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Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk

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ABSTRACT

BACKGROUND

The appropriate duration of dual antiplatelet therapy in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent remains unclear.

METHODS

One month after they had undergone implantation of a biodegradable-polymer sirolimus-eluting coronary stent, we randomly assigned patients at high bleeding risk to discontinue dual antiplatelet therapy immediately (abbreviated therapy) or to continue it for at least 2 additional months (standard therapy). The three ranked primary outcomes were net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (a composite of death from any cause, myocardial infarction, or stroke), and major or clinically relevant nonmajor bleeding; cumulative incidences were assessed at 335 days. The first two outcomes were assessed for noninferiority in the per-protocol population, and the third outcome for superiority in the intention-to-treat population.

RESULTS

Among the 4434 patients in the per-protocol population, net adverse clinical events occurred in 165 patients (7.5%) in the abbreviated-therapy group and in 172 (7.7%) in the standard-therapy group (difference, −0.23 percentage points; 95% confidence interval [CI], −1.80 to 1.33; P<0.001 for noninferiority). A total of 133 patients (6.1%) in the abbreviated-therapy group and 132 patients (5.9%) in the standard-therapy group had a major adverse cardiac or cerebral event (difference, 0.11 percentage points; 95% CI, −1.29 to 1.51; P=0.001 for noninferiority). Among the 4579 patients in the intention-to-treat population, major or clinically relevant nonmajor bleeding occurred in 148 patients (6.5%) in the abbreviated-therapy group and in 211 (9.4%) in the standard-therapy group (difference, −2.82 percentage points; 95% CI, −4.40 to −1.24; P<0.001 for superiority).

CONCLUSIONS

One month of dual antiplatelet therapy was noninferior to the continuation of therapy for at least 2 additional months with regard to the occurrence of net adverse clinical events and major adverse cardiac or cerebral events; abbreviated therapy also resulted in a lower incidence of major or clinically relevant nonmajor bleeding. (Funded by Terumo; MASTER DAPT ClinicalTrials.gov number, NCT03023020.)

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*A complete list of the MASTER DAPT investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Randomized trials have established the superiority of drug-eluting stents over bare-metal stents in patients at high bleeding risk receiving 1 month of dual antiplatelet therapy after undergoing percutaneous coronary intervention (PCI).[1-3] Nevertheless, these trials were not designed to assess the appropriate duration of dual antiplatelet therapy after the implantation of a drug-eluting stent. Studies of 1 month of dual antiplatelet therapy after the implantation of a drug-eluting stent have suggested that this regimen may mitigate bleeding risk without compromising safety, as compared with longer durations of treatment.[4-7] Some of these studies were nonrandomized,[7] did not select patients at high bleeding risk,[4-6] or included patients at low ischemic risk.[4]

Therefore, the appropriate duration of dual antiplatelet therapy for preventing ischemic complications, while limiting bleeding risk, in unselected patients at high bleeding risk after the implantation of a drug-eluting stent remains unclear. We conducted a randomized trial involving patients at high risk for bleeding who had undergone implantation of a biodegradable-polymer sirolimus-eluting stent, in order to evaluate 1 month of dual antiplatelet therapy as compared with a longer course of dual antiplatelet therapy with respect to clinical outcomes including ischemic events and bleeding.

Methods

Trial Oversight

The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen (MASTER DAPT) trial was an investigator-initiated, multicenter, randomized, open-label, noninferiority trial with sequential superiority testing. The trial was designed by the first and last authors and was approved by the institutional review board at each center.[8] The European Cardiovascular Research Institute acted as the trial sponsor and received grant support from Terumo (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The European Cardiovascular Research Institute and Terumo had no role in the trial design; in the collection, monitoring, analysis, or interpretation of the data; or in the writing of the manuscript. Editorial assistance was provided by a medical writer and was funded by the European Cardiovascular Research Institute. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Patients

Patients were considered to be candidates for participation in the trial if they had an acute or chronic coronary syndrome; had undergone successful PCI for one 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, if present, was planned[8]; and met one or more of the criteria for high bleeding risk (see the Supplementary Appendix). In addition, eligible patients were required to be free from adverse cardiovascular events (including a new acute coronary syndrome, symptomatic restenosis, stent thrombosis, stroke, or any revascularization resulting in the prolonged use of dual antiplatelet therapy) during the first month after the index PCI. Key exclusion criteria were the implantation of a stent other than the Ultimaster stent within 6 months before the index procedure, the implantation of a bioresorbable scaffold at any time before the index procedure, and treatment for in-stent restenosis or stent thrombosis. A full list of the inclusion and exclusion criteria is provided in the Supplementary Appendix. All the patients provided written informed consent.

Randomization and Follow-up

Patients who were free from ischemic and active (i.e., not resolved at the time of randomization) bleeding events and who adhered to a dual antiplatelet therapy regimen were screened for inclusion in the trial 30 to 44 days after the index procedure (defined either as a single procedure or as the last installment of a planned staged procedure). Patients were randomly assigned in a 1:1 ratio with the use of a central system to receive either open-label abbreviated dual antiplatelet therapy (abbreviated-therapy group) or standard dual antiplatelet therapy (standard-therapy group). Randomization was concealed with the use of a Web-based system. Randomization sequences were computer-generated with randomly selected block sizes of two, four, or six and stratified according to trial site, history of

acute myocardial infarction within the past 12 months, and clinical indication for 12 months of oral anticoagulation. Follow-up visits occurred at 60 days (within a window of ±14 days) and 150 days (±14-day window) after randomization, preferably as on-site visits, and at 335 days (±14-day window) after randomization, exclusively as an on-site visit. Follow-up data were obtained with a standardized questionnaire.

RANDOMIZED TREATMENT

Patients who had been randomly assigned to the abbreviated-therapy group immediately discontinued dual antiplatelet therapy and continued single antiplatelet therapy until the completion of the trial, except for patients who were receiving clinically indicated oral anticoagulation, who continued single antiplatelet therapy up to 6 months after the index procedure. Patients who had been randomly assigned to the standard-therapy group continued dual antiplatelet therapy for at least 5 additional months (6 months after the index procedure) or, for those receiving clinically indicated oral anticoagulation, for at least 2 additional months (3 months after the index procedure) with the continuation of single antiplatelet therapy thereafter. Single antiplatelet therapy consisted of aspirin or a $P2Y_{12}$ inhibitor. Antiplatelet and anticoagulant treatments were administered according to authorizations for use and locally approved regimens; detailed descriptions of the two treatment regimens are provided in the Supplementary Appendix.

TRIAL OUTCOMES

The trial protocol prespecified three ranked primary outcomes: net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (a composite of death from any cause, myocardial infarction, or stroke), and major or clinically relevant nonmajor bleeding, occurring between randomization and 335 days. Major bleeding was defined as a bleeding event of Bleeding Academic Research Consortium (BARC) type 3 or 5, and major or clinically relevant nonmajor bleeding was defined as a bleeding event of BARC type 2, 3, or 5.[9]

Secondary outcomes included the individual components of the three primary outcomes; a composite of death from cardiovascular causes, myocardial infarction, or stroke; death from cardiovascular or noncardiovascular causes; definite or probable stent thrombosis; and all bleeding events. Outcome events were adjudicated according to definitions of the Academic Research Consortium[10] and BARC by a committee whose members were unaware of the trial-group assignments (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The trial was designed to test hierarchically whether the abbreviated dual antiplatelet regimen, as compared with the standard dual antiplatelet regimen, would be noninferior with regard to net adverse clinical events, noninferior with regard to major adverse cardiac or cerebral events, and superior with regard to major or clinically relevant bleeding, as determined by the difference in the cumulative incidence at 335 days (abbreviated-therapy group minus standard-therapy group). The upper limit of the two-sided 95% confidence interval for the difference in the cumulative incidence had to exclude 3.6 percentage points for net adverse clinical events and 2.4 percentage points for major adverse cardiac and cerebral events to define noninferiority and had to exclude 0.0 percentage points for major or clinically relevant bleeding events to define superiority. These hypotheses were hierarchically tested, with preservation of alpha (a one-sided alpha of 0.025, corresponding to a two-sided alpha of 0.05).

We calculated that the enrollment of 4100 patients would provide the trial with 90% power to show noninferiority with regard to net adverse clinical events under an assumed cumulative incidence of 12.0% in each group, with 80% power to show noninferiority with regard to major adverse cardiac and cerebral events under an assumed incidence of 8.0% in each group, and with 90% power to show superiority with regard to major or clinically relevant bleeding under an assumed incidence of 6.5% in the standard-therapy group and 4.2% in the abbreviated-therapy group. The final sample size was increased to 4300 to account for an anticipated 5% of the patients withdrawing (owing to loss to follow-up, withdrawal of consent, or lack of adherence to the assigned regimen).

The primary analyses of net adverse clinical events and major adverse cardiac and cerebral events were performed in the per-protocol popu-

lation, which excluded patients who did not meet the selection criteria or did not implement the protocol-mandated therapy within 14 days after randomization. The primary analysis of bleeding outcomes was performed in the intention-to-treat population, which included all the patients who had undergone randomization. Differences in the cumulative incidences at 335 days and P values were calculated with the use of the Com-Nougue method.[11] Kaplan–Meier curves were created for the first two primary outcomes, and cause-specific Kaplan–Meier curves were created for the third primary outcome (with censoring at the time of the competing risk event of death not related to bleeding). Additional details about the statistical analysis are provided in the Supplementary Appendix.

RESULTS

ENROLLMENT AND TREATMENT OF THE PATIENTS

From February 28, 2017, to December 5, 2019, a total of 5204 patients (at 140 sites in 30 countries) underwent screening; 4520 patients underwent screening during the 1-month period after the index procedure, of whom 202 (5.2%) withdrew consent and 33 were lost to follow-up, and 684 underwent screening at the time of randomization (Fig. 1). A total of 4579 patients (88.0%) were randomly assigned to either the abbreviated-therapy group (2295 patients) or the standard-therapy group (2284 patients); the median time from the index PCI to randomization was 34 days in each group. A screening log for a sample subgroup of trial candidates showed that, of 2847 patients who underwent screening, 109 (3.8%) were enrolled in the trial (Table S1 in the Supplementary Appendix). Details regarding the 625 patients who provided written informed consent but did not undergo randomization and regarding the patients in the per-protocol population are provided in Tables S2 through S4.

The characteristics of the patients at baseline and their clinical presentation are shown in Table 1. Overall, the mean age of the patients was 76.0 years, 69.3% of the patients were men, 33.6% had diabetes, 19.1% had chronic kidney disease, 18.9% had heart failure, 12.4% had previously had a cerebrovascular event, and 10.6% had peripheral vascular disease; 36.4% of the patients were receiving concomitant oral anticoagulation. The distribution of the high-bleeding-risk criteria is shown in Table S5 (mean [±SD] number of criteria met per patient, 2.1±1.1). Of the 4579 patients who were included in the trial, 2211 (48.3%) had undergone coronary intervention for an acute coronary syndrome. Information on the lesion and procedural characteristics is provided in Tables S6 and S7.

After randomization, 2250 patients (98.0%) in the abbreviated-therapy group discontinued dual antiplatelet therapy, and 2276 patients (99.6%) in the standard-therapy group continued the treatment for a median of 157 days (interquartile range, 65 to 335). The median duration of dual antiplatelet therapy from the index PCI was 34 days (interquartile range, 31 to 39) in the abbreviated-therapy group and 193 days (interquartile range, 102 to 366) in the standard-therapy group. After randomization, clopidogrel was used as monotherapy in 53.9% of the patients in the abbreviated-therapy group and as part of dual antiplatelet therapy in 78.7% of the patients in the standard-therapy group. Medication use is shown in Tables S8 and S9 and Figure S1. Adherence to the assigned regimen was high in each group (Figs. S2 and S3).

PRIMARY OUTCOMES

Complete follow-up data at 335 days were available for 4547 patients (99.3%). A total of 32 patients (0.7%) either withdrew consent (22 patients) or were lost to follow-up (10) and had their data censored at the last contact (Fig. 1). In the per-protocol population, net adverse clinical events occurred in 165 patients (7.5%) in the abbreviated-therapy group and in 172 (7.7%) in the standard-therapy group (hazard ratio, 0.97; 95% confidence interval [CI], 0.78 to 1.20), for a difference in risk of −0.23 percentage points (95% CI, –1.80 to 1.33; P<0.001 for noninferiority). In the same population, 133 patients (6.1%) in the abbreviated-therapy group and 132 patients (5.9%) in the standard-therapy group had a major adverse cardiac and cerebral event (hazard ratio, 1.02; 95% CI, 0.80 to 1.30), for a difference in risk of 0.11 percentage points (95% CI, –1.29 to 1.51; P=0.001 for noninferiority). In the intention-to-treat population, the incidence of major or clinically relevant nonmajor bleeding was lower among patients in the abbreviated-therapy group than among those in the standard-therapy group (148 patients [6.5%] vs. 211 [9.4%]; hazard ratio, 0.68; 95% CI, 0.55 to 0.84), for a dif-

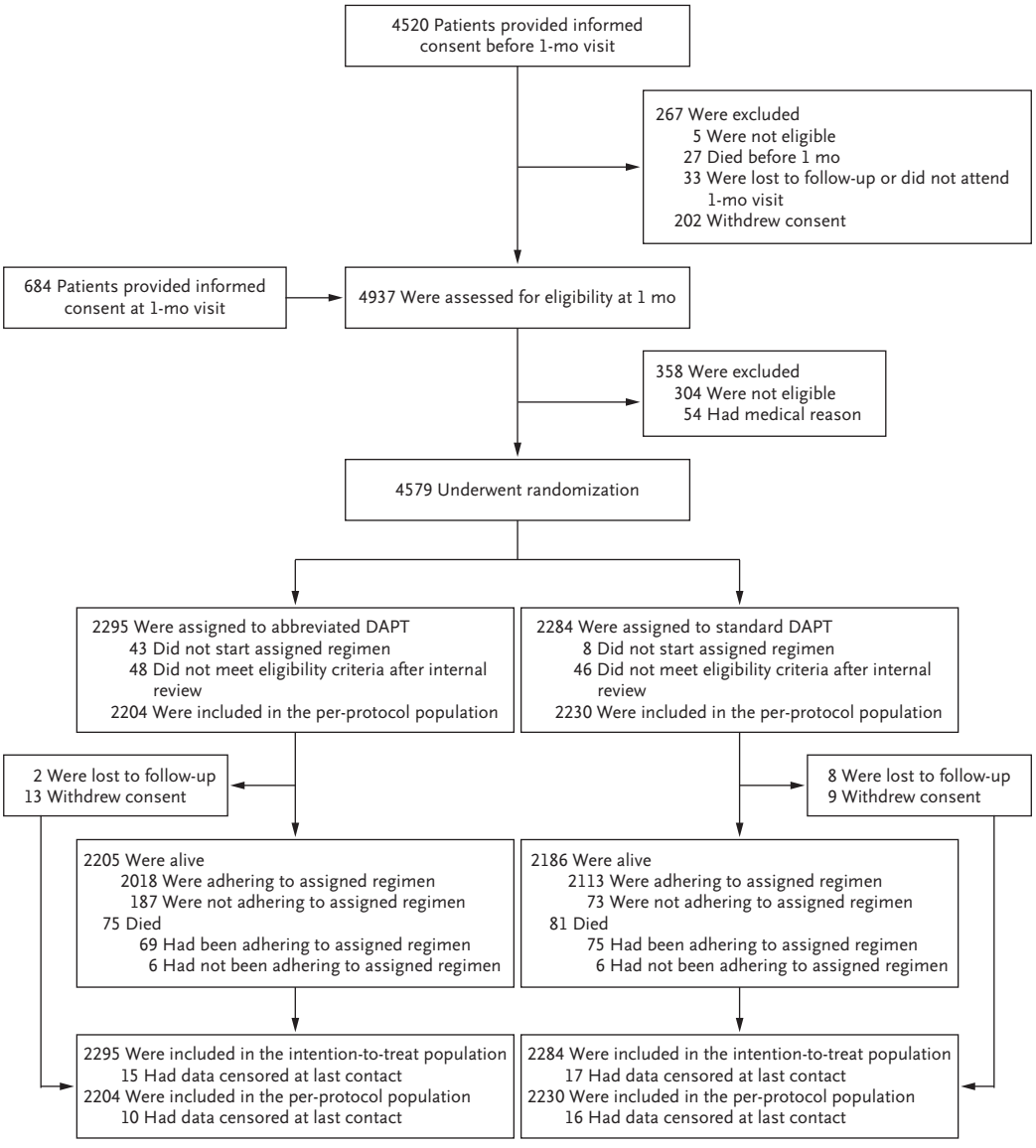


Figure 1. Randomization, Treatment, and Follow-up of the Patients.

Patients provided written informed consent either during the interval between the index percutaneous coronary intervention and the 1-month randomization visit or at the 1-month visit. Patients who provided consent before the 1-month visit could later be excluded (e.g., for death or withdrawal of consent), whereas those who provided consent at the 1-month visit were all included in the trial. Patients who did not start the assigned antiplatelet regimen were those who did not start the regimen within 14 days after randomization or who started a nonallowed regimen owing to an event occurring within 14 days after randomization. Patients who are indicated as receiving the assigned antiplatelet regimen were those who were noted as adhering to the regimen on day 335; if the information was not recorded on day 335, the latest available information on adherence was used. In the per-protocol population, one patient in the abbreviated-therapy group was lost to follow-up and nine withdrew consent; in the standard-therapy group, seven patients were lost to follow-up and nine withdrew consent. DAPT denotes dual antiplatelet therapy.

ference in risk of −2.82 percentage points (95% CI, −4.40 to −1.24; P<0.001 for superiority). Details are shown in Table 2 and Figure 2.

SECONDARY OUTCOMES

The Kaplan–Meier cumulative incidence of death from any cause was similar in the abbreviated-

Table 1. Characteristics and Clinical Presentation of the Patients at Baseline.*

Characteristic	Abbreviated Dual Antiplatelet Therapy (N=2295)	Standard Dual Antiplatelet Therapy (N=2284)
Age — yr	76.1±8.7	76.0±8.8
Male sex — no. (%)	1590 (69.3)	1581 (69.2)
Body-mass index†	27.25±4.68	27.44±4.74
Family history of coronary artery disease — no. (%)	556 (24.2)	553 (24.2)
Arterial hypertension — no. (%)	1766 (76.9)	1787 (78.2)
Diabetes mellitus — no. (%)	754 (32.9)	784 (34.3)
Hyperlipidemia — no. (%)	1542 (67.2)	1555 (68.1)
Smoking — no./total no. (%)		
Previous	874/2290 (38.2)	854/2276 (37.5)
Current	230/2290 (10.0)	184/2276 (8.1)
Peripheral vascular disease — no. (%)‡	243 (10.6)	242 (10.6)
Carotid artery disease — no. (%)	120 (5.2)	144 (6.3)
Heart failure — no. (%)	429 (18.7)	438 (19.2)
Left ventricular ejection fraction — %§	53.48±11.44	52.96±11.77
Previous myocardial infarction — no. (%)	434 (18.9)	430 (18.8)
Previous percutaneous coronary intervention — no. (%)	594 (25.9)	594 (26.0)
Previous cerebrovascular event — no. (%)	268 (11.7)	302 (13.2)
Previous coronary-artery bypass grafting — no. (%)	170 (7.4)	171 (7.5)
Chronic pulmonary disease — no. (%)	255 (11.1)	283 (12.4)
Chronic kidney disease — no. (%)¶	418 (18.2)	458 (20.1)
Liver disease — no. (%)	29 (1.3)	32 (1.4)
Atrial fibrillation — no. (%)	770 (33.6)	720 (31.5)
Oral anticoagulant — no. (%)‖	849 (37.0)	820 (35.9)
PRECISE-DAPT score**	26.81±10.91	26.71±11.06
Previous bleeding — no. (%)	165 (7.2)	155 (6.8)
Hemoglobin — g/liter	13.23±1.78	13.20±1.79
White-cell count — $\times 10^{-9}$/liter††	8.29±11.44	8.05±3.40
Creatinine clearance — ml/min/1.73 m^2‡‡	70.72±23.99	71.00±24.10
Clinical presentation		
Stable angina — no. (%)	922 (40.2)	927 (40.6)
Silent ischemia — no. (%)	245 (10.7)	274 (12.0)
Non–ST-elevation myocardial infarction — no. (%)	595 (25.9)	558 (24.4)
ST-elevation myocardial infarction — no. (%)	273 (11.9)	265 (11.6)
Unstable angina — no. (%)	260 (11.3)	260 (11.4)
Myocardial infarction of Killip class II, III, or IV — no. (%)	252 (11.0)	254 (11.1)
Cardiac arrest — no. (%)	26 (1.1)	32 (1.4)

* Plus–minus values are means ±SD. Data on race and ethnic group are not reported because of restrictions on obtaining this information from patients recruited in France.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Peripheral vascular disease was defined as intermittent claudication, peripheral-artery bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (≥6 cm in diameter), an ankle brachial index of no more than 0.90, or aortic plaque.
§ Data on the left ventricular ejection fraction were available for 2169 patients in the abbreviated-therapy group and for 2128 in the standard-therapy group.

Table 1. (Continued.)

¶ Chronic kidney disease was defined as kidney damage (pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area for at least 3 months.
‖ Oral anticoagulants were a vitamin K antagonist or a non–vitamin K antagonist oral anticoagulant.
** Scores on the PRECISE-DAPT, in which the components are the patient's age, previous bleeding, hemoglobin level, white-cell count, and creatinine clearance, range from 0 to 100. Patients with a score of 25 or higher are at high risk for bleeding.
†† The white-cell count was calculated at screening visit. One patient in the standard-therapy group had a PRECISE-DAPT score calculated without the white-cell count.
‡‡ The creatinine clearance was calculated with the use of the Modification of Diet in Renal Disease method.

therapy group and the standard-therapy group (3.3% and 3.6%, respectively), as were the cumulative incidences of myocardial infarction (2.7% and 2.2%, respectively) and definite or probable stent thrombosis (0.6% and 0.4%) (Table 2). A cerebrovascular event occurred in 17 patients (0.8%) in the abbreviated-therapy group and in 32 (1.4%) in the standard-therapy group. Stroke occurred in 12 patients (0.5%) in the abbreviated-therapy group and in 23 (1.0%) in the standard-therapy group; hemorrhagic stroke occurred in 1 and 5 patients, respectively.

The cumulative incidence of BARC type 2 bleeding was lower in the abbreviated-therapy group than in the standard-therapy group (4.5% vs. 6.8%; difference, −2.25 percentage points; 95% CI, −3.59 to −0.90), but the cumulative incidence of bleeding of type 3, 4, or 5 was similar in the two groups (2.3% and 2.6%, respectively). Fatal bleeding (BARC type 5) occurred in 2 patients (0.1%) in the abbreviated-therapy group and in 8 (0.4%) in the standard-therapy group (Table 2).

ADDITIONAL ANALYSES

Sensitivity analyses for noninferiority testing in the intention-to-treat population and for superiority testing in the per-protocol population yielded consistent results for the primary and secondary outcomes (Table 2 and Figs. S4 through S6). The effects of abbreviated therapy as compared with standard dual antiplatelet therapy on the incidences of the three primary outcomes were largely consistent across subgroups (Figs. S7 through S9).

DISCUSSION

Among patients at high risk for bleeding who had undergone implantation with a biodegradable-polymer sirolimus-eluting stent for an acute or chronic coronary syndrome, the discontinuation of dual antiplatelet therapy at a median of 34 days after PCI was noninferior to the continuation of dual antiplatelet therapy for a median duration of 193 days with regard to net adverse clinical events and major adverse cardiac or cerebral events and was superior with regard to major or clinically relevant nonmajor bleeding. Secondary efficacy outcomes were generally similar in the two groups. Treatment effects with regard to the three primary outcomes were consistent across subgroups.

The incidence of major or clinically relevant nonmajor bleeding in the intention-to-treat population (the third primary outcome) was 6.5% in the abbreviated-therapy group and 9.4% in the standard-therapy group (difference, −2.82 percentage points). The lower risk of bleeding in the abbreviated-therapy group was mainly due to the lower incidence of clinically relevant nonmajor bleeding events (BARC type 2) in this group than in the standard-therapy group (4.5% vs. 6.8%).

We recruited patients with a high bleeding risk regardless of clinical presentation and did not restrict the number, type, or location of target coronary lesions, provided that the lesions had been uniformly treated with a biodegradable-polymer sirolimus-eluting stent and were not due to in-stent restenosis or stent thrombosis. Patients were screened primarily at the time of stent implantation, and only a few of the potentially eligible patients (5.2%) withdrew before or at randomization. Our trial population differs from those in studies that excluded patients with acute coronary syndrome[12] and that limited the number, location, or complexity of treated lesions.[12,13] Our results therefore inform treatment decisions regarding dual antiplatelet therapy at 1 month after coronary intervention in patients at high risk for bleeding who do not have postprocedural ischemic events, including patients

Table 2. Composite Primary Outcomes and Secondary Outcomes in the Per-Protocol and Intention-to-Treat Populations.*

Outcome	Per-Protocol Population				Intention-to-Treat Population			
	Abbreviated DAPT (N=2204)	Standard DAPT (N=2230)	Hazard Ratio (95% CI)	Risk Difference (95% CI)	Abbreviated DAPT (N=2295)	Standard DAPT (N=2284)	Hazard Ratio (95% CI)	Risk Difference (95% CI)
	number (percent)			*percentage points*	*number (percent)*			*percentage points*
Composite primary outcomes†								
Net adverse clinical events	165 (7.5)	172 (7.7)	0.97 (0.78 to 1.20)	−0.23 (−1.80 to 1.33)	172 (7.5)	182 (8.0)	0.94 (0.76 to 1.15)	−0.48 (−2.03 to 1.08)
Major adverse cardiac or cerebral events	133 (6.1)	132 (5.9)	1.02 (0.80 to 1.30)	0.11 (−1.29 to 1.51)	138 (6.0)	138 (6.1)	0.99 (0.78 to 1.26)	−0.03 (−1.42 to 1.35)
Major or nonmajor clinically relevant bleeding	140 (6.4)	203 (9.2)	0.68 (0.55 to 0.85)	−2.78 (−4.37 to −1.20)	148 (6.5)	211 (9.4)	0.68 (0.55 to 0.84)‡	−2.82 (−4.40 to −1.24)
Secondary outcomes								
Death from cardiovascular causes, myocardial infarction, or stroke	100 (4.6)	97 (4.4)	1.04 (0.79 to 1.38)	—	103 (4.5)	102 (4.5)	1.00 (0.76 to 1.32)	—
Death	72 (3.3)	79 (3.6)	0.92 (0.67 to 1.26)	—	75 (3.3)	81 (3.6)	0.92 (0.67 to 1.26)	—
Death from cardiovascular causes	36 (1.7)	43 (2.0)	0.84 (0.54 to 1.31)	—	37 (1.6)	44 (2.0)	0.83 (0.54 to 1.29)	—
Death from noncardiovascular causes	27 (1.2)	27 (1.2)	1.01 (0.59 to 1.72)	—	29 (1.3)	28 (1.2)	1.03 (0.61 to 1.73)	—
Stroke or transient ischemic attack	16 (0.7)	31 (1.4)	0.52 (0.28 to 0.95)	—	17 (0.8)	32 (1.4)	0.53 (0.29 to 0.95)	—
Stroke	11 (0.5)	22 (1.0)	0.50 (0.24 to 1.04)	—	12 (0.5)	23 (1.0)	0.52 (0.26 to 1.04)	—
Ischemic stroke	10 (0.5)	17 (0.8)	—	—	11 (0.5)	18 (0.8)	—	—
Hemorrhagic stroke	1 (<0.1)	4 (0.2)	—	—	1 (<0.1)	5 (0.2)	—	—
Myocardial infarction	59 (2.7)	46 (2.1)	1.30 (0.88 to 1.91)	—	60 (2.7)	49 (2.2)	1.22 (0.84 to 1.78)	—
Definite or probable stent thrombosis	14 (0.6)	8 (0.4)	1.77 (0.74 to 4.22)	—	14 (0.6)	9 (0.4)	1.55 (0.67 to 3.57)	—
Definite	11 (0.5)	6 (0.3)	1.85 (0.69 to 5.01)	—	11 (0.5)	7 (0.3)	1.56 (0.61 to 4.03)	—
Probable	3 (0.1)	2 (0.1)	—	—	3 (0.1)	2 (0.1)	—	—

Bleeding								
BARC type								
Type 1 to 5	190 (8.7)	291 (13.2)	0.64 (0.53 to 0.77)	—	202 (8.9)	304 (13.5)	0.64 (0.54 to 0.76)	—
Type 2	97 (4.5)	150 (6.8)	—	—	102 (4.5)	152 (6.8)	—	—
Type 3 to 5	49 (2.3)	54 (2.5)	—	—	53 (2.3)	59 (2.6)	—	—
Type 4	0	0	—	—	0	0	—	—
Type 5	2 (0.1)	7 (0.3)	—	—	2 (0.1)	8 (0.4)	—	—
TIMI minor or major bleeding event§	38 (1.8)	44 (2.0)	0.87 (0.56 to 1.34)	—	41 (1.8)	48 (2.1)	0.85 (0.56 to 1.28)	—
Minor	15 (0.7)	20 (0.9)	—	—	16 (0.7)	21 (0.9)	—	—
Major	23 (1.1)	24 (1.1)	—	—	25 (1.1)	27 (1.2)	—	—
GUSTO moderate or severe bleeding event¶	44 (2.0)	46 (2.1)	0.96 (0.64 to 1.46)	—	48 (2.1)	51 (2.3)	0.93 (0.63 to 1.38)	—
Moderate bleeding event	36 (1.7)	35 (1.6)	—	—	40 (1.8)	38 (1.7)	—	—
Severe bleeding event	8 (0.4)	12 (0.6)	—	—	8 (0.4)	14 (0.6)	—	—

* The per-protocol population excluded patients who did not fulfill the selection criteria or did not implement protocol-mandated therapy within 14 days after randomization. The intention-to-treat population included all the patients who underwent randomization. Percentages were calculated as Kaplan–Meier estimates of the cumulative incidence at 335 days. Hazard ratios are shown for the primary outcomes and for principal secondary outcomes. The widths of the 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons and should not therefore be used for inference about treatment effects. DAPT denotes dual antiplatelet therapy.

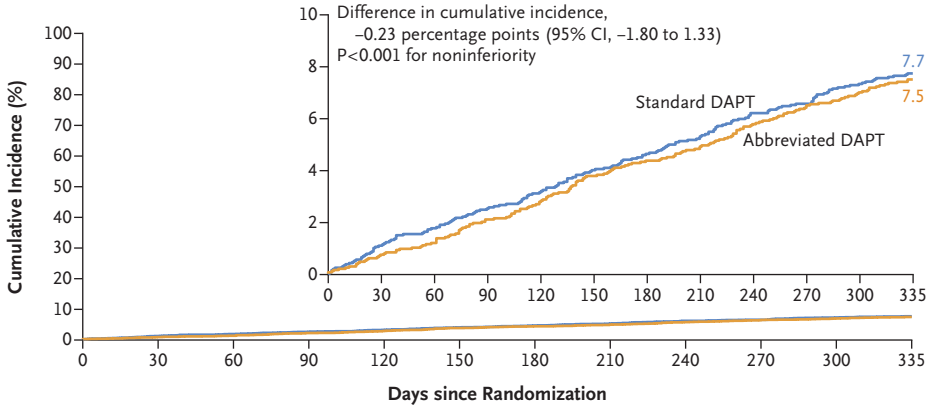
† The composite primary outcomes are listed in order of the prespecified hierarchical testing. The first primary outcome of net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, or major bleeding, defined as Bleeding Academic Research Consortium [BARC] type 3 or 5) and the second primary outcome of major adverse cardiac or cerebral events (a composite of death from any cause, myocardial infarction, or stroke) were assessed in the per-protocol population. The third primary outcome of major or nonmajor clinically relevant bleeding (defined as bleeding of BARC type 2, 3, or 5) was assessed in the intention-to-treat population.

‡ Although the Cox proportional-hazards ratio is reported for the outcome of major or nonmajor clinically relevant bleeding, it should be noted that this outcome violated the proportional-hazards assumption. The Cox hazard ratio is therefore provided for descriptive purposes only. In contrast, the calculation of the risk difference (estimated difference in cumulative incidence) was made with the Com-Nougue method,[11] which does not rely on the proportional-hazards assumption. For the other two primary end points, the proportional-hazards assumption was met.

§ Thrombolysis in Myocardial Infarction (TIMI) minor bleeding was defined as an observed decrease of at least 3 g per deciliter in the hemoglobin concentration or a decrease of at least 10 percentage points in the hematocrit. TIMI major bleeding was defined as an intracranial hemorrhage, a decrease of at least 5 g per deciliter in the hemoglobin concentration, or an absolute decrease of at least 15 percentage points in the hematocrit.

¶ Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) moderate bleeding was defined as bleeding that led to blood transfusion but did not result in hemodynamic compromise. GUSTO severe or life-threatening bleeding was defined as either intracranial hemorrhage or bleeding that caused hemodynamic compromise and led to intervention.

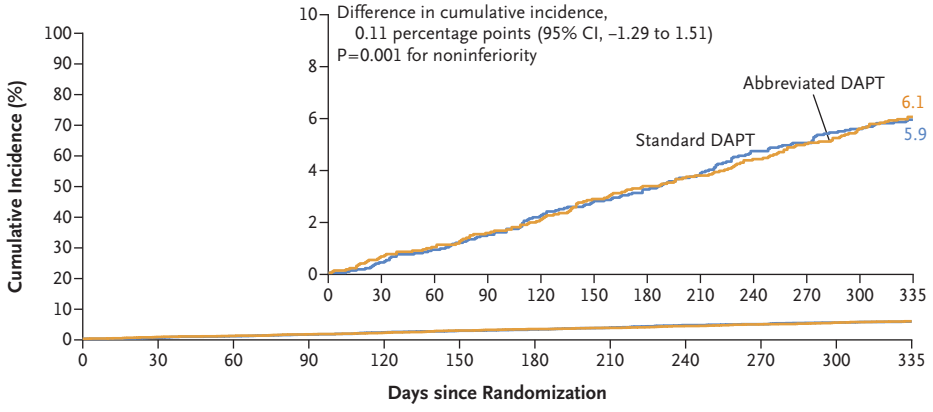
A Net Adverse Clinical Events



No. at Risk

Standard DAPT	2230	2203	2188	2169	2155	2137	2118	2102	2081	2068	2052	2041
Abbreviated DAPT	2204	2184	2173	2153	2138	2144	2101	2091	2070	2056	2044	2027

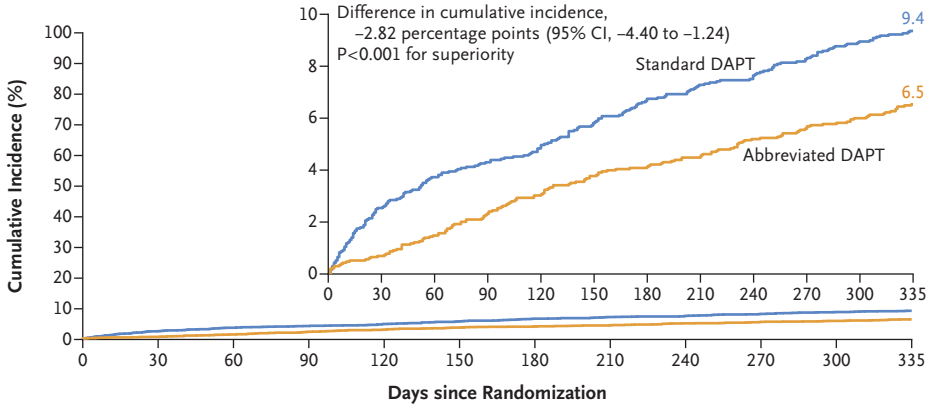
B Major Adverse Cardiac or Cerebral Events



No. at Risk

Standard DAPT	2230	2218	2207	2192	2176	2165	2149	2134	2113	2102	2090	2081
Abbreviated DAPT	2204	2186	2177	2164	2153	2135	2123	2114	2099	2086	2076	2058

C Major or Clinically Relevant Nonmajor Bleeding



No. at Risk

Standard DAPT	2284	2220	2186	2166	2147	2122	2094	2077	2060	2035	2015	1999
Abbreviated DAPT	2295	2269	2249	2223	2202	2173	2161	2150	2130	2117	2102	2078

Figure 2 (facing page). Cumulative Incidence of Three Primary Composite Outcomes at 335 Days.

The three ranked primary outcomes were a composite of death from any cause, myocardial infarction, stroke, or major bleeding (net adverse clinical events), which was assessed in the per-protocol population (Panel A); a composite of death from any cause, myocardial infarction, or stroke (major adverse cardiac or cerebral events), which was assessed in the per-protocol population (Panel B); and major or clinically relevant nonmajor bleeding, which was assessed in the intention-to-treat population (Panel C). The per-protocol population excluded patients who did not fulfill the selection criteria or did not implement protocol-mandated therapy within 14 days after randomization. The intention-to-treat population included all the patients who underwent randomization. Insets show the same data on enlarged y axes.

with clinical or angiographic features indicating a high ischemic risk.

The choices of the type of $P2Y_{12}$ inhibitor for dual antiplatelet therapy and the type of monotherapy after the discontinuation of dual antiplatelet therapy were at the discretion of the investigator. Clopidogrel was the most frequently used $P2Y_{12}$ inhibitor in the standard-therapy group and was the most frequently used monotherapy in the abbreviated-therapy group at the time of randomization and thereafter. This finding is consistent with those of previous trials that exclusively enrolled patients at high bleeding risk[2,3,14] and is consistent with guidelines.[15]

Two trials have compared 1 month of dual antiplatelet therapy with at least 12 months of dual antiplatelet therapy after PCI with drug-eluting stents.[4,6] The GLOBAL LEADERS trial showed that 1 month of dual antiplatelet therapy followed by ticagrelor monotherapy for an additional 23 months was not associated with lower all-cause mortality or with a lower incidence of new Q-wave myocardial infarction than 12 months of dual antiplatelet therapy followed by aspirin monotherapy for an additional 12 months.[6] In the STOPDAPT-2 trial, 1 month of dual antiplatelet therapy followed by clopidogrel monotherapy was associated with a lower risk of a composite of cardiovascular and bleeding events than 12 months of dual antiplatelet therapy.[4] However, patients in that trial were at low risk for ischemic events. In both these trials, patients were enrolled immediately after the PCI, and those at high risk for bleeding were not selected. The ISAR-TRIPLE trial, which compared 6 weeks of clopidogrel therapy with 6 months of clopidogrel therapy in 614 patients receiving oral anticoagulation who were also receiving aspirin after the implantation of a drug-eluting stent, showed no significant difference between the two treatment strategies with regard to a composite outcome of death, myocardial infarction, stroke, stent thrombosis, or major bleeding.[16]

Some limitations of our trial should be considered. Although the exclusion criteria were intended to be minimal, limited screening-log data suggested that approximately 4% of the patients who underwent screening (representing 21.5% of the eligible patients) were enrolled. Treatments were open-label, which reflects the impossibility of masking three oral $P2Y_{12}$ inhibitors and aspirin in a treatment-strategy trial. The duration of dual antiplatelet therapy was heterogeneous in the standard-therapy group. The type of monotherapy after the discontinuation of dual antiplatelet therapy in the abbreviated-therapy group also varied. The duration of dual antiplatelet therapy in the two trial groups was longer than is now recommended in patients receiving oral anticoagulation.[17,18] However, a very short duration of triple antithrombotic therapy is associated with higher rates of ischemic events than longer treatment.[14]

Our trial included patients at high bleeding risk who had undergone implantation of a biodegradable-polymer sirolimus-eluting stent; consequently, our results may not extend to patients who are not at high bleeding risk or who receive other stent types. Patients with in-stent restenosis or stent thrombosis were ineligible for this trial. The incidences of net adverse clinical events and major adverse cardiac and cerebral events were lower than expected, and noninferiority margins were wide; therefore, a modest increase in the incidence of such events cannot be ruled out with this duration of abbreviated therapy.

In this trial involving patients at high risk for bleeding who had undergone implantation of a biodegradable-polymer sirolimus-eluting stent, the discontinuation of dual antiplatelet therapy at a median of 34 days after PCI was noninferior to the continuation of treatment for a median duration of 193 days with regard to the incidence of net adverse clinical events and major adverse cardiac or cerebral events and was associated with a lower incidence of major or clinically relevant nonmajor bleeding.

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APPENDIX

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