ORIGINAL ARTICLE

Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents

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ABSTRACT

BACKGROUND

The potential benefits and risks of the use of dual antiplatelet therapy beyond a 12-month period in patients receiving drug-eluting stents have not been clearly established.

METHODS

In two trials, we randomly assigned a total of 2701 patients who had received drug-eluting stents and had been free of major adverse cardiac or cerebrovascular events and major bleeding for a period of at least 12 months to receive clopidogrel plus aspirin or aspirin alone. The primary end point was a composite of myocardial infarction or death from cardiac causes. Data from the two trials were merged for analysis.

RESULTS

The median duration of follow-up was 19.2 months. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy, as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval [CI], 0.80 to 3.36; P=0.17). The individual risks of myocardial infarction, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death from any cause did not differ significantly between the two groups. However, in the dual-therapy group as compared with the aspirin-alone group, there was a nonsignificant increase in the composite risk of myocardial infarction, stroke, or death from any cause (hazard ratio, 1.73; 95% CI, 0.99 to 3.00; P=0.051) and in the composite risk of myocardial infarction, stroke, or death from cardiac causes (hazard ratio, 1.84; 95% CI, 0.99 to 3.45; P=0.06).

CONCLUSIONS

The use of dual antiplatelet therapy for a period longer than 12 months in patients who had received drug-eluting stents was not significantly more effective than aspirin monotherapy in reducing the rate of myocardial infarction or death from cardiac causes. These findings should be confirmed or refuted through larger, randomized clinical trials with longer-term follow-up. (ClinicalTrials.gov numbers, NCT00484926 and NCT00590174.)

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This article (10.1056/NEJMoa1001266) was published on March 15, 2010, at NEJM.org.

N Engl J Med 2010;362:1374-82.

Several pivotal clinical trials have shown that the use of drug-eluting coronary stents is associated with significant reductions in the risks of restenosis and need for target-lesion revascularization, as compared with use of bare-metal coronary stents.[1] On the basis of the results of these trials, drug-eluting stents have been widely used for percutaneous coronary intervention (PCI) in clinical practice.[2] However, some longer-term studies have shown that drug-eluting stents, as compared with bare-metal stents, are associated with increased rates of late stent thrombosis, death, or myocardial infarction.[3,4] It has been proposed that the occurrence of late clinical events may be due to delayed arterial healing after the implantation of drug-eluting stents.[5]

Early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis in patients with drug-eluting stents.[6,7] Current PCI guidelines recommend that clopidogrel, at a dose of 75 mg daily, should be given for at least 12 months after implantation of drug-eluting stents if patients are not at high risk for bleeding.[8] However, the optimal duration of dual antiplatelet therapy and the risk–benefit ratio for long-term dual antiplatelet therapy remain uncertain for patients receiving drug-eluting stents. The findings of observational studies have been inconsistent,[9-17] and to date, no randomized trials have been performed to address this issue. We evaluated the effect of the use of dual antiplatelet therapy for more than 12 months on long-term clinical outcomes in patients who had undergone initial PCI with the placement of a drug-eluting stent.

METHODS

STUDY DESIGN

The current analysis merged data from two concurrent randomized, clinical trials comparing continuation and discontinuation of clopidogrel in patients who were free of major adverse cardiac or cerebrovascular events and major bleeding for at least a 12-month period after implantation of drug-eluting stents. The first trial was called Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE; ClinicalTrials.gov number, NCT00484926), and the second trial was called Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions — Late Coronary Arterial Thrombotic Events (ZEST-LATE; NCT00590174). The study designs of the two trials were similar; the main difference was that the ZEST-LATE trial included only patients who had participated in another randomized trial, Comparison of the Efficacy and the Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions (ZEST; NCT00418067) (for details see the Supplementary Appendix, available with the full text of this article at NEJM.org). The REAL-LATE trial enrolled a broader population of patients without limiting the clinical or lesion characteristics.

The REAL-LATE and ZEST-LATE trials were merged as the result of a decision of the executive committees, on the basis of the slower-than-anticipated enrollment in each of the trials and substantial similarities in their designs. The data and safety monitoring board, which was the same for both trials, agreed to the merger. (The members of the committees and board are listed in the Appendix. Details regarding each trial and the rationale for a merged analysis of the two trials are described in the Supplementary Appendix.)

The two study protocols were developed separately by the authors and approved by the ethics committee at each participating center. Both trials were conducted according to the principles of the Declaration of Helsinki regarding investigation in humans. There was no industry involvement in the design, conduct, financial support, or analysis of either of the two studies or in the decision to merge them. The first two authors prepared the first draft of the manuscript, and the executive committees helped to revise it. The senior author had full access to an independent database for any query regarding the analyses, and he assumes responsibility for the accuracy and completeness of the reported data.

STUDY POPULATION

Patients were eligible to enroll in the REAL-LATE trial if they had undergone implantation of drug-eluting stents at least 12 months before enrollment, had not had a major adverse cardiovascular event (myocardial infarction, stroke, or repeat revascularization) or major bleeding since implan-

tation, and were receiving dual antiplatelet therapy at the time of enrollment. Patients were excluded if they had contraindications to the use of antiplatelet drugs (e.g., a concurrent bleeding diathesis or a history of major bleeding) or had concomitant vascular disease requiring long-term use of clopidogrel or other established indications for clopidogrel therapy (e.g., a recent acute coronary syndrome). Patients were also excluded if, in the judgment of the investigator, they had noncardiac coexisting conditions that resulted in a life expectancy of less than 1 year or that might result in noncompliance with the study protocol or if they were participating in another drug or coronary-device study. Enrollment criteria for the ZEST-LATE trial were the same as those for the REAL-LATE trial, but participation was restricted to patients who had previously enrolled in the ZEST trial. All patients in both trials provided written informed consent.

TRIAL PROCEDURES AND FOLLOW-UP

Patients in both trials were randomly assigned to receive either clopidogrel (75 mg per day) plus low-dose aspirin (100 to 200 mg per day) or low-dose aspirin alone. The treatment-group assignments were made according to a preestablished, computer-generated randomization scheme, with stratification on the basis of site and type of drug (sirolimus, paclitaxel, or zotarolimus) in the drug-eluting stent. Both trials were open label; thus, the study subjects and the investigators were aware of the treatment assignments. All patients also received standard pharmacologic therapy (e.g., statins, beta-blockers, or angiotensin-converting–enzyme inhibitors), as appropriate, at the discretion of the investigator and other responsible clinicians. The use of appropriate background therapy was emphasized to the investigators, who were provided with international guidelines.[8]

Follow-up evaluations were performed every 6 months. At these visits, data pertaining to patients' clinical status, all interventions, outcome events, and adverse events were recorded. To ensure accurate assessment of compliance with the study-medication regimen, patients were asked whether they were taking aspirin or clopidogrel, as well as how many tablets they were taking and how long they had been taking them. If any antiplatelet medication had been discontinued, an attempt was made to determine the specific timing of this action. If there was uncertainty about the timing, the referring cardiologist or general practitioner was contacted for additional information.

END POINTS

The primary end point was the first occurrence of myocardial infarction or death from cardiac causes after assignment to a treatment group. The principal secondary end points were death from any cause; myocardial infarction; stroke (from any cause); stent thrombosis; repeat revascularization; a composite of myocardial infarction or death from any cause; a composite of myocardial infarction, stroke, or death from any cause; a composite of myocardial infarction, stroke, or death from cardiac causes; and major bleeding, according to the Thrombolysis in Myocardial Infarction (TIMI) definition.[18]

All deaths were considered to be from cardiac causes unless an unequivocal noncardiac cause could be established. The diagnosis of acute myocardial infarction was based on the universal definition of myocardial infarction.[19] Stroke, as detected by the occurrence of a new neurologic deficit, was confirmed by a neurologist and on imaging. Stent thrombosis was defined as the definite occurrence of a thrombotic event, according to the Academic Research Consortium classification.[20] Repeat revascularization was defined as any percutaneous or surgical revascularization procedure, irrespective of whether it was performed on a target or nontarget lesion.

All study end points were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of patients' treatment-group assignments.

STATISTICAL ANALYSIS

Assuming an event rate of 5.0% at 2 years for the primary end point among patients who were assigned to the aspirin-alone group, we estimated that 1812 patients (906 in each of the two groups) would need to be enrolled for the detection of a 50% reduction in the relative risk of the primary end point in the dual-therapy group as compared with the aspirin-alone group, with a statistical power of 80% at a two-sided significance level of 0.05. The assumed rate of the primary end point and the assumed relative risk reduction are based on historical data (see the Supplementary Appen-

dix). The planned sample size was increased by approximately 10% to allow for noncompliance and loss to follow-up, for a total overall enrollment goal of 2000 patients for each trial.

Data for all enrolled patients in both trials were included in the analysis of the primary and secondary clinical end points, according to the intention-to-treat principle. Differences between the two treatment groups were evaluated by means of Student's t-test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Cumulative event curves were generated by means of the Kaplan–Meier method. We used a Cox proportional-hazards model to compare clinical end points between the two groups.[21] The proportional-hazards assumption regarding the treatment assignments was confirmed by means of the Schoenfeld residuals test; no relevant violations of the assumption were found.[22]

An additional, stratified Cox regression analysis was performed to determine whether merging of the data from the two trials would influence the primary end point (see the Supplementary Appendix). The treatment effect was estimated separately for each trial, and the estimates were combined to provide an overall estimate of the treatment effect. A likelihood-ratio test was performed to assess the homogeneity of the data.

The trial data were held by the trial coordination center at the Asan Medical Center. Analyses were performed with the use of SAS software, version 9.1 (SAS Institute), by an independent statistician who was unaware of the treatment assignments. All reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS

From July 2007 through September 2008, a total of 2701 patients were enrolled at 22 cardiac centers in South Korea: 1625 enrolled in the REAL-LATE trial and 1076 enrolled in the ZEST-LATE trial. Of these patients, 1357 were assigned to receive clopidogrel plus aspirin and 1344 were assigned to receive aspirin monotherapy.

The two groups were well balanced with regard to most baseline characteristics (Table 1). The mean age was 62 years; 30% of the patients were women, and 26% had medically treated diabetes. Nearly half the patients had multivessel disease, and more than 60% had an acute coronary syndrome as the clinical indication for the initial PCI. Sirolimus-eluting stents were the type of drug-eluting stent most commonly used. Almost 90% of the patients were enrolled 12 to 18 months after the index procedure (Table 2).

FOLLOW-UP AND CLINICAL OUTCOMES

The median duration of follow-up was 19.2 months (interquartile range, 13.2 to 24.1) after randomization and 33.2 months (interquartile range, 28.1 to 37.6) after the index procedure. During the follow-up period, adherence to the assigned study treatment was approximately 90% at 12 months and approximately 80% at 24 months in the dual-therapy group and more than 90% at both 12 months and 24 months in the aspirin-alone group (Table 2). Follow-up with respect to the primary end point (the first occurrence of myocardial infarction or death from cardiac causes) was complete for 99.4% of patients in the dual-therapy group and for 99.3% of those in the aspirin-alone group.

During the follow-up period, 33 patients died, 21 of cardiac causes. A total of 17 patients had an acute myocardial infarction, 13 had a stroke, and 9 had definite stent thrombosis. Repeat revascularization was performed in 62 patients, and major bleeding occurred in 4 patients. No fatal bleeding was reported.

The Kaplan–Meier estimate of the event rate for the primary end point (myocardial infarction or death from cardiac causes) at 2 years was 1.8% in the dual-therapy group, as compared with 1.2% in the aspirin-alone group (hazard ratio, 1.65; 95% confidence interval [CI], 0.80 to 3.36; P=0.17) (Table 3 and Fig. 1A). There was no differential treatment effect between the REAL-LATE participants and the ZEST-LATE participants (see the Supplementary Appendix). There was also no significant difference between the two treatment groups in the risk of individual secondary end points (myocardial infarction, stroke, stent thrombosis, repeat revascularization, or death from any cause) (Table 3 and Fig. 1B and 1C). However, among patients assigned to receive dual antiplatelet therapy, as compared with those assigned to receive aspirin alone, there was a nonsignificant increase in the risk of the composite end point of myocardial infarction, stroke, or death from any cause (hazard ratio, 1.73; 95% CI, 0.99 to 3.00;

Table 1. Baseline Characteristics of the Patients, According to Treatment Group.*

Characteristic	Clopidogrel + Aspirin	Aspirin Alone	P Value
No. of patients	1357	1344	
Age — yr	62.0±9.8	61.9±9.9	0.97
Male sex — no. (%)	950 (70.0)	933 (69.4)	0.74
Diabetes mellitus — no. (%)	340 (25.1)	364 (27.1)	0.23
Hypertension — no. (%)	775 (57.1)	765 (56.9)	0.92
Hyperlipidemia — no. (%)	586 (43.2)	584 (43.5)	0.89
Current smoker — no. (%)	404 (29.8)	431 (32.1)	0.20
Previous coronary angioplasty — no. (%)	177 (13.0)	159 (11.8)	0.34
Previous myocardial infarction — no. (%)	51 (3.8)	45 (3.3)	0.57
Previous stroke — no. (%)	57 (4.2)	45 (3.3)	0.25
Ejection fraction — %	59.2±9.3	59.7±8.5	0.20
Multivessel disease — no. (%)	667 (49.2)	633 (47.1)	0.29
Clinical indication at the index procedure — no. (%)			0.79
Stable angina	514 (37.9)	500 (37.2)	
Unstable angina	543 (40.0)	559 (41.6)	
Non–ST-elevation myocardial infarction	145 (10.7)	144 (10.7)	
ST-elevation myocardial infarction	155 (11.4)	141 (10.5)	
Discharge medications — no. (%)			
Aspirin	1353 (99.7)	1339 (99.6)	0.73
Clopidogrel	1353 (99.7)	1343 (99.9)	0.38
ACE inhibitor	633 (46.6)	603 (44.9)	0.35
Beta-blockers	917 (67.6)	869 (64.7)	0.11
Calcium-channel blocker	730 (53.8)	739 (55.0)	0.54
Statin	1081 (79.7)	1058 (78.7)	0.55
No. of lesions stented	1872	1847	
Vessel treated — no. (%)†			0.35
Left anterior descending artery	912 (48.7)	921 (49.9)	
Left circumflex artery	372 (19.9)	334 (18.1)	
Right coronary artery	533 (28.5)	546 (29.6)	
Left main coronary artery	55 (2.9)	44 (2.4)	
Bifurcation — no. (%)	226 (12.1)	231 (12.5)	0.69
Ostial location — no. (%)	125 (6.7)	128 (6.9)	0.76
ACC–AHA lesion class B2 or C — no. (%)	1494 (79.8)	1461 (79.1)	0.59
Calcification — no. (%)	80 (4.3)	91 (4.9)	0.34
Total occlusion — no. (%)	219 (11.7)	190 (10.3)	0.17
Stents per lesion — no.	1.3±0.5	1.2±0.5	0.13
Stent length per lesion — mm	31.8±16.4	30.9±15.4	0.07
Type of drug-eluting stent — no. (%)			0.98
Sirolimus	1057 (56.5)	1052 (57.0)	
Paclitaxel	456 (24.4)	439 (23.8)	
Zotarolimus	350 (18.7)	347 (18.8)	
Other	9 (0.5)	9 (0.5)	

* Plus–minus values are means ±SD. Data are given for the intention-to-treat population. Percentages may not total 100 because of rounding. ACC denotes American College of Cardiology, ACE angiotensin-converting enzyme, and AHA American Heart Association.

† Data regarding the vessel treated were missing for two lesions in patients receiving aspirin alone.

Table 2. Timing of Randomization and Adherence to the Study Treatment during the Follow-up Period, According to Treatment Group.*

Variable	Clopidogrel + Aspirin (N = 1357)	Aspirin Alone (N = 1344)	P Value
Time from index procedure to randomization			0.86
12–18 Mo — no. (%)	1189 (87.6)	1187 (88.3)	
>18–24 Mo — no. (%)	167 (12.3)	156 (11.6)	
>24 Mo — no. (%)	1 (0.1)	1 (0.1)	
Median (interquartile range) — mo	12.8 (12.2–14.6)	12.8 (12.2–14.8)	
Receipt of aspirin — no./total no. (%)			
At randomization	1348/1357 (99.3)	1338/1344 (99.6)	0.45
6 Mo after randomization	1338/1349 (99.2)	1328/1333 (99.6)	0.14
12 Mo after randomization	1129/1143 (98.8)	1103/1117 (98.7)	0.95
18 Mo after randomization	752/759 (99.1)	722/730 (98.9)	0.37
24 Mo after randomization	327/333 (98.2)	313/318 (98.4)	0.82
Receipt of clopidogrel — no./total no. (%)			
At randomization	1335/1357 (98.4)	59/1344 (4.4)	<0.001
6 Mo after randomization	1297/1349 (96.1)	78/1332 (5.9)	<0.001
12 Mo after randomization	1011/1143 (88.5)	72/1117 (6.4)	<0.001
18 Mo after randomization	654/758 (86.3)	46/730 (6.3)	<0.001
24 Mo after randomization	276/333 (82.9)	14/318 (4.4)	<0.001

* Percentages and medians (and interquartile ranges) are from the intention-to-treat analysis.

P=0.051) (Table 3 and Fig. 1D) and of the composite end point of myocardial infarction, stroke, or death from cardiac causes (hazard ratio, 1.84; 95% CI, 0.99 to 3.45; P=0.06). The risk of TIMI-defined major bleeding was similar in the two groups.

DISCUSSION

In this combined analysis of data from two randomized multicenter trials, we found no significant benefit associated with clopidogrel continuation (use of clopidogrel plus aspirin) as compared with clopidogrel discontinuation (use of aspirin alone), after 12 months, in reducing the incidence of myocardial infarction or death from cardiac causes in patients who had received drug-eluting coronary stents. The rates of composite outcomes (myocardial infarction, stroke, death [from any cause or from cardiac causes]) were higher with clopidogrel plus aspirin than with aspirin alone, but this difference was not significant.

An observational analysis from the Basel Stent Cost-Effectiveness Trial — Late Thrombotic Events (BASKET-LATE; Current Controlled Trials number, ISRCTN75663024) suggested that clopidogrel discontinuation at 6 months might be associated with higher rates of death and myocardial infarction among patients receiving drug-eluting stents than among those receiving bare-metal stents.[9] This observation is consistent with the recently reported high rates of death and myocardial infarction among patients with drug-eluting stents, in the Duke registry[10] and in a diabetic population,[11] who discontinued clopidogrel at 6 months or even at 12 months. These results have led to uncertainty about the minimal necessary duration of dual antiplatelet therapy after implantation of a drug-eluting stent. In contrast, several observational studies of patients with drug-eluting stents have shown that continuation of clopidogrel therapy after 6 or 12 months did not appear to reduce the risks of stent thrombosis and late clinical events, findings that suggest that discontinuation of clopidogrel therapy after approximately 1 year might have a favorable risk–benefit ratio.[12-17] However, these studies were all limited by a lack of randomization and by selection bias, small numbers of patients, and relatively short follow-up periods.

Table 3. Outcome Rates at 12 Months and 24 Months, According to Treatment Group.*

Outcome	Total No. of Events		Cumulative Event Rate at 12 Mo		Cumulative Event Rate at 24 Mo		Hazard Ratio (95% CI)†	P Value
	Clopidogrel + Aspirin	Aspirin Alone	Clopidogrel + Aspirin	Aspirin Alone	Clopidogrel + Aspirin	Aspirin Alone		
Primary end point: MI or death from cardiac causes	20	12	0.7	0.5	1.8	1.2	1.65 (0.80–3.36)	0.17
Secondary end points								
Death from any cause	20	13	0.5	0.5	1.6	1.4	1.52 (0.75–3.50)	0.24
MI	10	7	0.4	0.3	0.8	0.7	1.41 (0.54–3.71)	0.49
Stroke	9	4	0.3	0.3	1.0	0.3	2.22 (0.68–7.20)	0.19
Stent thrombosis, definite	5	4	0.2	0.1	0.4	0.4	1.23 (0.33–4.58)	0.76
Repeat revascularization	36	26	1.7	1.1	3.1	2.4	1.37 (0.83–2.27)	0.22
MI or death from any cause	27	17	0.8	0.8	2.3	1.7	1.57 (0.85–2.88)	0.15
MI, stroke, or death from any cause	35	20	1.1	1.1	3.2	1.8	1.73 (0.99–3.00)	0.05
MI, stroke, or death from cardiac causes	28	15	1.0	0.8	2.7	1.3	1.84 (0.99–3.45)	0.06
Major bleeding, according to TIMI criteria‡	3	1	0.2	0.1	0.2	0.1	2.96 (0.31–28.46)	0.35

* For the total number of events for each type of end point, first events only are counted. Cumulative rates of events are based on Kaplan–Meier estimates. All deaths were considered to be from cardiac causes unless an unequivocal noncardiac cause could be established. MI denotes myocardial infarction.

† Hazard ratios are for the dual-therapy group as compared with the aspirin-alone group.

‡ Thrombolysis in Myocardial Infarction (TIMI) major bleeding refers to adjudicated events in accordance with previously used TIMI criteria.[18]

The nonsignificant increase in the risk of death (from cardiac causes or from any cause), myocardial infarction, or stroke in our study was not anticipated. Because these were secondary end points, and because of the small number of events, these findings should be interpreted with caution and the interpretation must be speculative. The results seem most likely to be due to chance, although a similar unexpected result was seen in a lower-risk subgroup of patients in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (NCT00050817).[23]

Several limitations of our study should be considered. Although the sample size was based on data from previous studies, the rate of the primary end point was lower than expected, for reasons that remain unclear. Therefore, our study was underpowered to detect a clinically significant difference in the outcomes we evaluated. This disparity between the expected and observed event rates might be explained in part by differences in clinical or lesion characteristics, interventional practice, or race or ethnic group between our population of patients and those enrolled in earlier studies, as previously noted.[13,24,25] Given the relatively infrequent occurrence of death, myocardial infarction, or stent thrombosis, our findings should be confirmed or refuted through larger randomized, clinical trials with long-term follow-up, such as the Dual Antiplatelet Therapy (DAPT) trial (NCT00977938).[26]

From a methodologic standpoint, the fact that our trials were not blinded could have led to bias on the part of both patients and investigators. However, data collection, data processing, event adjudication, and statistical analyses were conducted by independent research personnel, independent clinicians, and independent statisticians, all of whom were unaware of the treatment-group assignments. In addition, the interval between the index procedure and trial enrollment varied among patients. Therefore, we were not able to determine precisely the optimal time for discontinuation of clopidogrel. Finally, since we evaluated the first generation of drug-eluting stents, the applicability of our findings to the next generation of drug-eluting stents, which appear to be associated with a different frequency of stent thrombosis, may be limited.

In conclusion, in our study, extended use of dual antiplatelet therapy, for more than 12 months, was

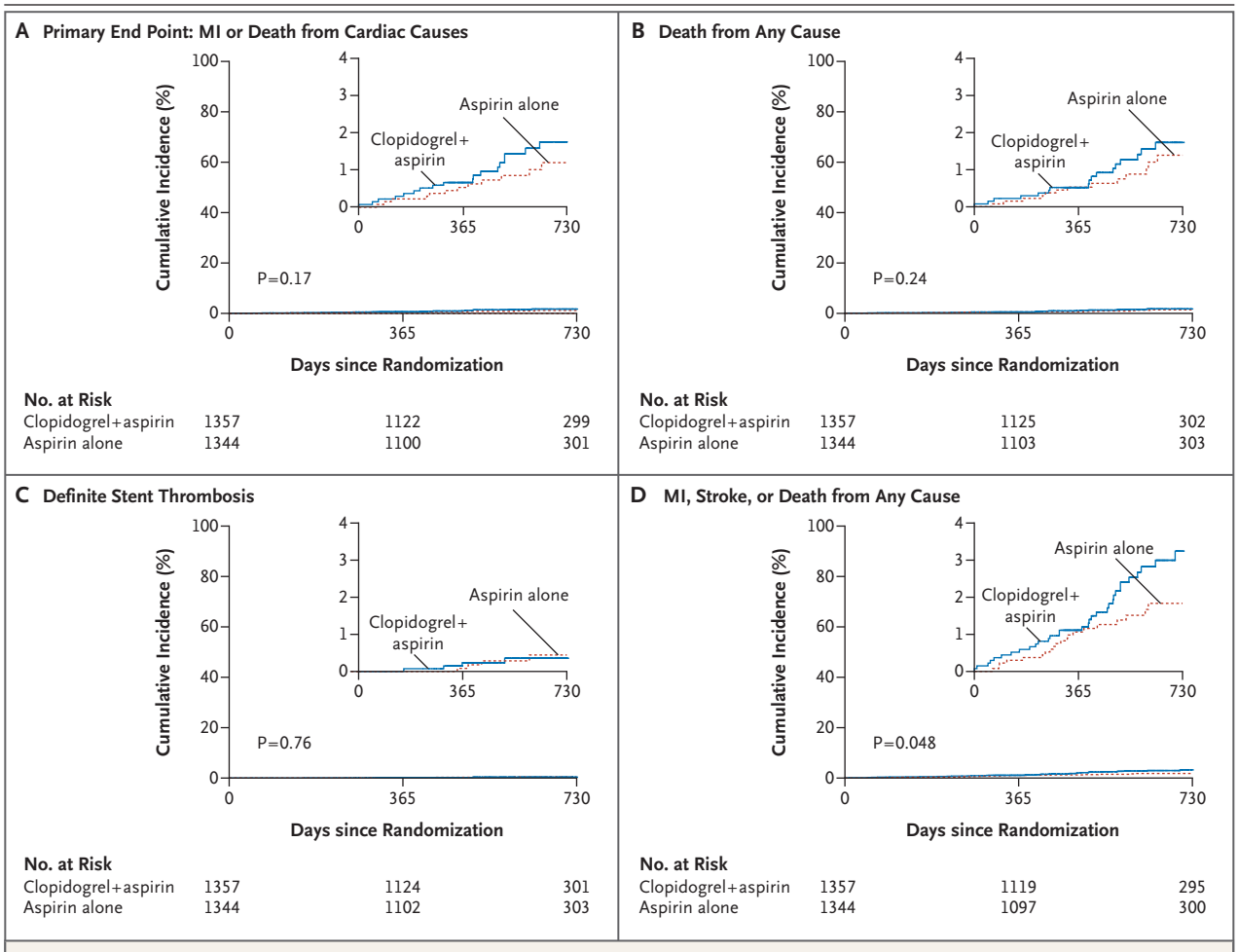

Figure 1. Cumulative Incidence of the Primary End Point and Selected Secondary End Points, According to Treatment Group.

Cumulative-incidence curves are shown for the primary end point of myocardial infarction (MI) or death from cardiac causes (Panel A), death from any cause (Panel B), definite stent thrombosis (Panel C), and the secondary composite end point of death from any cause, MI, or stroke (Panel D). P values were calculated with the use of the log-rank test.

not significantly more effective than aspirin monotherapy in reducing the risk of myocardial infarction or death from cardiac causes among patients who had received drug-eluting stents and had not subsequently had ischemic or bleeding events. However, the study had insufficient statistical power to allow for a firm conclusion regarding the safety of clopidogrel discontinuation after 12 months. Larger clinical trials will be necessary to resolve this issue.

Supported by grants from the Cardiovascular Research Foundation of South Korea and the Korea Health 21 Research and Development Project, Ministry of Health and Welfare (0412-CR02-0704-0001).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the study investigators, members of the participating centers, and study coordinators of the REAL-LATE trial and the ZEST-LATE trial for their efforts to collect the clinical data that made this study possible and to ensure the accuracy and completeness of the trial data.

APPENDIX

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