ORIGINAL ARTICLE

Extended Dual Antiplatelet Therapy for Multivessel Coronary Artery Disease

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ABSTRACT

BACKGROUND

Patients with multivessel coronary artery disease often receive 12 months of dual antiplatelet therapy (DAPT) after stenting to reduce the risk of ischemic events. Whether extending DAPT beyond 12 months in event-free patients with multivessel disease provides a benefit is uncertain.

METHODS

We conducted an open-label, randomized trial at 97 centers in China. Patients 18 to 75 years of age with multivessel coronary artery disease who had no major ischemic or bleeding events while receiving DAPT for 12 months after implantation of a drug-eluting stent were randomly assigned in a 1:1 ratio to receive an additional 12 months of DAPT (clopidogrel plus aspirin) or aspirin monotherapy. The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary safety end point was clinically relevant or major bleeding (i.e., a bleeding event of Bleeding Academic Research Consortium [BARC] type ≥2; BARC types range from 0 to 5, with higher values indicating greater severity of bleeding).

RESULTS

A total of 8250 patients were randomly assigned to receive extended DAPT (4125 patients) or aspirin monotherapy (4125 patients). The median follow-up was 34.3 months. A primary efficacy end-point event occurred in 222 patients in the DAPT group and in 266 patients in the aspirin-monotherapy group (36-month Kaplan–Meier cumulative incidence, 5.8% vs. 6.8%; hazard ratio, 0.82; 95% confidence interval [CI], 0.69 to 0.98; P=0.03). Clinically relevant or major bleeding occurred in 51 patients in the DAPT group and in 57 patients in the aspirin-monotherapy group (36-month Kaplan–Meier cumulative incidence, 1.4% vs. 1.5%; hazard ratio, 0.89; 95% CI, 0.61 to 1.30; P=0.54).

CONCLUSIONS

Among patients with multivessel coronary artery disease who were in stable condition 12 months after implantation of a drug-eluting stent, extending DAPT with clopidogrel and aspirin for an additional 12 months led to a lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than continuing aspirin alone, without an increased risk of bleeding. (Funded by the National Natural Science Foundation of China and others; DAPT-MVD ClinicalTrials.gov number, NCT04624854.)

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Multivessel coronary artery disease, which has a prevalence of 40 to 60% among patients undergoing percutaneous coronary intervention (PCI),[1,2] increases the ongoing risk of myocardial infarction and death. In addition to ischemic events originating from previously treated coronary lesions, thrombotic events often arise from untreated segments of the coronary tree.[3-5]

Patients with multivessel disease at low risk for bleeding, especially those with acute coronary syndromes, routinely receive 12 months of dual antiplatelet therapy (DAPT) after implantation of a drug-eluting stent to reduce the risk of ischemic events.[6,7] Whether the potential benefits of further extending the duration of DAPT in these patients outweigh the risk of bleeding is uncertain.[8-10] Although guidelines provide a class Ia recommendation for extended DAPT in selected patients at high ischemic risk,[6,7] evidence from previous trials is difficult to generalize to high-risk patients with multivessel disease.

To address this uncertainty, we designed the Dual Antiplatelet Therapy in Patients with Coronary Multivessel Disease (DAPT-MVD) trial. We aimed to determine the efficacy and safety of extending DAPT with clopidogrel plus aspirin, as compared with aspirin monotherapy, for an additional 12 months in patients with multivessel disease who remained event-free 12 months after implantation of a drug-eluting stent.

Methods

Trial Design and Oversight

We conducted an open-label, assessor-blinded, randomized trial at 97 centers in China. The trial design has been published previously.[11] The protocol and statistical analysis plan were approved by the ethics committees of the participating centers and are available with the full text of this article at NEJM.org. All the patients provided written informed consent.

The trial was designed and led by the steering committee, and the conduct of the trial was overseen by the Chinese Society of Cardiology. An independent data and safety monitoring board reviewed safety data in an unblinded fashion and at regular intervals during the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Committee members and participating investigators are listed in the Supplementary Appendix, available at NEJM.org.

Trial Population

Eligible patients were 18 to 75 years of age, had multivessel coronary artery disease, and had remained in stable condition for 12 months after implantation of a drug-eluting stent without major ischemic or bleeding events. Multivessel disease was defined as two or more major epicardial coronary arteries with a diameter stenosis of at least 50%, with up to 30% diameter stenosis in the left main coronary artery.[12,13] Patients with planned use of anticoagulants or contraindications to platelet P2Y12-receptor blockers during the trial period were excluded. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

Randomization, Treatment, and Follow-up

At 12 months after PCI, eligible patients were randomly assigned in a 1:1 ratio to receive open-label clopidogrel (75 mg daily) plus aspirin (75 to 150 mg daily) (DAPT group) or aspirin alone (75 to 150 mg daily) (aspirin-monotherapy group) for an additional 12 months. The randomization sequence was generated by an independent statistician and conducted with the use of an interactive Web-response system. After 1 year of protocol-mandated therapy (i.e., 2 years after PCI), treatment was switched to an antiplatelet regimen selected by the treating physician.

Clinical or telephone follow-up was conducted at 1, 3, 6, 9, 12, and 36 months after randomization to assess the patients' clinical status and medication use and to identify clinical events. Follow-up concluded when the last patient completed 12 months of follow-up, at which time an additional visit was scheduled for all the patients who had not yet completed 36 months of follow-up. Mortality data were also sought from the China Death Surveillance System.

End Points

The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke and was assessed in a time-to-event analysis, according to the first event that occurred between randomization and the latest follow-up visit, which was determined in relation to the time the last enrolled patient completed 1 year of follow-up.

Secondary efficacy end points included death from any cause, death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, a net adverse clinical event (a composite of ischemic events or a bleeding event of Bleeding Academic Research Consortium [BARC] type 2 to 5),[14] a composite of death from cardiovascular causes or hospitalization for a cardiovascular or cerebrovascular event, urgent revascularization, any repeat revascularization, and definite or probable stent thrombosis. BARC types include 0 (no bleeding), 1 (mild bleeding that is not medically actionable), 2 (nonmajor bleeding that is medically actionable), 3 (major bleeding), 4 (bypass surgery–related bleeding), and 5 (fatal bleeding).

The primary safety end point was clinically relevant or major bleeding (i.e., a bleeding event of BARC type ≥2). The secondary safety end point was major bleeding (i.e., a bleeding event of BARC type ≥3). An independent clinical-events committee, the members of which were unaware of the treatment assignments, adjudicated all efficacy and bleeding end points. End-point definitions are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of an assumed 5% annual rate of primary efficacy end-point events in the aspirin-monotherapy group.[9] Allowing for loss to a follow-up in 5% of the patients and nonadherence in 3%, we estimated that 8250 patients would provide the trial with 80% power at a two-sided alpha level of 0.05 to detect a 20% lower risk of a primary efficacy end-point event in the DAPT group than in the aspirin-monotherapy group (i.e., a hazard ratio of 0.80).[10]

Primary efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization, regardless of whether they received the intended treatment. The per-protocol population included all the patients who had undergone randomization and had no major protocol deviations, and the end points in the per-protocol population were analyzed as supportive evidence. The safety population included all the patients who had undergone randomization and received at least one dose of DAPT or aspirin monotherapy; patients were assessed on the basis of their randomized treatment assignment. The safety analysis period was defined as the time from randomization until 7 days after receipt of the last dose of clopidogrel or aspirin.

The primary efficacy and safety end points were analyzed with the use of an unadjusted Cox regression model to calculate the hazard ratio and 95% confidence interval. Proportional-hazards assumptions for the primary efficacy and safety end points were confirmed by Schoenfeld residual plots. Kaplan–Meier survival curves were displayed according to trial group and compared with the use of a log-rank test. The cumulative incidence of events at 12, 24, and 36 months was reported. In addition, covariate-adjusted analysis was performed with the following covariates: age, sex, body-mass index, diabetes, hypertension, hyperlipidemia, and history of smoking and alcohol use. Complete data on all covariates were available, and thus imputation was not performed. Subgroup analyses were performed with the use of unadjusted Cox models. A sensitivity analysis of the primary efficacy end point was performed by incorporating a random effect for trial site in the Cox model to evaluate site-level influence on the treatment effect. Furthermore, a win ratio analysis was conducted to account for the clinical hierarchy of the composite end-point components. Time-to-event secondary and safety end points were also analyzed with unadjusted and adjusted Cox models, as was done in the primary end-point analysis. The number and percentage of patients with at least one serious adverse event were calculated for each trial group.

No interim analyses were conducted. Confidence intervals for secondary and exploratory end points were not adjusted for multiple comparisons, and the widths of the confidence intervals should not be used to infer treatment effect; inferences drawn from them may not be reproducible. All P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with SAS statistical software, version 9.4 (SAS Institute), or R software, version 4.4.3 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

Between October 28, 2020, and March 12, 2024, a total of 9127 patients at 97 sites in China were assessed for eligibility (Table S1 in the Supple-

mentary Appendix). Of these, 877 patients were ineligible, and 8250 patients (90.4%) underwent randomization. The mean (±SD) time from the index PCI to randomization was 378.6±19.8 days. All the patients had been receiving DAPT before randomization; DAPT included aspirin plus clopidogrel (5534 patients [67.1%]) or aspirin plus ticagrelor (2716 patients [32.9%]). Patients were randomly assigned to receive either extended DAPT with aspirin plus clopidogrel (4125 patients) or aspirin monotherapy (4125 patients) for an additional 12 months (Fig. 1).

Baseline clinical and procedural characteristics appeared to be well balanced between the two trial groups (Table 1). The mean patient age was 61 years; 2497 patients (30.3%) were female, and 2323 (28.2%) had diabetes. Nearly all the patients (8109 [98.3%]) had presented with an acute coronary syndrome before the index PCI, including 2806 (34.0%) with a myocardial infarction. Additional details on the clinical and procedural characteristics of the patients at baseline and the representativeness of the trial population are provided in Tables S2, S3, and S4. Among 8245 patients, PCI with drug-eluting stent implantation was performed on a single vessel in 6552 (79.5%) and on multiple vessels in 1693 (20.5%).

The median follow-up was 34.3 months (interquartile range, 24.3 to 42.2). During this period, 151 patients (1.8%) were lost to follow-up (Fig. 1 and Table S5), although survival data were available for all patients. A total of 179 patients (2.2%) had major protocol deviations, most commonly nonadherence to the assigned treatment (170 patients [2.1%]) (Fig. 1). After the 12-month trial period, nearly all the patients in both trial groups received aspirin monotherapy (Table S6).

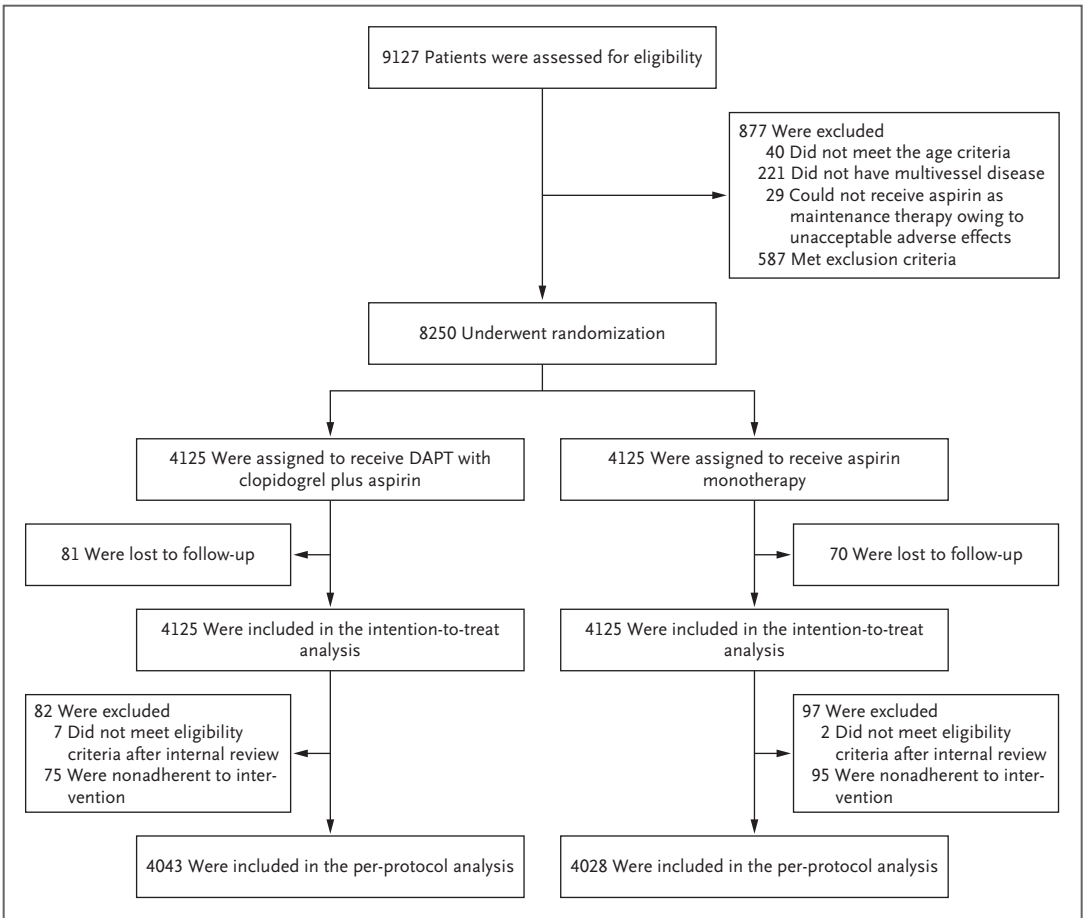

Figure 1. Randomization, Treatment, and Follow-up.
DAPT denotes dual antiplatelet therapy.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	DAPT (N=4125)	Aspirin Monotherapy (N=4125)
Age — yr	60.5±8.8	60.5±8.9
Female sex — no. of patients (%)	1223 (29.6)	1274 (30.9)
Body-mass index†	25.3±2.9	25.3±2.9
Diabetes mellitus — no. of patients (%)	1187 (28.8)	1136 (27.5)
Hypercholesterolemia — no. of patients (%)	1534 (37.2)	1540 (37.3)
Hypertension — no. of patients (%)	2244 (54.4)	2170 (52.6)
Cigarette smoker within the past year — no. of patients (%)	1434 (34.8)	1355 (32.8)
Indication for index PCI — no. of patients (%)		
STEMI	946 (22.9)	994 (24.1)
NSTEMI	417 (10.1)	449 (10.9)
Unstable angina	2695 (65.3)	2608 (63.2)
Stable angina	67 (1.6)	74 (1.8)
Medication use before enrollment — no. of patients (%)		
Aspirin plus clopidogrel	2773 (67.2)	2761 (66.9)
Aspirin plus ticagrelor	1352 (32.8)	1364 (33.1)
No. of diseased vessels — no. of patients (%)‡		
Two-vessel disease§	1849 (44.8)	1938 (47.0)
Three-vessel disease	2273 (55.1)	2186 (53.0)
Location of diseased vessels — no. of patients (%)¶		
Left anterior descending artery	3846 (93.2)	3782 (91.7)
Left circumflex artery	3192 (77.4)	3112 (75.4)
Right coronary artery	3475 (84.2)	3534 (85.7)
Time from the index PCI to randomization — days	378.8±19.9	378.4±19.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. DAPT denotes dual antiplatelet therapy, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Four patients had single-vessel disease (3 in the DAPT group and 1 in the aspirin-monotherapy group).
§ Among the patients with two-vessel disease, 14 (7 in each trial group) presented with 50% or greater stenosis in both the left anterior descending artery and the dominant ramus intermedius.
¶ Patients with lesions in the ramus intermedius were included in the group with lesions in the left anterior descending artery.

EFFICACY END POINTS

In the intention-to-treat population, a primary efficacy end-point event occurred in 222 patients in the DAPT group and in 266 patients in the aspirin-monotherapy group (36-month Kaplan–Meier cumulative incidence, 5.8% vs. 6.8%; hazard ratio, 0.82; 95% confidence interval [CI], 0.69 to 0.98; P=0.03) (Table 2, Fig. 2, and Fig. S1). The results of covariate-adjusted analysis, with a hazard ratio of 0.82 (95% CI, 0.68 to 0.98), appeared to be consistent with those of the primary analysis (Table S7), as were the results from crude and adjusted primary end-point analyses in the per-protocol analyses (Fig. S2 and Table S8) and sensitivity analyses (Tables S9 and S10). A subgroup analysis of the primary end point is shown in Figure 3. The results of a hierarchical analysis also seemed to be consistent with those of the primary analysis (win ratio, 1.22; 95% CI, 1.01 to 1.46) (Fig. S3). At 12 months, the Kaplan–Meier cumulative incidence was 2.0% in the DAPT group and 2.4% in the aspirin-monotherapy group

Table 2. Major Adverse Cardiovascular, Cerebrovascular, and Bleeding Events (Intention-to-Treat Population).

End Point	DAPT (N=4125)	Aspirin Monotherapy (N=4125)	Hazard Ratio (95% CI)	P Value
	*no. of patients with event (estimated %)**			
Efficacy end points				
Primary efficacy end point: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke†	222 (5.8)	266 (6.8)	0.82 (0.69–0.98)	0.03
Secondary efficacy end points‡				
Death from any cause	120 (3.1)	116 (3.0)	1.02 (0.79–1.32)	—
Death from cardiovascular causes	73 (2.0)	75 (1.9)	0.96 (0.70–1.33)	—
Nonfatal stroke	97 (2.5)	120 (3.1)	0.80 (0.61–1.04)	—
Nonfatal myocardial infarction	67 (1.8)	97 (2.5)	0.68 (0.50–0.93)	—
Safety end points§				
BARC type 2–5 bleeding	51 (1.4)	57 (1.5)	0.89 (0.61–1.30)	0.54
BARC type 3–5 bleeding	29 (0.8)	33 (0.9)	0.87 (0.53–1.43)	0.59

* Percentages are Kaplan–Meier estimates of the cumulative incidence of end-point events at 36 months after randomization.
† The primary efficacy end point was assessed in a time-to-event analysis, according to the first event that occurred between randomization and the latest follow-up visit, which was determined in relation to the time the last enrolled patient completed 1 year of follow-up.
‡ For the secondary efficacy end points, the widths of the confidence interval have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
§ Bleeding Academic Research Consortium (BARC) types include 0 (no bleeding), 1 (mild bleeding that is not medically actionable), 2 (nonmajor bleeding that is medically actionable), 3 (major bleeding), 4 (bypass surgery–related bleeding), and 5 (fatal bleeding).

(overall incidence in the trial population, 2.2%), and the corresponding values at 24 months were 3.3% and 4.3% (overall, 3.8%).

Secondary efficacy end points are shown in Table 2, Table S11, and Figure S4. Death from any cause occurred in 120 patients in the DAPT group and in 116 patients in the aspirin-monotherapy group (36-month Kaplan–Meier cumulative incidence, 3.1% and 3.0%, respectively; hazard ratio, 1.02; 95% CI, 0.79 to 1.32); death from cardiovascular causes in 73 patients and 75 patients, respectively (36-month Kaplan–Meier cumulative incidence, 2.0% and 1.9%; hazard ratio, 0.96; 95% CI, 0.70 to 1.33); nonfatal stroke in 97 patients and 120 patients, respectively (36-month Kaplan–Meier cumulative incidence, 2.5% and 3.1%; hazard ratio, 0.80; 95% CI, 0.61 to 1.04); nonfatal myocardial infarction in 67 patients and 97 patients, respectively (36-month Kaplan–Meier cumulative incidence, 1.8% and 2.5%; hazard ratio, 0.68; 95% CI, 0.50 to 0.93); a net adverse clinical event in 255 patients and 295 patients, respectively (36-month Kaplan–Meier cumulative incidence, 6.7% and 7.5%; hazard ratio, 0.85; 95% CI, 0.72 to 1.01); and stent thrombosis in no patients and 2 patients, respectively (36-month Kaplan–Meier cumulative incidence, 0% and 0.1%).

SAFETY END POINTS

Clinically relevant or major bleeding (BARC type ≥2) occurred in 51 patients in the DAPT group and in 57 patients in the aspirin-monotherapy group (36-month Kaplan–Meier cumulative incidence, 1.4% and 1.5%, respectively; hazard ratio, 0.89; 95% CI, 0.61 to 1.30; P=0.54) (Table 2 and Fig. 2). Major bleeding (BARC type ≥3) occurred in 29 patients in the DAPT group and in 33 patients in the aspirin-monotherapy group (36-month Kaplan–Meier cumulative incidence, 0.8% and 0.9%, respectively; hazard ratio, 0.87; 95% CI, 0.53 to 1.43; P=0.59) (Table 2). A total of 1750 serious adverse events occurred in 1143 patients (27.7%) in the DAPT group, and 1701 serious adverse events occurred in 1156 patients (28.0%) in the aspirin-monotherapy group (P=0.77) (Table S12).

DISCUSSION

Among patients with multivessel disease who had remained event-free while receiving DAPT

for 12 months after implantation of a drug-eluting stent, our trial, with a median follow-up of 34.3 months, showed that an additional 12 months of DAPT with clopidogrel and aspirin led to a lower risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than aspirin monotherapy. The risk of clinically relevant or major bleeding (BARC type ≥2) was similar in the two trial groups, as was the risk of major bleeding (BARC type ≥3).

In previous trials of extended DAPT, ischemic benefits were consistently offset by increased rates of major bleeding.[9,15,16] In contrast, our trial is distinguished by its unique patient risk–benefit profile, in which the benefits and risks of an additional 12 months of DAPT, as compared with aspirin monotherapy, were evaluated among nonelderly patients with multivessel disease, most of whom presented with an acute coronary syndrome and were free from major ischemic or bleeding events while receiving DAPT for 1 year after implantation of a drug-eluting stent. In this patient population with a relatively high ischemic risk but low bleeding risk, extended DAPT with clopidogrel and aspirin for an additional year resulted in an 18% lower risk of a composite of ischemic events (the primary end point) than aspirin monotherapy during a median follow-up of 34.3 months, which was driven by a 32% lower risk of myocardial infarction. It is notable that this reduction in the risk of ischemic events occurred without an increase in the risk of clinically relevant or major bleeding or in the risk of death, which has been seen in some earlier trials involving patients at higher risk for bleeding.[9] The benefit of extended DAPT was consistent across most prespecified subgroups, with the possible exception of patients with a high body-mass index, a known predictor of impaired clopidogrel response.[17]

In a landmark analysis, the clinical benefit of extended DAPT became apparent after the sixth month of extended therapy and was sustained for 12 months after treatment cessation (Fig. S5). The reduction in the risk of myocardial infarction with extended DAPT that was observed in our trial was driven mainly by fewer events arising from nontarget coronary segments rather than from stented target sites (Fig. S6). Beyond its direct antithrombotic effects, inhibition of the adenosine diphosphate receptor in the second year after an acute coronary syndrome — a high-risk period for plaque progression[18] — may stabilize untreated vulnerable plaques, a beneficial effect that may persist after its discontinuation. Although the mechanisms underlying these observations are uncertain, they may involve P2Y12-receptor–mediated amelioration of lipid

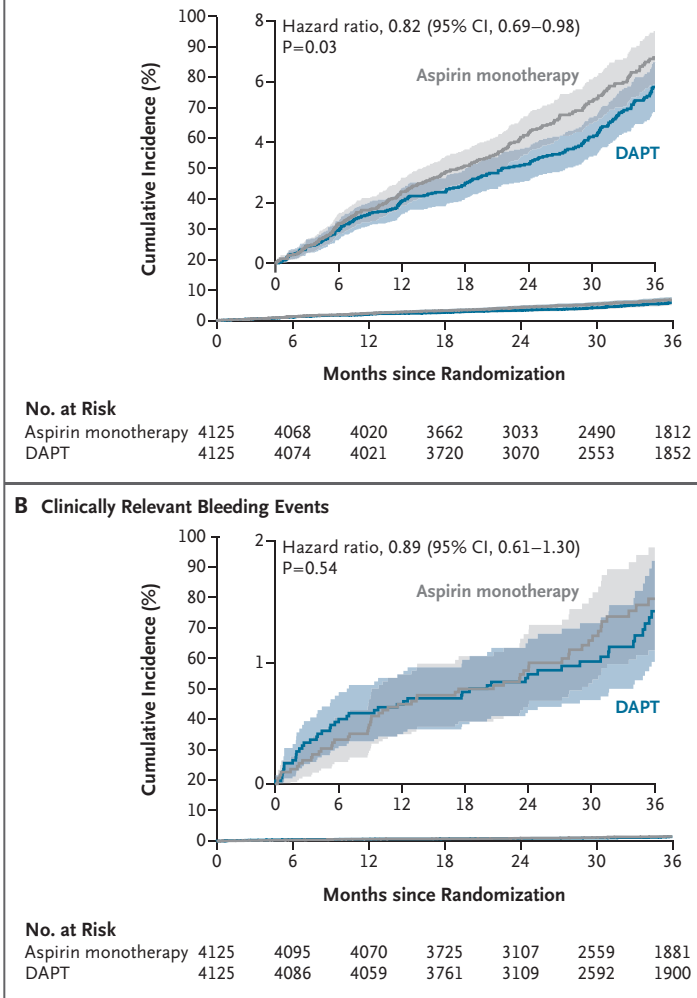

Figure 2. Cumulative Incidence of Primary Efficacy and Safety End-Point Events (Intention-to-Treat Population).

Time-to-first-event curves are shown for the primary efficacy end point in Panel A and the primary safety end point in Panel B. The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction. The primary safety end point was clinically relevant or major bleeding, defined as a bleeding event of Bleeding Academic Research Consortium (BARC) type 2 to 5. BARC types include 0 (no bleeding), 1 (mild bleeding that is not medically actionable), 2 (non-major bleeding that is medically actionable), 3 (major bleeding), 4 (bypass surgery–related bleeding), and 5 (fatal bleeding). The blue and gray shaded areas indicate the 95% confidence intervals for the Kaplan–Meier curves for the DAPT group and the aspirin monotherapy group, respectively. The insets show the same data on an expanded y axis.

accumulation in vascular smooth-muscle cells and prevention of intracellular iron overload in macrophages and other inflammatory cell lines.[19,20] In this regard, the patients with multivessel disease and recent acute coronary syndromes in our trial had a greater burden of untreated atherosclerosis and ongoing inflammation than those with single-vessel disease and chronic coronary syndromes.

The incidence of a primary efficacy end-point event in the period between randomization and 12 months was 2.2%, which was lower than anticipated among patients with multivessel disease.[12] This finding may be attributable to the trial inclusion criterion stipulating that patients needed to be in clinically stable condition and event-free for 1 year after PCI, which led to the selection of a trial population with a favorable risk profile. Nevertheless, the 6.8% cumulative incidence of a primary end-point event at 3 years among patients in the aspirin-monotherapy group underscores the substantial residual ischemic risk that persists, even in this cohort of patients in clinically stable condition, and the sample size was large enough to show a benefit with extended DAPT. Our results suggest that for patients with multivessel disease who present with an acute coronary syndrome, a standard 12-month duration of DAPT may be insufficient, even in those without ischemic or bleeding events up to that point.[6] These results are concordant with those of previous trials that showed the value of extended antiplatelet therapy in high-risk secondary-prevention cohorts.[9,15]

Our trial has several limitations. First, the open-label design could have introduced bias,[21]

Subgroup	No. of Patients	DAPT	Aspirin Monotherapy	Hazard Ratio for a Primary End-Point Event (95% CI)
		No. of patients with event/total no. (%)		
Overall	8250	222/4125 (5.8)	266/4125 (6.8)	0.82 (0.69–0.98)
Age				
<60 yr	3483	70/1742 (4.2)	88/1741 (5.3)	0.78 (0.57–1.07)
≥60 yr	4767	152/2383 (6.9)	178/2384 (7.9)	0.84 (0.68–1.04)
Sex				
Female	2497	67/1223 (6.0)	83/1274 (7.4)	0.82 (0.59–1.13)
Male	5753	155/2902 (5.7)	183/2851 (6.5)	0.82 (0.66–1.02)
Body-mass index				
<28	7076	191/3539 (5.9)	238/3537 (7.0)	0.79 (0.65–0.95)
≥28	1174	31/586 (5.4)	28/588 (5.3)	1.12 (0.67–1.87)
Diabetes mellitus				
No	5927	146/2938 (5.4)	179/2989 (6.0)	0.81 (0.65–1.01)
Yes	2323	76/1187 (6.7)	87/1136 (9.0)	0.83 (0.61–1.13)
Hypertension				
No	3836	93/1881 (5.0)	112/1955 (5.7)	0.85 (0.65–1.12)
Yes	4414	129/2244 (6.6)	154/2170 (7.8)	0.79 (0.63–1.00)
Hyperlipidemia				
No	5176	135/2591 (5.5)	151/2585 (6.1)	0.88 (0.70–1.11)
Yes	3074	87/1534 (6.2)	115/1540 (7.9)	0.74 (0.56–0.98)
History of smoking				
No	5461	158/2691 (6.2)	180/2770 (7.0)	0.89 (0.72–1.10)
Yes	2789	64/1434 (5.0)	86/1355 (6.3)	0.70 (0.51–0.96)
History of alcohol use				
No	6922	188/3415 (6.0)	234/3507 (7.1)	0.81 (0.67–0.98)
Yes	1328	34/710 (5.0)	32/618 (5.0)	0.93 (0.57–1.51)

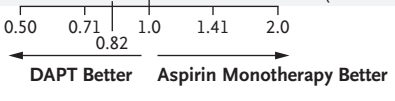

Figure 3. Prespecified Subgroup Analysis of the Primary Efficacy End Point.

Unadjusted hazard ratios for the primary efficacy end point (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) are shown with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The body-mass index is the weight in kilograms divided by the square of the height in meters.

although this possibility was mitigated by means of blinded end-point assessment.[22] Second, because we compared 12 additional months of clopidogrel plus aspirin with aspirin monotherapy after PCI, our investigation does not provide information about the relative safety and efficacy of alternative regimens (e.g., those that include a more potent P2Y12 inhibitor or clopidogrel monotherapy).[23-26] Third, our cohort was exclusively Chinese, potentially restricting generalizability. Although diabetes was prevalent in our trial population, obesity was uncommon, which is noteworthy given that clopidogrel may be metabolized more efficiently and thus have greater platelet inhibition in persons without obesity.[17] It is also noteworthy that many of the events that occurred during follow-up were strokes rather than coronary artery–related events. The percentage of patients with unstable angina was higher than that in other trials owing to the infrequent use of high-sensitivity troponins in China. In addition, *CYP2C19* loss-of-function alleles, which are prevalent among East Asian patients, reduce clopidogrel bioactivation[27]; extended DAPT may be associated with greater ischemic benefits and a higher risk of bleeding in a Western population. Fourth, the present results apply to a population with a high risk of ischemic events (e.g., patients with multivessel disease) and a low risk of bleeding (e.g., nonelderly patients who were event-free for 1 year while receiving DAPT). Whether prolonging DAPT would be beneficial in patients at lower ischemic risk or higher bleeding risk is uncertain. Finally, despite a lower-than-anticipated incidence of events, the cumulative incidence of an adverse ischemic event was 5.8% among patients receiving extended DAPT, a finding that indicates that the clopidogrel–aspirin regimen is insufficient to eliminate long-term risks among patients with multivessel disease in otherwise stable condition. Future research exploring alternative antithrombotic strategies, potentially incorporating new antiinflammatory[28,29] or lipid-lowering therapies,[30-32] to further reduce residual risk is warranted.

Among patients with multivessel coronary artery disease who had remained event-free 12 months after implantation of a drug-eluting stent, extending DAPT with clopidogrel plus aspirin for an additional 12 months resulted in a lower risk of ischemic events than continuing aspirin alone during a median follow-up of 34.3 months, without an increased risk of bleeding.

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