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Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

A Randomized, Controlled Trial

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Background—The risks and benefits of long-term dual antiplatelet therapy remain unclear.

Methods and Results—This prospective, multicenter, open-label, randomized comparison trial was conducted in 24 clinical centers in Korea. In total, 5045 patients who received drug-eluting stents and were free of major adverse cardiovascular events and major bleeding for at least 12 months after stent placement were enrolled between July 2007 and July 2011. Patients were randomized to receive aspirin alone (n=2514) or clopidogrel plus aspirin (n=2531). The primary end point was a composite of death resulting from cardiac causes, myocardial infarction, or stroke 24 months after randomization. At 24 months, the primary end point occurred in 57 aspirin-alone group patients (2.4%) and 61 dual-therapy group patients (2.6%; hazard ratio, 0.94; 95% confidence interval, 0.66–1.35; $P=0.75$). The 2 groups did not differ significantly in terms of the individual risks of death resulting from any cause, myocardial infarction, stent thrombosis, or stroke. Major bleeding occurred in 24 (1.1%) and 34 (1.4%) of the aspirin-alone group and dual-therapy group patients, respectively (hazard ratio, 0.71; 95% confidence interval, 0.42–1.20; $P=0.20$).

Conclusions—Among patients who were on 12-month dual antiplatelet therapy without complications, an additional 24 months of dual antiplatelet therapy versus aspirin alone did not reduce the risk of the composite end point of death from cardiac causes, myocardial infarction, or stroke.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01186146.

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Key Words: aspirin ■ clopidogrel ■ coronary disease ■ stents

Drug-eluting stents have been shown to be superior to bare metal stents in terms of patient outcome in that they are associated with lower repeat revascularization rates and similar rates of death and myocardial infarction.¹⁻³ However, there

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is concern about the risk of late stent thrombosis after drug-eluting stent implantation.^{4,5} After the safety and efficacy of these devices were extensively evaluated, it was suggested that prolonged dual antiplatelet therapy should be given for at least 12 months after implantation of drug-eluting stents.⁶

Clinical Perspective on p 312

At present, the guidelines recommend that dual antiplatelet therapy should be given either for 6 to 12 months⁷ or for at least 12 months⁸ after drug-eluting stent implantation unless patients are at high risk for bleeding. However, these recommendations are based largely on registry data,^{9–11} and the optimal duration of dual antiplatelet therapy remains poorly defined. Currently, large-scale, randomized, clinical trials are being performed to address questions about the appropriate duration of dual antiplatelet therapy in patients who have received drug-eluting stents.^{12,13} We have previously reported that, compared with aspirin alone, continuation of dual antiplatelet therapy for >12 months after drug-eluting stent implantation is not beneficial.¹⁴ Furthermore, the long-term dual-therapy arm was associated with a trend toward increased risk of cardiac death, myocardial infarction, and stroke. To confirm this observation, the Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event (DES LATE) trial was designed. In this trial, we tested the hypothesis that 12-month dual antiplatelet therapy may provide better protection against cardiovascular events than >12 months of dual antiplatelet therapy after implantation of drug-eluting stents.

Methods

Trial Design

DES LATE was a prospective, multicenter, open-label, randomized comparison trial conducted in 24 clinical centers in Korea. The study, an extension of the previously conducted research,¹⁴ was the result of the executive committee's recommendation to clarify our previous findings (DES LATE; www.clinicaltrials.gov; number NCT01186146). The data and safety monitoring board allowed the

seamless extension of the first trial. The study overview was summarized in Figure 1 (the online-only Data Supplement provides a detailed description of the study extension), and the study investigators were the same as in the first trial. The study was approved by the institutional review board at each institution, and written informed consent was obtained from all participants. DES LATE was an investigator-initiated trial without any company involvement in the design or execution of the trial or in the analysis or reporting of the data.

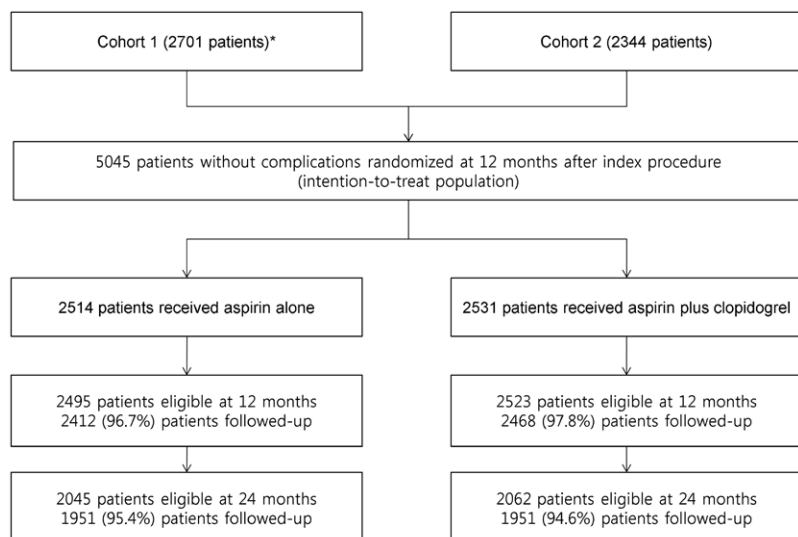
Eligible Criteria

Patients were eligible for participation in the study if they had undergone implantation with 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 implantation, and were receiving dual antiplatelet therapy at the time of enrollment. The time from the index procedure to randomization ranged from 12 to 18 months. The exclusion criteria included contraindications to the use of antiplatelet drugs, concomitant vascular disease that required the long-term use of clopidogrel or other established indications for clopidogrel therapy (eg, recent acute coronary syndrome), and noncardiac coexisting conditions with a life expectancy of <1 year.

Randomization and Treatment Schema

Patients were randomly allocated to receive either low-dose aspirin alone (100 to 200 mg/d) or clopidogrel (75 mg/d) plus low-dose aspirin. The treatment group assignments were made according to a pre-established, computer-generated randomization scheme that involved stratification on the basis of the site and the type of drug in the drug-eluting stent. Because the trial was an open-label trial, the study subjects and the investigators were aware of the treatment assignments. All patients also received the drug with the appropriate standard of care, which was provided at the investigator's discretion. The investigators were reappraised of the appropriate evidence-based background medical therapy that is based on contemporary international guidelines.⁸

Follow-up evaluations were performed every 6 months. At these visits, the data pertaining to patient clinical status, interventions, adverse events, and drug compliance were recorded. To ensure accurate assessment of compliance with the study medication regimen, patients were asked whether they were taking aspirin, whether they were taking clopidogrel, how many tablets they were taking, and how long they had been taking them. If any antiplatelet medication had



*Cohort from REAL-LATE and ZEST-LATE

Figure 1. Study overview. REAL-LATE indicates REAL-world patients treated with drug-eluting stent implantation and Late coronary Arterial Thrombotic Events; and ZEST-LATE, Zotarolimus-Eluting stent, Sirolimus-eluting stent, or paclitaxel-eluting stent implantation for coronary lesions-Late coronary Arterial Thrombotic Events.

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 a composite of death resulting from cardiac causes, myocardial infarction, or stroke 24 months after randomization. The secondary end points were death from any cause; myocardial infarction; stroke; stent thrombosis; repeat revascularization; a composite of death resulting from cardiac causes or myocardial infarction; a composite of death from any cause, myocardial infarction, or stroke; major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition¹⁵; and a composite of death resulting from cardiac causes, myocardial infarction, stent thrombosis, stroke, or TIMI major bleeding.

All deaths were considered to have resulted 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.¹⁶ Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and imaging. Stent thrombosis was defined as the definite occurrence of a thrombotic event according to the Academic Research Consortium classification.¹⁷ Repeat revascularization was defined as any percutaneous or surgical revascularization procedure regardless of whether it was performed on a target or nontarget lesion. All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was unaware of the treatment assignments.

Statistical Analysis

The sample size was calculated by assuming primary end-point incidences of 1.3% and 2.7% for the aspirin-alone and dual-therapy groups, respectively (relative risk, 0.5), at 24 months with the log-rank test.¹⁴ A final sample size of 5000 patients for 2 groups would provide a statistical power of 80% with a 2-sided α level of 0.05 on the assumption that 10% would be lost to follow-up.

The data for all patients enrolled in the first cohort and the extended second cohort were included in the analysis, and all analyses were based on the intention-to-treat principle by an independent statistician (S.H.). Differences between the 2 treatment groups were evaluated by use of the Student *t* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Cumulative event rates were calculated by use of the Kaplan-Meier method, and a Cox proportional hazards model was used to compare the 2 groups in terms of the clinical end points when the stratification variable was the cohort. To determine whether merging of the data from the 2 cohorts would be appropriate, we conducted a homogeneity test using a likelihood test, indicating that the assumption of homogeneity was not violated ($\chi^2=0.034$; $df=1$; $P=0.85$). The proportional hazards assumption on treatment assignments was confirmed by use of the Schoenfeld residuals test; no relevant violations of the assumption were found. Analyses were performed by an independent statistician who was unaware of the treatment assignments. R software version 15.1 was used for this assessment. All reported *P* values are 2 sided, and values of $P<0.05$ were considered to indicate statistical significance.

Results

Study Participants

Between July 2007 and July 2011, a total of 5045 patients were recruited in the trial: 2701 patients in the first cohort (July 2007–September 2009) and 2344 patients in the second cohort (August 2010–July 2011). Of these, 2514 were randomly assigned to receive aspirin-alone therapy, and the remaining 2531 received dual antiplatelet therapy.

Table 1. Baseline Characteristics of the Patients

Characteristic	Aspirin Alone (n=2514)	Clopidogrel+Aspirin (n=2531)
Age	62.3±10.1	62.5±10.0
Male sex, n (%)	1749 (69.6)	1749 (69.1)
Diabetes mellitus, n (%)	709 (28.2)	709 (28.0)
Hypertension, n (%)	1423 (56.6)	1479 (58.4)
Current smoker, n (%)	722 (28.7)	693 (27.4)
Previous coronary angioplasty, n (%)	276 (11.0)	313 (12.4)
Previous myocardial infarction, n (%)	92 (3.7)	103 (4.1)
Previous stroke, n (%)	89 (3.5)	15 (4.5)
Ejection fraction	59.4±8.7	59.3±9.4
Multivessel disease, n (%)	1184 (47.1)	1279 (50.5)
Clinical indication at the index procedure, n (%)		
Stable angina	956 (38.0)	1011 (39.9)
Unstable angina	971 (38.6)	930 (36.7)
Non-ST-segment-elevation myocardial infarction	266 (10.6)	268 (10.6)
ST-segment-elevation myocardial infarction	314 (12.5)	314 (12.4)
Others	7 (0.3)	8 (0.3)
Discharge medication, n (%)		
Aspirin	2504 (99.6)	2521 (99.6)
Clopidogrel	2502 (99.5)	2521 (99.6)
ACE inhibitor	1253 (49.8)	1298 (51.3)
β -Blocker	1623 (64.6)	1685 (66.6)
Calcium-channel blocker	1237 (49.2)	1210 (47.8)
Statin	2070 (82.3)	2080 (82.2)
Vessel treated, n	3498	3603
Left anterior descending artery, n (%)	1768 (50.6)	1781 (49.5)
Left circumflex artery, n (%)	651 (18.6)	715 (19.9)
Right coronary artery, n (%)	972 (27.8)	976 (27.1)
Left main coronary artery, n (%)	90 (2.6)	112 (3.1)
Graft, n (%)	5 (0.1)	0
Others, n (%)	8 (0.2)	11 (0.3)
Multivessel intervention, n (%)	765 (30.4)	839 (33.1)
ACC/AHA lesion class B ₂ or C, n (%)	2734 (78.2)	2838 (78.8)
Bifurcation, n (%)	475 (13.6)	477 (13.2)
Calcification, n (%)	172 (4.9)	168 (4.7)
Total occlusion, n (%)	393 (11.2)	407 (11.3)
Stents per lesion, n	1.2±0.5	1.3±0.5
Stent length per lesion, mm	29.9±15.4	30.8±16.3
Type of drug-eluting stent, n (%)		
Sirolimus	1551 (44.3)	1566 (43.5)
Paclitaxel	709 (20.3)	738 (20.5)
Zotarolimus	664 (19.0)	682 (18.9)
Everolimus	364 (10.4)	427 (11.9)
Others	210 (6.0)	190 (5.3)

Data are mean±SD when appropriate. ACC/AHA indicates American College of Cardiology/American Heart Association; and ACE, angiotensin-converting enzyme.

The 2 patient groups were largely similar in terms of their baseline characteristics (Table 1 and Tables I–IV in the online-only Data Supplement). The mean age of the whole cohort was 62.4±10.0 years; 69% (3498 of 5045) were men; 58% (2902 of 5045) had a history of hypertension; 28% (1418 of 5045) had diabetes mellitus; 28% (1415 of 5045) were current smokers; 48% (2436 of 5045) had multivessel diseases; and 61% (3063 of 5045) had acute coronary syndrome at the time of the index procedure. Older-generation drug-eluting stents (paclitaxel- and sirolimus-eluting stents) were used in 64% (4564 of 7101) of the treated lesions, whereas new-generation drug-eluting stents were used in the remaining 36% (2537 of 7101) of the treated lesions. Most patients were enrolled between 12 and 18 months after implantation of drug-eluting stents (Table 2).

Follow-up

The median length of follow-up after randomization was 42.0 months (interquartile range, 24.7–50.7 months). Follow-up was complete for 97.2% (4880 of 5018), 95% (3902 of 4107), and 87.7% (1663 of 1897) of the eligible patients at 12, 24, and 48 months, respectively (Figure 1).

During the course of the study, adherence to the assigned study treatment in the aspirin-alone group was 98.2% (2361 of 2405) and 97.2% (1975 of 2032) at 12 and 24 months, respectively. In the aspirin-alone group, 8.1% of patients were taking dual antiplatelet therapy at 24 months. For the dual-therapy group, these adherence rates were 88.6% (2157 of

2435) and 79.4% (1625 of 2046), respectively (Table 2 and Table IV in the online-only Data Supplement).

End Points

The primary end point of death resulting from cardiac causes, myocardial infarction, or stroke at 24 months occurred in 57 aspirin-alone group patients (2.4%) and 61 dual-therapy group patients (2.6%; hazard ratio, 0.94; 95% confidence interval [CI], 0.66–1.35; $P=0.75$; Table 3). The 2 groups were also similar in terms of cumulative rates of the primary end point through the entire treatment period (Figure 2A and Tables V–VIII in the online-only Data Supplement). The results were the same after adjustment for the factors that showed imbalance during the randomization. Age and sex did not affect the relationships between the treatments and the primary end point; this was also true for the prespecified subgroups (Figure 3). Similar findings were observed in cohort 2 (Table VI and Figure I in the online-only Data Supplement), and an interaction between the 2 cohorts in terms of the primary end point was not found (P for interaction=0.76).

At 24 months, death resulting from any cause occurred in 32 aspirin-alone group patients (1.4%) and 46 dual-therapy group patients (2.0%; hazard ratio, 0.71; 95% CI, 0.45–1.10; $P=0.12$; Table 3 and Figure 2B). Definite stent thrombosis occurred in 11 aspirin-alone group patients (0.5%) and 7 dual-therapy group patients (0.3%; hazard ratio, 1.59; 95% CI, 0.61–4.09; $P=0.34$; Table 3 and Figure 2C). The 2 groups also had similar results in terms of the other secondary clinical outcomes (Table 3).

Table 2. Timing of Randomization and Adherence to the Study Medication(s) in the Clopidogrel+Aspirin and Aspirin-Alone Groups

Variable	Aspirin Alone (n=2514), n (%)	Clopidogrel+Aspirin (n=2531), n (%)	P Value
Time from the index procedure to randomization			0.66
12–18 mo, n (%)	2046 (81.4)	2039 (80.6)	
>18–24 mo, n (%)	292 (11.6)	315 (12.4)	
>24 mo, n (%)	176 (7.0)	177 (7.0)	
Median (interquartile range), mo	13.2 (12.1–16.1)	13.3 (12.1–16.4)	
Compliance with aspirin treatment, n/total (%)			
At randomization	2503/2514 (99.6)	2516/2531 (99.4)	0.44
6 mo after randomization	2400/2426 (98.9)	2442/2473 (98.7)	0.55
12 mo after randomization	2361/2405 (98.2)	2380/2361 (97.7)	0.29
18 mo after randomization	2218/2257 (98.3)	2248/2299 (97.8)	0.23
24 mo after randomization	1975/2032 (97.2)	1958/2045 (95.7)	0.012
36 mo after randomization	1605/1662 (96.6)	1600/1693 (94.5)	<0.004
48 mo after randomization	761/797 (95.5)	759/817 (92.9)	0.027
Compliance with clopidogrel treatment, n/total (%)			
At randomization	81/2514 (3.2)	2494/2531 (98.5)	<0.001
6 mo after randomization	140/2285 (5.8)	2359/2473 (95.4)	<0.001
12 mo after randomization	169/2407 (7.0)	2157/2435 (88.6)	<0.001
18 mo after randomization	172/2102 (7.6)	1909/2329 (82.0)	<0.001
24 mo after randomization	164/2032 (8.1)	1625/2046 (79.4)	<0.001
36 mo after randomization	147/1662 (8.8)	1089/1693 (64.3)	<0.001
48 mo after randomization	91/706 (11.4)	463/818 (56.6)	<0.001

Table 3. Efficacy and Bleeding Outcomes at the 24-Month Follow-up

End Point	Cumulative Event Rate at 24 mo		Hazard Ratio (95% CI)*	P Value
	Aspirin Alone (n=2514)	Clopidogrel+ Aspirin (n=2531)		
Efficacy				
Cardiac death, myocardial infarction, or stroke (primary end point)	57 (2.4)	61 (2.6)	0.94 (0.66–1.35)	0.75
Death, myocardial infarction, or stroke	69 (3.0)	78 (3.3)	0.89 (0.65–1.24)	0.49
Cardiac death or myocardial infarction	41 (1.8)	43 (1.9)	0.96 (0.63–1.48)	0.86
Death				
Death from any cause	32 (1.4)	46 (2.0)	0.71 (0.45–1.10)	0.12
Cardiac death	19 (0.8)	28 (1.2)	0.68 (0.38–1.23)	0.20
Myocardial infarction	27 (1.2)	19 (0.8)	1.43 (0.80–2.58)	0.23
Stroke				
Any stroke	21 (0.9)	21 (0.9)	1.01 (0.55–1.85)	0.98
Ischemic stroke	13 (0.6)	15 (0.6)	0.88 (0.42–1.84)	0.73
Stent thrombosis, definite	11 (0.5)	7 (0.3)	1.59 (0.61–4.09)	0.34
Repeat revascularisation	65 (2.8)	81 (3.5)	0.81 (0.58–1.12)	0.20
Bleeding				
TIMI major†	24 (1.1)	34 (1.4)	0.71 (0.42–1.20)	0.20
Fatal	4 (0.2)	1 (0.04)	4.02 (0.45–36.0)	0.21
Intracranial	3 (0.1)	5 (0.2)	0.60 (1.44–2.52)	0.49
Net clinical outcome				
Cardiac death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	74 (3.2)	89 (3.8)	0.84 (0.62–1.14)	0.26

CI indicates confidence interval; and TIMI, Thrombolysis in Myocardial Infarction.

*The hazard ratio for 24-month follow-up period is for the aspirin-alone group compared with the dual-therapy group.

†TIMI major bleeding refers to events that were adjudicated on the basis of previously used TIMI criteria.¹⁵

Bleeding Outcomes

At 24 months, TIMI major bleeding occurred in 24 aspirin-alone group patients (1.1%) and 34 dual-therapy group patients (1.4%; hazard ratio, 0.71; 95% CI, 0.42–1.20; $P=0.20$; Table 3). However, by the end of the follow-up period, the aspirin-alone group had a lower rate of TIMI major bleeding than the dual-therapy group (hazard ratio, 0.67; 95% CI, 0.47–0.95; $P=0.026$; Figure 2D). There was no significant heterogeneity across all major subgroups, except that cohort 2 exhibited a higher rate of TIMI major bleeding (Table VII in the online-only Data Supplement).

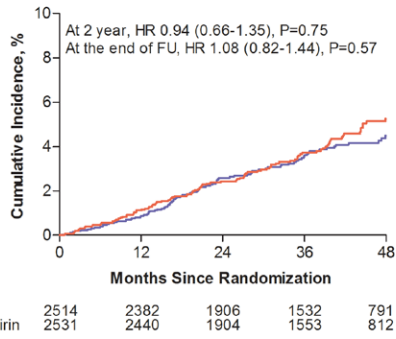
The net clinical outcome of death from cardiac causes, myocardial infarction, stent thrombosis, stroke, or TIMI major bleeding occurred in 74 aspirin-alone group patients (3.2%) and 89 dual-therapy group patients (3.8%; hazard ratio, 0.84; 95% CI, 0.62–1.14; $P=0.26$; Table 3).

Discussion

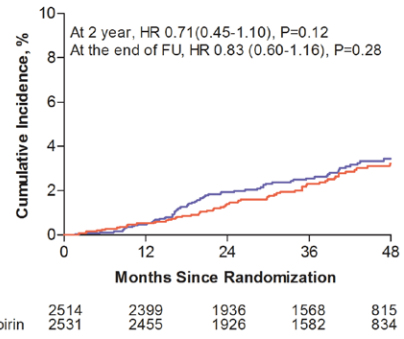
The DES LATE study showed that, in stable patients receiving drug-eluting stents, aspirin monotherapy compared with dual antiplatelet therapy for >12 months did not reduce the risk of death resulting from cardiac causes, myocardial infarction, or stroke. However, aspirin monotherapy was associated with lower risk of TIMI major bleeding during the follow-up period. These findings suggest that the 2 antiplatelet strategies provide similar protection against ischemic events with less risk of bleeding in aspirin monotherapy.

In a registry study from Duke University, patients who had received drug-eluting stents and were then given clopidogrel for >12 months had a lower risk of death or myocardial infarction than those who received clopidogrel for <12 months; this was not observed for patients who received bare metal stents.¹⁰ In other registry studies, however, the use of dual antiplatelet therapy for >12 months after drug-eluting stent implantation did not reduce the rate of death, myocardial infarction, stent thrombosis, or stroke.^{9,11} In contrast to these inconsistent observational studies, several small randomized studies have shown that dual antiplatelet therapy for >6 to 12 months after drug-eluting stent implantation is similar to aspirin monotherapy in terms of rates of death, myocardial infarction, stent thrombosis, or stroke.^{18–22} These studies included the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial, in which 1443 patients who had received drug-eluting stents were given 6 or 12 months of dual antiplatelet therapy. The 6-month therapy was not inferior to the 12-month therapy in terms of the rate of target vessel failure at 12 months.¹⁸ Similarly, in the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial, 2013 patients were treated with 4 different types of stents and then randomly allocated to receive 6 or 24 months of clopidogrel therapy in addition to aspirin.¹⁹ There was no benefit associated with continuing clopidogrel therapy compared with discontinuing clopidogrel after 6 months. However, dual antiplatelet therapy for 24 months was

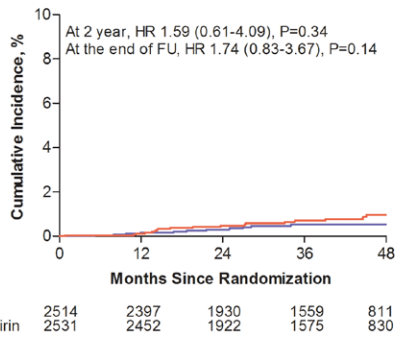
A Death from cardiac cause, MI or stroke



B Death from any causes



C Definite stent thrombosis



D TIMI major bleeding

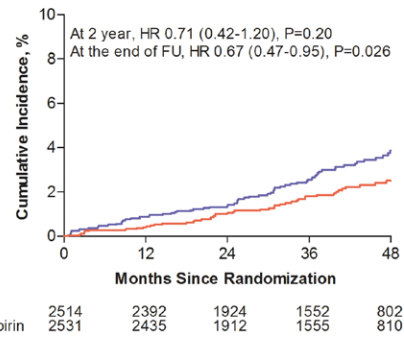


Figure 2. Kaplan–Meier estimates of primary and secondary end points at the end of follow-up (FU). Shown are the cumulative incidences of the primary end point of death resulting from cardiac causes, myocardial infarction (MI), or stroke (**A**); death resulting from any cause (**B**); definite stent thrombosis (**C**); and Thrombolysis in Myocardial Infarction (TIMI) major bleeding (**D**). The dual-therapy group is shown in blue and aspirin-alone group in red. HR indicates hazard ratio.

associated with a significantly higher bleeding rate. Moreover, the recent Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following E-ZES Implantation (RESET) trial showed that 3 months of dual antiplatelet therapy after Endeavor zotarolimus-eluting stent implantation was not inferior to 12 months of dual antiplatelet therapy after implantation with other drug-eluting stents.²⁰ However, all studies to date are underpowered for the detection of significant differences in hard clinical outcomes because of the small numbers of patients and the low numbers of clinical events.

Our previous report showed that dual antiplatelet therapy for >12 months after drug-eluting stent implantation was not more effective than aspirin monotherapy in terms of reducing the rate of the primary end point of death resulting from cardiac causes or myocardial infarction.¹⁴ Moreover, the dual-therapy group tended to have a higher risk of the combined end point of death resulting from cardiac causes, myocardial infarction, or stroke than the aspirin-alone group (hazard ratio, 1.84; 95% CI, 0.99–3.45; $P=0.06$). Although these unexpected findings are probably attributable to chance, similar findings have been noted in several other studies,^{15,23,24} which indicates the need for caution when selecting between potent antiplatelet therapies. In the large Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, patients with multiple risk factors who received aspirin plus clopidogrel had a higher rate of death resulting from cardiovascular causes than the patients who received aspirin alone (3.9% versus 2.2%; $P=0.01$).²³ It has been speculated that intraplaque hemorrhage may cause rapid

plaque progression with acute ischemic events.^{25,26} In the present study, however, dual antiplatelet therapy did not increase the risk of the composite end point of death resulting from cardiac causes, myocardial infarction, or stroke at 24 months compared with aspirin alone. The groups also did not differ significantly in terms of the individual risks of death resulting from any cause, myocardial infarction, stent thrombosis, or stroke. Subgroup analysis revealed that long-term dual antiplatelet therapy did not provide extra benefits to patients with high-risk features such as left main coronary artery disease, bifurcation disease, diffuse disease, multivessel disease, or older drug-eluting stents. However, at the end of the follow-up period, dual antiplatelet therapy was associated with a higher risk of TIMI major bleeding. These findings are in line with those of previous studies^{18–20} and meta-analysis data.^{21,22} Thus, dual antiplatelet therapy for >12 months after implantation of drug-eluting stents is not associated with a reduction in ischemic events and may even increase the risk of major bleeding. Furthermore, new-generation drug-eluting stents have remarkably reduced the risk of late stent thrombosis and seem to be safer than older drug-eluting stents and bare metal stents.^{27,28} In our study, there was no difference in the primary end point between 12 versus >12 months of dual antiplatelet therapy after implantation of new-generation drug-eluting stents, suggesting that prolonged dual antiplatelet therapy might not be needed. However, whether a longer duration of dual antiplatelet therapy is warranted in the current drug-eluting stent era requires further study.

The present study had several limitations. First, the trial design aimed to seamlessly extend the first trial. Thus,

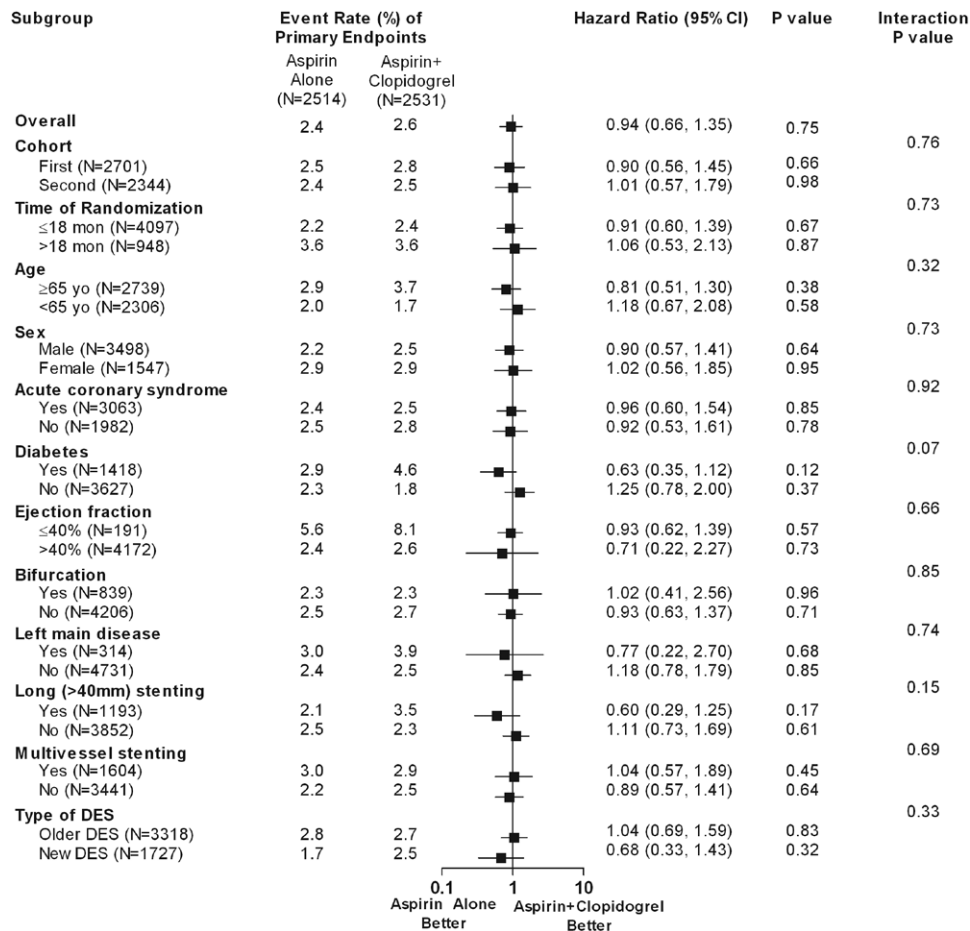


Figure 3. Hazard ratios for the primary endpoint in various subgroups. Subgroup analyses were performed with Cox proportional hazards regression. The older drug-eluting stents are paclitaxel- and sirolimus-eluting stents. CI indicates confidence interval; and DES, drug-eluting stents.

potential confounders across cohorts may have biased the results. However, the 2 cohorts did not differ significantly in terms of treatment effects. Second, the study was an open-label trial without a placebo control. Third, because the study was an open-label trial, a modest number of patients switched therapies. Thus, patients and physicians were not blinded to the duration of clopidogrel. To limit bias, the clinical events were assessed by members of an independent clinical event adjudication committee; moreover, the data were analyzed by an independent statistician. Fourth, the adherence rate in the dual-therapy group was relatively low, which may have had the potential to influence the study findings. Fifth, only patients who received drug-eluting stents and had been free of adverse clinical events for at least 12 months were enrolled, and our study may be still underpowered because of low event rates. Thus, it may not be appropriate to extrapolate the findings of the present study to high-risk populations such as those with recurrent events within 12 months after the index procedure.

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Dr S.J. Park had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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CLINICAL PERSPECTIVE

Drug-eluting stents have been shown to be superior to bare metal stents in terms of patient outcome. However, there is concern about the risk of late stent thrombosis after drug-eluting stent implantation. At present, the guidelines recommend that dual antiplatelet therapy should be given either for 6 to 12 months or for at least 12 months after drug-eluting stent implantation unless patients are at high risk for bleeding. These recommendations are based largely on registry data, and the optimal duration of dual antiplatelet therapy remains poorly defined. In the Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event (DES LATE) trial, we compared the effect of 12 versus >12 months of dual antiplatelet therapy in 5045 patients who received drug-eluting stents and were free of major adverse cardiovascular events and major bleeding for at least 12 months after stent placement. The 2 treatment strategies did not differ significantly in terms of the primary end point (a composite of death resulting from cardiac causes, myocardial infarction, or stroke 24 months after randomization) with a potential risk of major bleeding. These findings support the notion that the benefits of dual antiplatelet therapy after implantation of drug-eluting stents may not extend beyond 12 months.

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I. Supplementary Methods

1) Detailed Description of the Study Extension

The DES LATE trial is an extension study of the previous trial of the same name, which evaluated the effect of dual antiplatelet therapy for more than 12 months on long-term clinical outcomes in 2701 stable patients who received drug-eluting stents.¹ That study found that dual antiplatelet therapy for longer than 12 months was not more effective than aspirin monotherapy in terms of reducing the rate of the primary end point, namely, death from cardiac causes or myocardial infarction (hazard ratio, 1.65; 95% CI, 0.80 to 3.6; P=0.17). Unexpectedly, however, the dual-therapy group showed a statistically insignificant increase relative to the aspirin-alone group in both the composite risk of death from any cause, myocardial infarction, or stroke (hazard ratio, 1.73; 95% CI, 0.99 to 3.00; P = 0.051) and the risk of the composite end point of death from cardiac causes, myocardial infarction, or stroke (hazard ratio, 1.84; 95% CI, 0.99 to 3.45; P=0.06). These trial results raised concerns regarding the safety of prolonged dual antiplatelet therapy after drug-eluting stent implantation. However, these findings were inconclusive because both end points were secondary end points that involved a small number of events. Interestingly, similar findings were observed in a subgroup of patients who had a history of transient ischemic attack or stroke in the Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38)². These findings were also observed in a lower risk subgroup of patients in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance (CHARISMA) trial.³

The principle investigator requested an extension of the study and the decision to continue patient recruitment was made by the Executive Committee on May 20, 2010. The Data and Safety Monitoring Board agreed to seamlessly extend the first trial on June 9, 2010. This decision was made for two reasons. First, there are no published data with sufficient power to clarify this issue. Second, this kind of clinical trial is difficult to conduct because of low patient participation and poor compliance. The modified protocol was approved by the ethics committee at each participating center.

The sample size was calculated on the basis of assumed and estimated 2-year primary end point rates of 1.3% and 2.7% in the aspirin monotherapy and dual antiplatelet therapy groups, respectively (relative risk 0.5), with a type I error of 0.05 and a type II error of 0.20.¹ With an anticipated dropout rate of 10%, a final sample size of 5000 patients was deemed to provide an adequate number of evaluable patients. The trial design was

modified so that a sufficient number of patients could be enrolled. As a result, patient recruitment was extended to 5045 patients. Thus, there were two patient cohorts. In the first cohort, 2701 patients were recruited between July, 2007, and September, 2009. After approval by the Data and Safety Monitoring Board, an additional 2344 patients (second cohort) were continuously enrolled between August, 2010, and July, 2011.

The members of the Executive Committee and the Data and Safety Monitoring Board were the same in both study periods, except J.-B. Lee. The data for all patients enrolled in the first and second cohorts were merged for the DES LATE trial, and analyses of the data were performed by an independent statistician according to the intention-to-treat principle.

2) Trial Organization and Committees

Study Sites and Hospitals: The Heart Institute (S.-J.Park, C.W.Lee, J.-M.Ahn, D.-W.Park, S.-J.Kang, S.-W.Lee, Y.-H.Kim, S.-W.Park) and the Division of Biostatistics (S.-C.Yun), the Center for Medical Research and Information, University of Ulsan College of Medicine, Asan Medical Center, Seoul; Korea University Guro (S.-W.Rha) and Anam (D.-S.Lim) Hospitals, Seoul; Ulsan University Hospital, Ulsan (S.-G.Lee); Chungnam National University Hospital, Daejeon (I.-W.Seong); Chonnam National University Hospital, Gwangju (M.-H.Jeong); Yonsei University Wonju College of Medicine, Wonju Christian Hospital, Wonju (J.-H.Yoon); Keimyung University Dongsan Medical Center, Daegu (S.-H.Hur); The Catholic University of Korea, Yeouido St. Mary's Hospital, Seoul (Y.-S.Choi); National Health Insurance Corporation, Ilsan Hospital, Ilsan (J.-Y.Yang); Soon Chun Hyang University Hospital Bucheon, Bucheon (N.-H.Lee); Hallym University Sacred Heart Hospital, Anyang (H.-S.Kim); Kangwon National University Hospital, Chuncheon (B.-K.Lee); Daegu Catholic University Medical Center, Daegu (K.-S.Kim); Kwangju Christian Hospital, Kwangju (S.-U.Lee); Chonbuk National University Hospital, Jeonju (J.-K.Chae.); GangNeung Asan Medical Center, Gangneung (S.-S.Cheong); Sam Anyang Hospital, Anyang (I.-W.Suh); Kyungpook National University Hospital, Daegu (H.-S.Park.); Dongguk University Gyeongju Hospital, Gyeongju (D.-Y.Nah); The Catholic University of Korea, Incheon St. Mary's Hospital, Incheon (D.-S.Jeon); The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul (K.-B.Seung); Veterans Hospital Service Medical Center (K.Lee); Inje University College of Medicine, Busan Paik Hospital, Busan (J.-S.Jang) - all in South Korea.

Executive Committee: S.-J. Park, D.-W.Park, Y.-H.Kim, S.-W.Lee, C.W. Lee, S.-W. Park; Data and Safety Monitoring Board: M.-S. Lee (University of Ulsan College of Medicine), J.-B.Lee (University of Ulsan College of Medicine), G.-Y. Cho (Seoul National University Bundang Hospital); Event Adjudication Committee: J.-J.Kim (University of Ulsan College of Medicine), J.-Y. Lee (University of Ulsan College of Medicine), W.-J. Kim (University of Ulsan College of Medicine).

II. Supplementary Tables

Table 1. Baseline Characteristics of the Patients in Cohort 2.^a

Characteristic	Aspirin Alone	Clopidogrel + Aspirin	P value
No. of Patients	(N=1170)	(N=1174)	
Age	62.8±10.2	63.1±10.1	0.52
Male sex	816 (69.7%)	799 (68.1%)	0.38
Diabetes mellitus	345 (29.5%)	369 (31.4%)	0.31
Hypertension	658 (56.2%)	704 (60.0%)	0.07
Current smoker	291 (24.9%)	289 (24.6%)	0.89
Previous coronary angioplasty	117 (10.0%)	136 (11.6%)	0.22
Previous myocardial infarction	47 (4.0%)	52 (4.4%)	0.62
Previous stroke	44 (3.8%)	58 (4.9%)	0.16
Ejection fraction	59.0±8.9	59.4±9.5	0.42
Multivessel disease	537 (45.9%)	599 (51.0%)	0.013
Clinical indication at the index procedure			0.65
Stable angina	456 (39.0%)	497 (42.4%)	
Unstable angina	412 (35.2%)	387 (33.0%)	
Non-ST elevation myocardial infarction	122 (10.4%)	123 (10.5%)	
ST-elevation myocardial infarction	173 (14.8%)	159 (13.5%)	
Others	7 (0.6%)	8 (0.7%)	
Discharge medication			
Aspirin	1165 (99.6%)	1168 (99.5%)	0.77
Clopidogrel	1159 (99.1%)	1168 (99.5%)	0.22
ACE inhibitor	650 (55.6%)	665 (56.6%)	0.60
Beta-blocker	754 (64.4%)	768 (65.4%)	0.62
Calcium-channel blocker	498 (42.6%)	480 (40.9%)	0.41
Statin	1012 (86.5%)	999 (85.1%)	0.33
Vessel treated†	1651	1731	0.47

Left anterior descending artery	847 (51.4%)	869 (50.4%)	
Left circumflex artery	317 (19.2%)	343 (19.9%)	
Right coronary artery	426 (25.9%)	443 (25.7%)	
Left main coronary artery	46 (2.8%)	57 (3.3%)	
Graft	3 (0.2%)	0	
Others	8 (0.5%)	11 (0.6%)	
Multivessel intervention	373 (31.9%)	423 (36.0%)	0.03
ACC-AHA lesion class B ₂ or C	1273 (77.1%)	1344 (77.6%)	0.71
Bifurcation	244 (14.8%)	251 (14.5%)	0.82
Calcification	81 (4.9%)	88 (5.1%)	0.81
Total occlusion	203 (12.3%)	188 (10.9%)	0.19
Stents per lesion	1.2±0.5	1.2±0.5	0.04
Stent length per lesion	28.9±15.5	29.6±16.2	0.17
Type of drug-eluting stent			0.30
Sirolimus	499 (30.2%)	509 (29.4%)	
Paclitaxel	270 (16.4%)	282 (16.3%)	
Zotarolimus	317 (19.2%)	332 (19.2%)	
Everolimus	364 (22.0%)	427 (24.7%)	
Others	210 (6.0%)	190 (5.3%)	

^aData are mean (SD) or number (%). †A total of 12 values are missed. ACC denotes American College of Cardiology, ACE angiotensin-converting enzyme, and AHA American Heart Association.

Table 2. Timing of Randomization and Adherence to the Study Medications in Cohort 2.

Variable	Aspirin Alone (N=1170)	Clopidogrel+Aspirin (N=1174)	P Value
Time from the index procedure to randomization			0.76
12-18 Mo	859 (73.4%)	850 (72.4%)	
>18-24 Mo	136 (11.6%)	148 (12.6%)	
>24 Mo	175 (15.0%)	176 (15.0%)	
Median (interquartile range)—mo	13.2 (12.1, 16.1)	13.3 (12.1,16.4)	
Compliance with Aspirin			
Treatment—no./total no.			
At randomization	1165/1170 (99.6%)	1168/1174 (99.5%)	0.77
6 Mo after randomization	1093/1072 (98.1%)	1104/1124 (98.2%)	0.80
12 Mo after randomization	1089/1116 (97.6%)	1089/1125 (96.8%)	0.26
18 Mo after randomization	951/985 (96.5%)	961/1004 (95.7%)	0.34
24 Mo after randomization	725/763 (95.0%)	705/754 (93.5%)	0.20
36 Mo after randomization	373/393 (94.9%)	370/405 (91.4%)	0.048
Compliance with Clopidogrel			
Treatment—no./total no.			
At randomization	22/1148 (1.9%)	1159/1174 (98.7%)	<0.001
6 Mo after randomization	62/1031 (5.7%)	1062/1124 (94.5%)	<0.001
12 Mo after randomization	79/1118 (7.1)	1006/1125 (89.4%)	<0.001
18 Mo after randomization	75/992 (7.6%)	850/1014 (83.8%)	<0.001
24 Mo after randomization	64/763 (8.4%)	623/754 (82.6%)	<0.001
36 Mo after randomization	32/393 (8.1%)	274/405 (67.7%)	<0.001

Table 3. Baseline Characteristics of the Patients in Cohorts 1 and 2^a

	Cohort 1	Cohort 2	P value
Characteristic	(N=2701)	(N=2344)	
<hr/>			
No. of Patients			
Age—yr	62.5±10.0	62.3±10.1	0.48
Male sex	1883 (69.7%)	1615 (68.9%)	0.54
Diabetes mellitus	704 (26.1%)	714 (30.5%)	0.001
Hypertension	1540 (57.0%)	1362 (58.1%)	0.44
Current smoker	835 (30.9%)	580 (24.7%)	<0.001
Previous coronary angioplasty	336 (12.4%)	253 (10.8%)	0.07
Previous myocardial infarction	96 (3.6%)	99 (4.2%)	0.22
Previous stroke	102 (3.8%)	102 (4.4%)	0.30
Ejection fraction	59.3±9.4	59.4±8.7	0.69
Multivessel disease	1300 (48.1%)	1136 (48.5%)	0.81
Clinical indication at the index procedure			<0.001
Stable angina	1014 (37.5%)	953 (40.7%)	
Unstable angina	1102 (40.8%)	799 (34.1%)	
Non-ST-elevation myocardial infarction	289 (10.7%)	245 (10.5%)	
ST-elevation myocardial infarction	296 (11.0%)	332 (14.2%)	
Others	0	15 (0.6%)	
Discharge medication			
Aspirin	2692 (99.7%)	2333 (99.5%)	0.44
Clopidogrel	2696 (99.8%)	2327 (99.3%)	0.004
ACE inhibitor	1236 (45.8%)	1315 (56.1%)	<0.001
Beta-blocker	1786 (66.1%)	1522 (64.9%)	0.37
Calcium-channel blocker	1469 (54.4%)	978 (41.7%)	<0.001
Statin	2139 (79.2%)	2011 (85.8%)	<0.001
Vessel treated			0.09

Left anterior descending artery	1781 (49.5%)	1768 (50.6%)	
Left circumflex artery	715 (19.9%)	651 (18.6%)	
Right coronary artery	976 (27.1%)	972 (27.8%)	
Left main coronary artery	112 (3.1%)	90 (2.6%)	
Graft	0	5 (0.1%)	
Others	11 (0.3%)	8 (0.2%)	
Multivessel intervention			
ACC-AHA lesion class B ₂ or C	2838 (78.8%)	2734 (78.2%)	0.53
Bifurcation	477 (13.2%)	475 (13.6%)	0.67
Calcification	168 (4.7%)	172 (4.9%)	0.62
Total occlusion	407 (11.3%)	393 (11.2%)	0.94
Stents per lesion	1.3±0.5	1.2±0.5	0.003
Stent length per lesion	31.3±15.9	29.3±15.8	<0.001
Type of drug-eluting stent			0.25
Sirolimus	1566 (43.5%)	1551 (44.3%)	
Paclitaxel	738 (20.5%)	709 (20.3%)	
Zotarolimus	682 (18.9%)	664 (19.0%)	
Everolimus	427 (11.9%)	364 (10.4%)	
Others	190 (5.3%)	210 (6.0%)	

^aPlus-minus values are means ±SD. ACC denotes American College of Cardiology, ACE angiotensin-converting enzyme, and AHA American Heart Association.

Table 4. Timing of Randomization and Adherence to the Study Medications of Cohorts 1 and 2

Variable	Cohort 1 (N=2701)	Cohort 2 (N=2344)	P Value
Time from index procedure to randomization			<0.001
12-18 Mo	2376 (88.0%)	1709 (72.9%)	
>18-24 Mo	323 (12.0%)	284 (12.1%)	
>24 Mo	2 (0.1%)	351 (15.0%)	
Median (interquartile range)—mo	12.8 (11.9, 14.7)	14.2 (12.4, 18.7)	
Compliance with Aspirin Treatment—no./total no. (%)			
At randomization	2686/2701 (99.4)	2333/2344 (99.5)	0.67
6 Mo after randomization	2666/2682 (99.4)	2176/2217 (98.2)	<0.001
12 Mo after randomization	2563/2599 (98.6)	2178/2241 (97.2)	<0.001
18 Mo after randomization	2554/2567 (99.5)	1912/1989 (96.1)	<0.001
24 Mo after randomization	2503/2560 (97.8)	1430/1517 (94.3)	<0.001
36 Mo after randomization	2462/2557 (96.3)	743/798 (93.1)	<0.001
48 Mo after randomization	2326/2471 (94.1)	366/384 (95.3)	0.35
Compliance with Clopidogrel Treatment—no./total no.(%)			
At randomization	1394/2701 (51.6)	1181/2344 (50.4)	0.39
6 Mo after randomization	1375/2681 (51.3)	1124/2217 (50.7)	0.68
12 Mo after randomization	1241/2599 (47.7)	1085/2243 (48.4)	0.67
18 Mo after randomization	1156/2597 (44.5)	925/2006 (46.1)	0.28
24 Mo after randomization	1102/2561 (43.0)	687/1517 (45.3)	0.16
36 Mo after randomization	930/2557 (36.4)	306/798 (38.3)	0.31
48 Mo after randomization	846/2472 (34.2)	136/248 (35.4)	0.65

Table 5. Efficacy and Bleeding Outcomes in Cohort 1.

End Point	Cumulative Event at 48 Mo, N (%)		Hazard Ratio (95% CI) ^a	P Value
	Aspirin Alone (N=1170)	Clopidogrel+ Aspirin (N=1174)		
Efficacy				
Cardiac death, myocardial infarction, or stroke (primary end point)	68 (5.3)	59 (4.5)	1.10 (0.79-1.55)	0.57
Death, myocardial infarction or stroke	81 (6.3)	77 (5.9)	1.02 (0.76-1.38)	0.90
Cardiac death or myocardial infarction	45 (3.5)	38 (2.8)	1.08 (0.71-1.64)	0.72
Death				
Death from any cause	37 (2.9)	46 (3.5)	0.76 (0.50-1.14)	0.19
Cardiac death	24 (1.9)	26 (2.0)	0.80 (0.47-1.38)	0.43
Myocardial infarction	26 (2.0)	16 (1.2)	1.60 (0.87-2.94)	0.13
Stroke				
Any stroke	26 (2.0)	26 (2.1)	0.97 (0.57-1.64)	0.91
Ischemic stroke	18 (1.4)	16 (1.3)	1.06 (0.56-2.02)	0.86
Stent thrombosis, definite	13 (1.0)	8 (0.6)	1.76 (0.74-4.20)	0.20
Repeat revascularization	87 (6.8)	92 (7.2)	0.95 (0.72-1.26)	0.73
Bleeding				

TIMI major ^b	23 (1.8)	40 (3.2)	0.61 (0.38-0.99)	0.045
Fatal	1 (0.1)	2 (0.2)	0.50 (0.05-5.53)	0.57
Intracranial	2 (0.2)	9 (0.7)	0.22 (0.05–1.03)	0.054
Net clinical outcome				
Cardiac death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	84 (6.69)	91 (7.0)	0.91 (0.69–1.21)	0.52

^aThe hazard ratio throughout the entire treatment period is for the aspirin-alone group as compared to the dual-therapy group.

^bThrombolysis in Myocardial Infarction (TIMI) major bleeding refers to events that were adjudicated on the basis of previously used TIMI criteria.⁴

Table 6. Efficacy and Bleeding Outcomes in Cohort 2.

End Point	Cumulative Event at 24 Mo, N (%)		Hazard Ratio (95% CI) ^a	P Value
	Aspirin Alone (N=1170)	Clopidogrel+ Aspirin (N=1174)		
Efficacy				
Cardiac death, myocardial infarction, or stroke (primary end point)	24 (2.4)	24 (2.5)	1.04 (0.63-1.72)	0.87
Death, myocardial infarction or stroke	31 (3.2)	34 (3.5)	1.06 (0.69-1.62)	0.79
Cardiac death or myocardial infarction	17 (1.7)	17 (1.8)	1.11 (0.61-2.03)	0.74
Death				
Death from any cause	13 (1.5)	19 (1.9)	1.00 (0.56-1.79)	0.99
Cardiac death	5 (0.5)	9 (0.9)	0.73 (0.29-1.81)	0.49
Myocardial infarction	13 (1.2)	9 (1.0)	1.38 (0.63-2.99)	0.42
Stroke				
Any stroke	11 (1.2)	9 (0.9)	1.09 (0.50-2.39)	0.83
Ischemic stroke	6 (0.6)	7(0.7)	1.01 (0.36-2.89)	0.98
Stent thrombosis, definite	4 (0.4)	3 (0.3)	1.69 (0.40-7.06)	0.48
Repeat revascularization	25 (2.5)	38 (4.0)	0.72 (0.45-1.14)	0.16
Bleeding				

TIMI major ^b	17 (1.8)	20 (1.9)	0.74 (0.43-1.28)	0.28
Fatal	3 (0.3)	0	NA ^c	NA ^c
Intracranial	3 (0.3)	2 (0.2)	0.80 (0.21-2.97)	0.74
Net clinical outcome				
Cardiac death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	38 (3.9)	41 (4.1)	0.93 (0.63-1.38)	0.72

^aThe hazard ratio throughout the entire treatment period is for the aspirin-alone group as compared to the dual-therapy group.

^bThrombolysis in Myocardial Infarction (TIMI) major bleeding refers to events that were adjudicated on the basis of previously used TIMI criteria.⁴

^cNA denotes not applicable.

Table 7. Efficacy and Bleeding Outcomes at 24 Months for Cohorts 1 and 2

End Point	Cohort 1	Cohort 2	Hazard Ratio	P Value
	(N=2701)	(N=2344)	(95% CI) ^a	
Efficacy				
Cardiac death, myocardial infarction, or stroke (primary end point)	2.6	2.5	1.05 (0.76, 1.45)	0.76
Cardiac death or myocardial infarction	1.9	1.7	1.06 (0.72, 1.55)	0.79
Cardiac death	1.2	0.7	1.38 (0.80, 2.38)	0.25
Myocardial infarction	0.9	1.1	0.90 (0.54, 1.49)	0.67
Stroke				
Any stroke	0.8	1.1	0.66 (0.55, 1.51)	0.71
Ischemic stroke	0.6	0.7	0.70 (0.59, 2.20)	0.70
Stent thrombosis, definite	0.4	0.4	1.41 (0.61, 3.26)	0.42
Repeat revascularization	3.1	3.3	1.20 (0.90, 1.59)	0.21
Death from any cause	1.7	1.7	0.84 (0.58, 1.23)	0.38
Bleeding				
TIMI major ^b	0.8	1.9	0.47(0.32, 0.70)	<0.001
Fatal	0.1	0.2	0.40 (0.08, 1.89)	0.25
Intracranial	0.1	0.3	0.43 (0.17, 1.12)	0.08
Net clinical outcome				
Cardiac death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	3.1	4.0	0.82 (0.63, 1.06)	0.12

^aHazard ratios are for cohort 1 as compared to cohort 2.

^bThrombolysis in Myocardial Infarction (TIMI) major bleeding refers to events adjudicated on the basis of previously used TIMI criteria.⁴

Table 8. Efficacy and Bleeding Outcomes throughout the Entire Study Period

End Point	Cumulative Event Rate		Cumulative Event Rate		Hazard Ratio (95% CI) ^a	P Value
	at 24 Mo		at 48 Mo			
	Aspirin Alone (N=2514)	Clopidogrel+ Aspirin (N=2531)	Aspirin Alone (N=2514)	Clopidogrel+ Aspirin (N=2531)		
Efficacy						
Cardiac death, myocardial infarction, or stroke (primary end point)	2.4	2.6	5.1	4.4	1.08 (0.82–1.44)	0.57
Death, myocardial infarction or stroke	3.0	3.3	6.5	6.0	1.03 (0.81–1.32)	0.80
Cardiac death or myocardial infarction	1.8	1.9	3.4	2.8	1.09 (0.77–1.53)	0.63
Death						
Death from any cause	1.4	2.0	3.1	3.5	0.83 (0.60-1.16)	0.28
Cardiac death	0.8	1.2	1.6	1.8	0.78 (0.49-1.24)	0.30
Myocardial infarction	1.2	0.8	2.1	1.3	1.51 (0.94-2.44)	0.09
Stroke						
Any stroke	0.9	0.9	2.1	2.1	1.01 (0.65-1.56)	0.98
Ischemic stroke	0.6	0.6	1.4	1.2	1.05 (0.61-1.82)	0.87
Stent thrombosis, definite	0.5	0.3	1.0	0.5	1.74 (0.83-3.66)	0.14

Repeat revascularization	2.8	3.5	6.3	7.0	0.88 (0.69-1.12)	0.30
Bleeding						
TIMI major ^b	1.1	1.4	2.5	3.9	0.67 (0.47-0.95)	0.026
Fatal	0.2	0.04	0.2	0.1	2.49 (0.48-12.8)	0.28
Intracranial	0.1	0.2	0.3	0.8	0.43 (0.16-1.11)	0.08
Net clinical outcome						
Cardiac death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	3.2	3.8	7.0	7.2	0.92 (0.73-1.16)	0.47

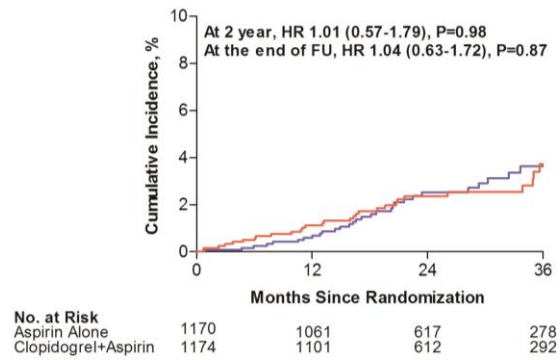
^aThe hazard ratio throughout the entire treatment period is for the aspirin-alone group as compared to the dual-therapy group.

^bThrombolysis in Myocardial Infarction (TIMI) major bleeding refers to events that were adjudicated on the basis of previously used TIMI criteria.⁴

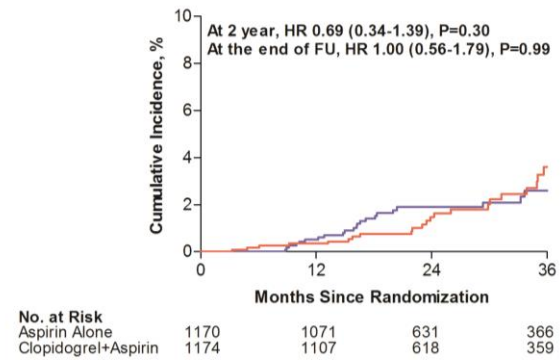
III. Supplementary Figure and Legends

Figure 1. Kaplan–Meier Estimates of Primary and Secondary End Points in Cohort 2. The cumulative incidences of the primary end point of death from cardiac causes, myocardial infarction, or stroke (A), death from any cause (B), definite stent thrombosis (C), and TIMI major bleeding (D) are shown. The dual-therapy group is shown in blue and aspirin-alone group in red.

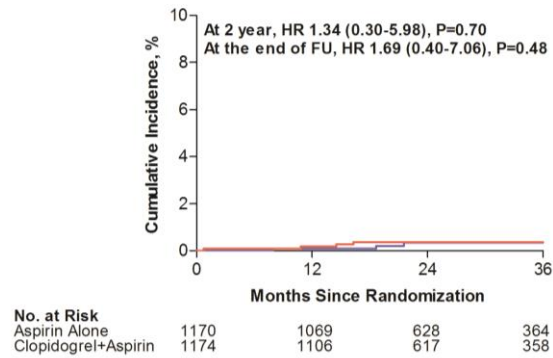
A Death from cardiac cause, MI or stroke



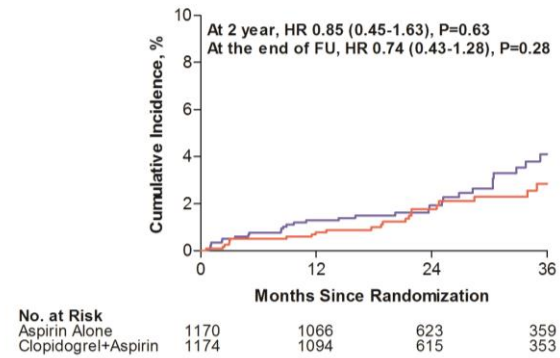
B Death from any causes



C Definite stent thrombosis



D TIMI Major Bleeding



IV. Supplementary References

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