC] 2 or 3),[9] ie, at time *n*, with *n* in days 0-335 after randomization (see Supplemental Tables 1 and 2), and were removed from the risk set after *n*. Nonadherence included failure either to continue or discontinue any protocol mandated treatment(s). Nonadherence was centrally adjudicated and has been counted as a nonadherence pattern for this analysis only if it occurred for nonclinically justified reasons, which were prespecified in the statistical analytic plan (Supplemental Table 2). Second, for adherent patients up to *t* (*t* in days 0-335 days after randomization), and nonadherent patients up to *n*, daily probabilities of not incurring NARC 2 or 3 were calculated. The model included all baseline characteristics reported in **Table 1**, as well as prasugrel after last percutaneous coronary intervention (PCI), ticagrelor after last PCI, use of OAC at *t* or *n*, any NARC 1 up to *t* or *n*, and splines for each time window where changes in antiplatelet therapy (APT) were allowed (Supplemental Table 2) as predictors. This second step was performed separately for each randomized arm and both stratified subgroups (patients with or without OAC). Third, cumulative probabilities of not incurring NARC 2 or 3 for each patient up to each *t* or *n* (up to a maximum of 335 days) were calculated (ie, until first NARC 2 or 3, until death, or until lost-to-follow-up, whichever came first). Fourth, inverse-cumulative probabilities for each patient up to each *t* or *n* were calculated (ie, these were the censor-weights for patients always adherent up to last information or death at *t*, and the censor-weights for the patients eventually nonadherent up to the first major nonadherence NARC 2 or 3 at *n* [after which they are removed from the risk set]). Fifth, IPCW were then derived from patient identifier cluster-robust logistic regressions for the first occurrence of the event at each day $t = 0$ to 335; the resulting ORs can be interpreted as HRs, as the daily event rates were very small.[10] An illustration of the principles followed by the IPCW technique and the density distribution of the censoring weights in the current trial is provided in Supplemental Figure 1. All analyses were performed in the ITT population and in the per-protocol (PP) population, which was defined as patients meeting eligibility criteria and who have implemented the allocated treatment within 14 days after randomization. We performed landmark analyses at 150 days because SAPT was to be stopped after this time-frame in patients with OAC allocated to the abbreviated-treatment group.

RESULTS

PATIENT ENROLLMENT AND TREATMENT. From February 28, 2017, through December 5, 2019, 5,204 patients (at 140 sites in 30 countries) were screened and 4,579 (88.1%) were randomized to an abbreviated (n = 2,295) or a standard (n = 2,284) dual antiplatelet regimen at a median of 34 days after the index PCI. The per-protocol population consisted of 4,434 patients (abbreviated, n = 2,204; standard, n = 2,230).

A total of 464 (20.2%) patients in the abbreviated-treatment and 214 (9.4%) in the standard-treatment groups incurred NARC 2 or 3, with greater prevalence in the OAC group of both randomized arms and largely caused by higher than recommended antiplatelet treatment intensity in the experimental arm, mostly occurring after 150 days (**Figure 1, Central Illustration**). The distribution of NARC adherence

TABLE 3 Clinical Outcomes Stratified by Indication to OAC at Inverse Probability-of-Censoring Weights Analysis

	Indication for OAC				No Indication for OAC				
Intention-to-Treat Population	Abbreviated DAPT (n = 848)	Standard DAPT (n = 818)	HR (95% CI)	*P* Value	Abbreviated DAPT (n = 1,447)	Standard DAPT (n = 1,466)	HR (95% CI)	*P* Value	P_{int}
Coprimary composite endpoint of all-cause death, myocardial infarction, stroke, and bleeding BARC 3 or 5 (NACE)	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 endpoint of all-cause death, myocardial infarction, stroke (MACE)	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 endpoint of bleeding BARC 2, 3, or 5	61/22	91/3	0.67 (0.48-0.93)	0.018	50/15	109/8	0.40 (0.23-0.69)	<0.001	0.11
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)	0.034	10/4	16/3	0.70 (0.32-1.54)	0.37	0.096
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
Bleeding BARC 3 or 5	19/8	33/3	0.59 (0.33-1.04)	0.068	21/7	27/4	0.86 (0.48-1.51)	0.59	0.36
Bleeding BARC 2	44/16	64/1	0.69 (0.47-1.02)	0.062	32/10	82/5	0.34 (0.19-0.62)	<0.001	0.06

Values are number of overall events/number of events not used for the analysis caused by their occurrence after a NARC 2 or 3 event.
OAC = oral anticoagulation medication; other abbreviations as in Table 2.

rates over time is shown in Supplemental Figure 2 and Supplemental Table 3. In the abbreviated-treatment group, patients with NARC 2 or 3 were more frequently men and had higher prevalence of peripheral arterial disease, history of heart failure, indication to OAC, prior coronary artery bypass grafting, and prior bleeding with an overall greater PRECISE DAPT score (**Table 1**). In the standard-treatment group, patients with NARC 2 or 3 had more frequent known aortic valve stenosis, indication to OAC, and history of systemic embolism events (**Table 1**). In the abbreviated-treatment group, patients with NARC 2 or 3 underwent a more complex procedure, with higher number of overall and complex lesions and greater mean stent length, whereas no such pattern was observed among patients with or without NARC 2 or 3 in the standard-treatment group (Supplemental Table 4).

IPCW ANALYSES OF PRIMARY OUTCOMES. In the ITT population, NACE (HR: 1.01; 95% CI: 0.88-1.27; $P = 0.96$) and MACE (HR: 1.07; 95% CI: 0.83-1.40; $P = 0.59$) did not differ with abbreviated compared with standard treatment duration, with consistent findings in patients with or without indication to OAC (*P* for interaction = 0.70 and 0.90, respectively) (**Tables 2 and 3, Figure 2, Central Illustration**). The rate of major or clinically relevant nonmajor bleeding was lower with abbreviated compared with standard DAPT (HR: 0.51; 95% CI: 0.60-0.73; $P < 0.001$), as it remained lower with abbreviated DAPT in both OAC (HR: 0.67; 95% CI: 0.48-0.93; $P = 0.018$) and non-OAC groups (HR: 0.40; 95% CI: 0.23-0.69; $P < 0.001$, *P* for interaction = 0.11 and 0.089, respectively (**Tables 2 and 3, Figure 1, Central Illustration**). The analyses in the PP population yielded identical results (Supplemental Tables 5 and 6).

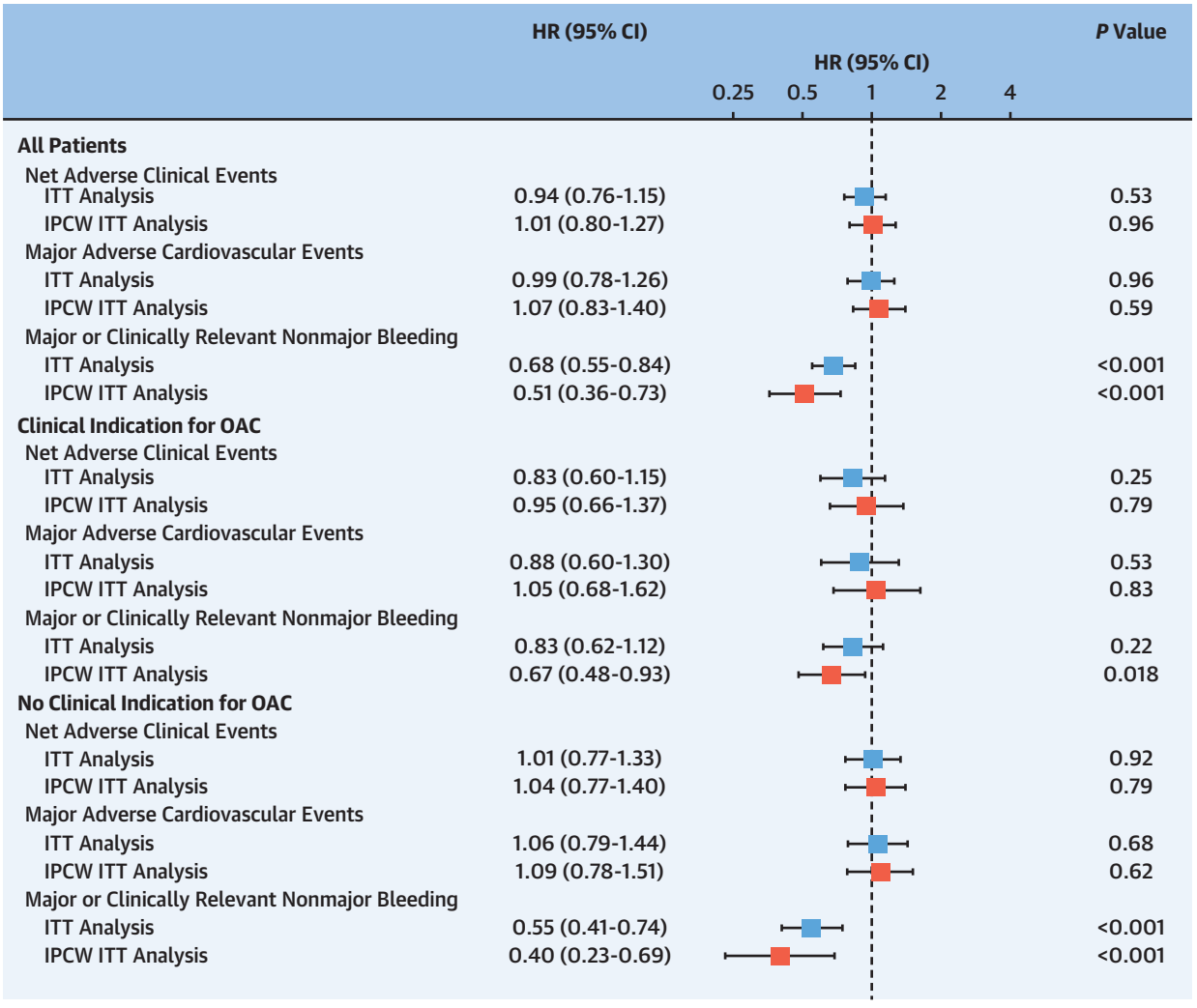
IPCW ANALYSES OF SECONDARY OUTCOMES. The rates of all-cause death did not differ between groups in the ITT population (HR: 0.94; 95% CI: 0.66-1.34; $P = 0.73$) (**Table 2**), with consistent findings in patients with or without indication to OAC (*P* values for interaction = 0.90) (**Table 3**). There was no between group difference for the rates of myocardial infarction, which was consistent in patients with or without OAC (**Table 3**).

The rates of cerebrovascular accidents were lower with abbreviated compared with standard DAPT In the reweighted ITT (HR: 0.47; 95% CI: 0.23-0.97; $P = 0.04$) population (**Table 2**), with no clear evidence of interaction across OAC strata (*P* for interaction = 0.096) (**Table 3**).

BARC 3 or 5 bleeding did not differ between groups (**Table 2**), with consistent findings in patients with or without indication to OAC (**Table 3**), whereas BARC 2 bleeding was lower with abbreviated compared with standard DAPT (HR: 0.48; 95% CI: 0.33-0.71; $P < 0.001$), as it remained lower with abbreviated DAPT in patients without OAC (HR: 0.34; 95% CI: 0.19-0.62; $P < 0.001$) and trended lower in patients with OAC (HR: 0.69; 95% CI: 0.47-1.02; $P = 0.062$, *P* for interaction = 0.06). These findings were confirmed in the PP population (Supplemental Tables 5 and 6).

IPCW LANDMARK ANALYSES. In the ITT population, tests for treatment-by-time (from randomization to

FIGURE 2 **ITT and IPCW Analyses at 11 Months Postrandomization**

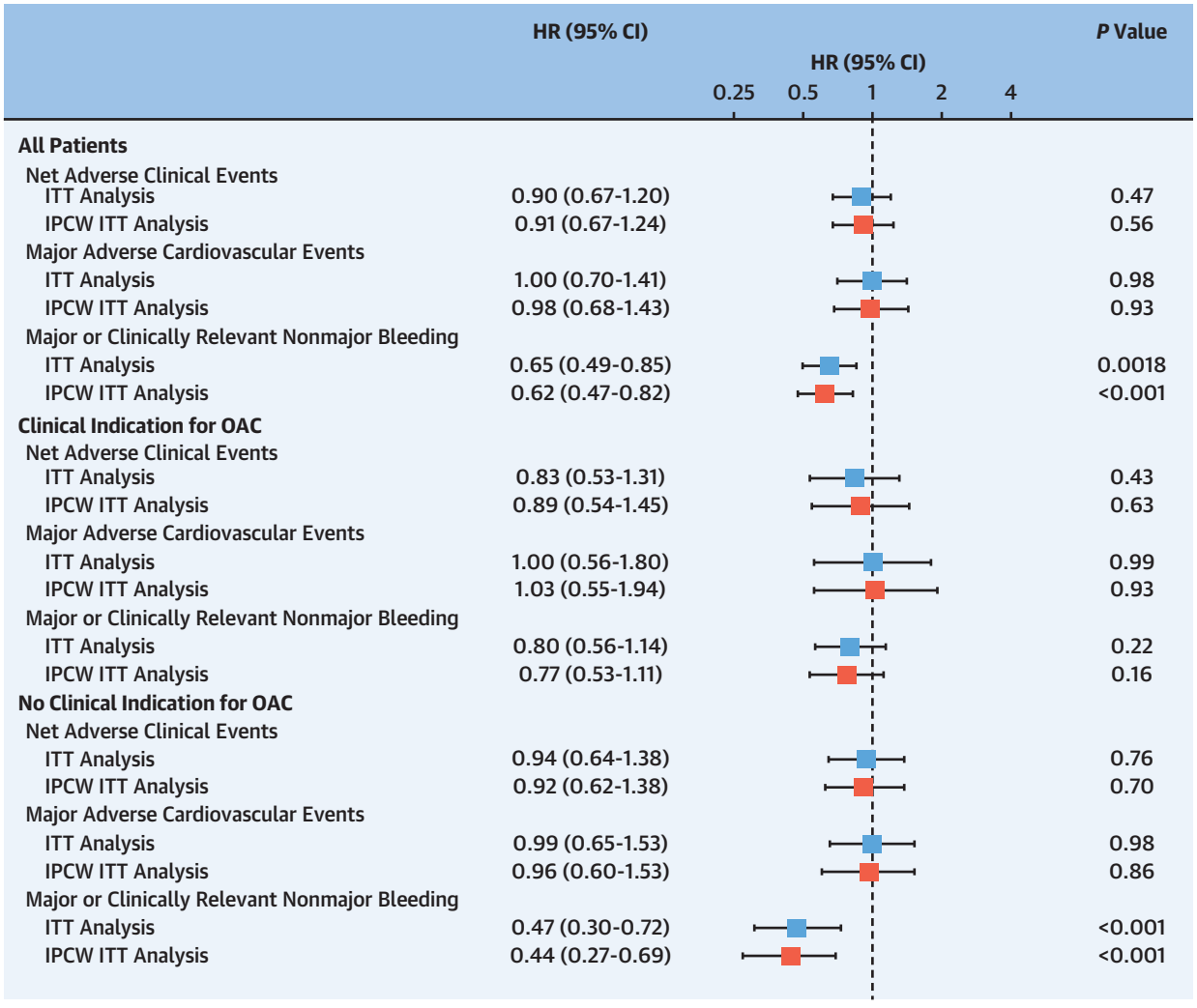


Study results following the intention-to-treat (ITT) principle (ie, assuming all patients adhered to the protocol-mandated regimens) are shown 1-to-1 with the results applying the inverse probability-of-censoring weights (IPCW) modeling in the ITT population, which corrects for nonadherence patterns and simulates the results had all patients followed the study protocol, unless deviations where clinically justifiable. The IPCW analyses confirmed the ITT results in the overall and nonanticoagulation (OAC) study populations showing similar rates of net adverse clinical and major cardiac or cerebral events between groups and lower major or clinically-relevant nonmajor bleeding with abbreviated compared with standard treatment. In the OAC population, major or clinically relevant nonmajor bleeding was reduced only at IPCW analysis, which, unlike ITT, accounted for the high nonadherence rate observed in this patient subset, mainly caused by overtreatment, as shown in **Figure 1**.

150 days and from 150 to 335 days) interactions were negative for the 3 primary endpoints in the overall or stratified OAC and non-OAC populations (Supplemental Table 7).

There were no between-group differences of NACE or MACE within or after the first 5 months after randomization in the overall or stratified reweighted populations (**Figures 3 and 4,** Supplemental Table 7). Major or clinically relevant nonmajor bleeding was lower with abbreviated treatment within and after the first 5 months following randomization in the overall and non-OAC ITT reweighted population, whereas it was lower with abbreviated treatment after (HR: 0.47; 95% CI: 0.22-0.99; $P = 0.047$), but not before 150 days at reweighted ITT analyses among OAC patients (**Figures 3 and 4**). The reweighted analyses in the PP population yielded consistent findings (Supplemental Table 7).

FIGURE 3 **ITT and IPCW Analyses at 150 Days Postrandomization**

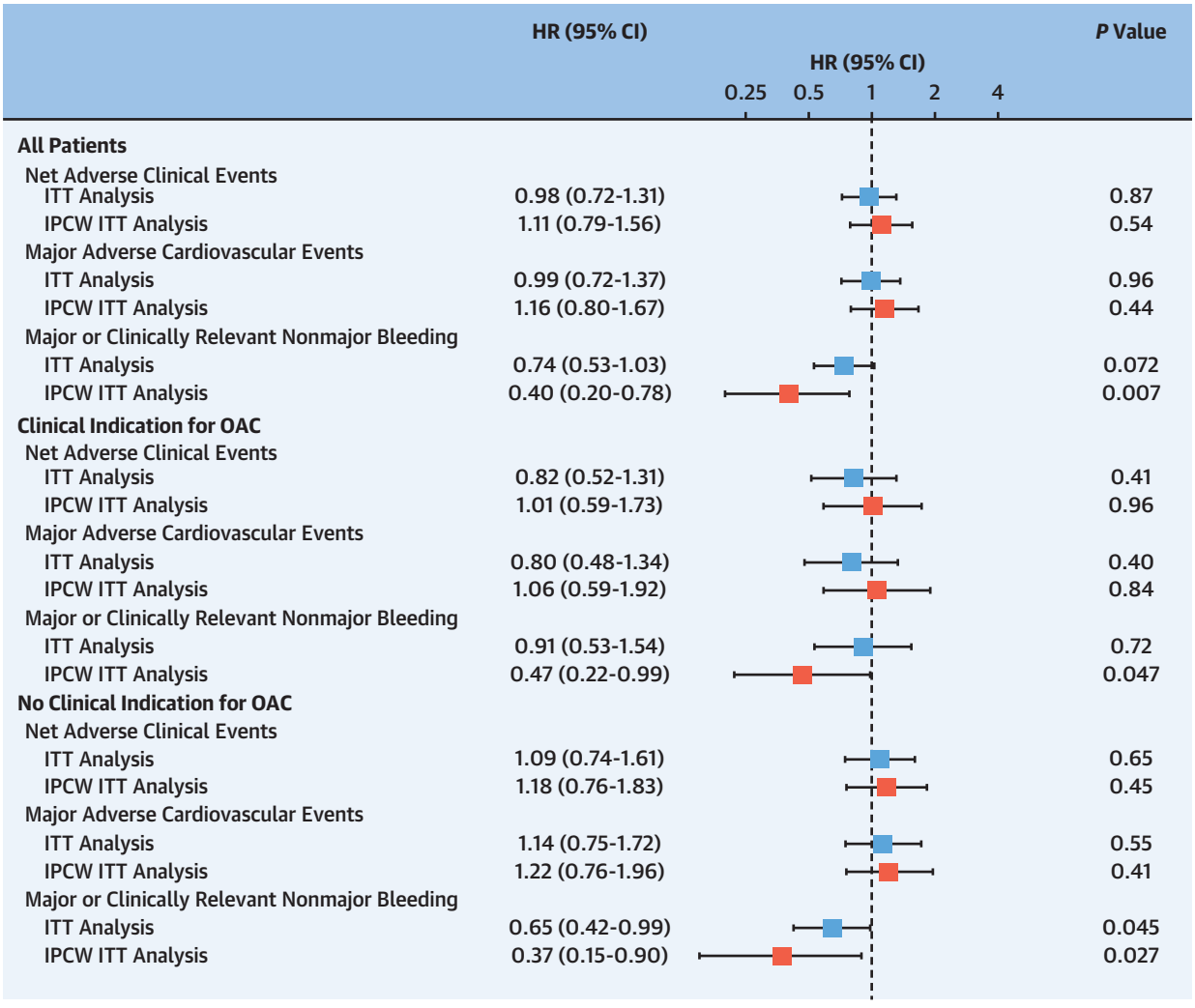


Study results following the ITT principle (ie, assuming all patients adhered to the protocol-mandated regimens are shown, from randomization to 150 days, 1-to-1 with the results applying the IPCW) modeling in the ITT population, which corrects for nonadherence patterns and simulates the results had all patients followed the study protocol, unless deviations where clinically justifiable. The IPCW analyses confirmed the ITT results showing similar rates of net adverse clinical and major cardiac or cerebral events between groups and lower major or clinically relevant nonmajor bleeding with abbreviated compared with standard treatment in the overall and nonanticoagulation (OAC) study populations, whereas the rates of major or clinically relevant nonmajor bleeding did not differ with abbreviated compared with standard treatment in OAC patients. Abbreviations as in Figure 2.

DISCUSSION

In this prespecified per-protocol analysis of the MASTER DAPT trial, we found that NACE and MACE did not differ in patients with abbreviated compared with standard DAPT treatment, whereas the former group was associated with lower rates of major or clinically relevant nonmajor bleeding, which was consistently observed both in patients with or without OAC in the weighted ITT or PP populations. This is at variance with the primary findings observed in these 2 subpopulations at ITT analysis, in which a clear bleeding benefit with abbreviated treatment was observed in patients without OAC, but not in patients with OAC, with borderline treatment-by-group interaction for the primary bleeding endpoint ($P = 0.06$) and a significant interaction testing for BARC 2 ($P = 0.02$).[5] In our current IPCW analyses, interaction testing results were attenuated for the primary bleeding endpoint and no longer significant for BARC

FIGURE 4 ITT and IPCW Landmark Analyses Between 151 and 335 Days



Study results following the ITT principle (ie, assuming all patients adhered to the protocol-mandated regimens) are shown, from 151 to 335 days, to 1-to-1 with the results applying the Inverse IPCW modeling in the ITT population, which corrects for nonadherence patterns and simulates the results had all patients followed the study protocol, unless deviations where clinically justifiable. The IPCW analyses confirmed the ITT results in the overall and nonanticoagulation (OAC) study populations showing similar rates of net adverse clinical and major cardiac or cerebral events between groups and lower major or clinically relevant nonmajor bleeding with abbreviated compared with standard treatment. In the OAC population, major or clinically relevant nonmajor bleeding was reduced only at IPCW analysis, which, unlike ITT, accounted for the high nonadherence rate observed in this patient subset, mainly because of single antiplatelet therapy continuation instead of discontinuation after 150 days.

2, suggesting a potential quantitative more than a qualitative interaction with abbreviated vs standard DAPT across OAC subgroups. This means that a significant bleeding benefit with abbreviated compared with standard treatment was observed in both patients with and without OAC, although the magnitude of the benefit might have been greater in the latter than the former groups.

Albeit high overall, adherence to protocol-mandated treatment decreased over time, especially in OAC patients in whom failure to discontinue single-antiplatelet therapy 5 months after randomization occurred in almost one-quarter of the patients allocated to the abbreviated treatment and was largely caused by higher than recommended antiplatelet treatment intensity.[4,5]

As expected, patients with nonadherence patterns differed from those who adhered to the protocol-mandated regimens in our study. In particular, nonadherent patients in the abbreviated treatment group

had greater prevalence of high-risk clinical characteristics, such as peripheral arterial disease, history of heart failure, and greater PRECISE DAPT score,[11,12] and underwent more complex procedures. This observation highlights the limitations of a naïve per-protocol analysis, which, by simply excluding these patients from the moment of nonadherence onwards, has the potential to bias the results.[1] We have implemented a state-of-the-art approach, which assigns more weight to adherent patients who have similar profile to those censored because of nonadherence, to estimate a more unbiased treatment effect had no patient deviated from the protocol-mandated regimens. A similar approach has been recently used to estimate the treatment effects of 30-month vs 12-month DAPT duration in a contemporary U.S. population.[13]

The findings of the current non-naïve (ie, IPCW-based) per-protocol analysis provided entirely consistent results for NACE and MACE with the ITT analysis in the overall or OAC and non-OAC populations, suggesting no excess of events with an abbreviated compared with a standard DAPT regimens. These results confirm our primary observations that an abbreviated DAPT regimen is not associated with greater risks of NACE or MACE compared with standard treatment. However, the reweighted rates of major or clinically relevant nonmajor bleeding were lower with abbreviated compared with a standard DAPT not only in the overall and non-OAC populations, but also among OAC patients. Interestingly, the bleeding benefit among OAC patients did not accrue from the first 5 months after randomization, where 1-month DAPT was largely compared with 3-month DAPT, but rather thereafter, where OAC monotherapy was compared with OAC and a single-antiplatelet therapy.

Importantly, the nonadherence pattern observed in the experimental arm in the OAC population resulted in identical treatment in both the experimental and control groups after 6 months, consisting of OAC and single antiplatelet therapy, in a large proportion of patients. This has ultimately biased the appraisal of the bleeding benefit associated with OAC monotherapy compared with OAC and SAPT in the primary study findings. Our findings reinforce the importance of accounting and correcting for nonadherence in clinical trials in order to derive more unbiased treatment effects, therefore complementing ITT analyses.

The present observation that correcting for nonadherence with IPCW analyses affected the primary study results only among OAC patients and mainly after the first 150 days is consistent with the observation that nonadherence rates where highest among OAC patients after 150 days (ie, 6 months after PCI).

Although North American and European guidelines[14-16] recommend stopping antiplatelet therapy after 6 months in an OAC population that is at high bleeding risk (Level of Evidence: C), no previous trial had investigated the benefits and risks of omitting antiplatelet therapy after 6 months in this setting. In our trial, patients with OAC allocated to the abbreviated-treatment group were to discontinue any concomitant antiplatelet treatment 5 months after randomization (ie, 6 months after PCI) and continue with OAC monotherapy. The high attrition rate observed in our study toward this protocol-recommended regimen (which accounts for the majority of NARC 2 or 3 nonadherences in the trial) highlights the uncertainty among clinicians on this consensus-based recommendation, even in the setting of a randomized trial. Although the primary results of our trial failed to show a clear benefit of stopping antiplatelet after 6 months,[5] the present IPCW analysis, which mainly corrected for higher than recommended antiplatelet treatment intensity in the OAC group, supports guideline recommendations and for the first time provides evidence that discontinuation of antiplatelet therapy 6 months after stent implantation in patients with OAC has potential to be associated with lower rates of bleeding risk without an increase in ischemic events.

These observations are consistent with those from previous trials, which did not show greater ischemic protection and yet showed bleeding risk mitigation with OAC alone 1 or more years after coronary stenting.[17,18]

STUDY LIMITATIONS. Adherence to study medications was assessed by inspecting clinical records during follow-up and by patient interviewers, which is known to suffer from the recollection bias and overestimates the true adherence rates.[9] This study was not powered for relatively rare yet relevant endpoints such as myocardial infarction or stent thrombosis; therefore, even after accounting for nonadherence patterns, our findings cannot exclude that an abbreviated treatment regimen may not be associated with a small increase of these endpoints, which were numerically, albeit not significantly, higher with the experimental regimen. This residual uncertainty should be interpreted taking into account that our primary study findings showed that an abbreviated antiplatelet therapy was associated with

lower rates of cerebrovascular accidents, which remained consistent after accounting for nonadherence in the present analysis. This analysis does not inform on the role of type of single-antiplatelet regimen after DAPT discontinuation, because both aspirin and $P2Y_{12}$ inhibitor were allowed and continuation of either of the 2 was considered per-protocol. Temporary (NARC 2) or permanent (NARC 3) nonadherence was uniformly defined as 3 or more days of missed drug intake across the 4 antiplatelet therapies, which may have overestimated the number of temporary nonadherence rates occurring on aspirin, clopidogrel, or prasugrel, which have a longer pharmacological half-life than ticagrelor. We did not correct for multiplicity; therefore, a potential bias generated by the multiple comparisons cannot be excluded. Our trial included patients at high bleeding risk who underwent biodegradable-polymer sirolimus-eluting stent implantation; consequently, our results may not extend to patients who are not at high bleeding risk or who receive other stent types.

CONCLUSIONS

In the current per-protocol analysis of the MASTER DAPT trial of patients at high risk for bleeding who had undergone biodegradable-polymer sirolimus-eluting stent implantation, 1-month DAPT, compared with at least 3-month DAPT, did not increase NACE or MACE but was associated with a lower rate of major or clinically relevant nonmajor bleeding, both in patients with and without indication to OAC. By mainly correcting nonadherence patterns in OAC patients in the abbreviated treatment group, this analysis suggests, for the first time, that discontinuation of SAPT at 6 months after PCI is associated with less bleeding without an increase of ischemic events in this patient subset.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with indications for OAC at high risk of bleeding, DAPT longer than 1 month after PCI or antiplatelet monotherapy beyond 6 months increases bleeding complications without reducing ischemic events or mortality.

TRANSLATIONAL OUTLOOK: Future studies should seek to identify anticoagulated patients facing a high risk of coronary ischemic events who might benefit from extended antiplatelet therapy following PCI.

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KEY WORDS acetylsalicylic acid, drug-eluting stent, dual antiplatelet therapy, high bleeding risk, $P2Y_{12}$ inhibitor

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.