ORIGINAL ARTICLE

Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes

The CURRENT–OASIS 7 Investigators*

ABSTRACT

BACKGROUND

Clopidogrel and aspirin are widely used for patients with acute coronary syndromes and those undergoing percutaneous coronary intervention (PCI). However, evidence-based guidelines for dosing have not been established for either agent.

METHODS

We randomly assigned, in a 2-by-2 factorial design, 25,086 patients with an acute coronary syndrome who were referred for an invasive strategy to either double-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and either higher-dose aspirin (300 to 325 mg daily) or lower-dose aspirin (75 to 100 mg daily). The primary outcome was cardiovascular death, myocardial infarction, or stroke at 30 days.

RESULTS

The primary outcome occurred in 4.2% of patients assigned to double-dose clopidogrel as compared with 4.4% assigned to standard-dose clopidogrel (hazard ratio, 0.94; 95% confidence interval [CI], 0.83 to 1.06; P=0.30). Major bleeding occurred in 2.5% of patients in the double-dose group and in 2.0% in the standard-dose group (hazard ratio, 1.24; 95% CI, 1.05 to 1.46; P=0.01). Double-dose clopidogrel was associated with a significant reduction in the secondary outcome of stent thrombosis among the 17,263 patients who underwent PCI (1.6% vs. 2.3%; hazard ratio, 0.68; 95% CI, 0.55 to 0.85; P=0.001). There was no significant difference between higher-dose and lower-dose aspirin with respect to the primary outcome (4.2% vs. 4.4%; hazard ratio, 0.97; 95% CI, 0.86 to 1.09; P=0.61) or major bleeding (2.3% vs. 2.3%; hazard ratio, 0.99; 95% CI, 0.84 to 1.17; P=0.90).

CONCLUSIONS

In patients with an acute coronary syndrome who were referred for an invasive strategy, there was no significant difference between a 7-day, double-dose clopidogrel regimen and the standard-dose regimen, or between higher-dose aspirin and lower-dose aspirin, with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke. (Funded by Sanofi-Aventis and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00335452.)

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Clopidogrel (Plavix, Sanofi-Aventis and Bristol-Myers Squibb) and aspirin are commonly used for the treatment of cardiovascular disease, yet the optimal doses are uncertain.[1,2] The benefits of clopidogrel in patients with acute coronary syndromes, as well as in those undergoing percutaneous coronary intervention (PCI), are well established.[3-10] As compared with the standard dose of clopidogrel used in early trials, more recent studies have shown that doubling the loading and maintenance doses of clopidogrel leads to greater, more rapid, and more uniform platelet inhibition, which may further improve clinical outcomes.[1,11-18] This hypothesis is consistent with the results of recent clinical trials, which have shown a benefit of more potent adenosine diphosphate (ADP)–receptor blockers, such as prasugrel[19] and ticagrelor,[20] as compared with the standard dose of clopidogrel.

Uncertainty regarding the optimal dose of aspirin for the prevention and treatment of cardiovascular disease has resulted in wide geographic variations in practice patterns.[21] The European Society of Cardiology guidelines recommend low doses of aspirin (≤100 mg daily) after PCI,[22] whereas the American Heart Association–American College of Cardiology guidelines[23] recommend higher doses of aspirin (162 to 325 mg daily). This discrepancy reflects the lack of data from randomized trials directly comparing aspirin doses. Although indirect comparisons in trials evaluating different doses of aspirin versus placebo have shown similar reductions in vascular events,[2] observational analyses have suggested a dose-dependent increase in the risk of bleeding associated with aspirin.[21,24]

The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial was designed to determine whether a doubling of the loading and initial maintenance doses of clopidogrel is superior to the standard-dose regimen and whether higher-dose aspirin (300 to 325 mg daily) is superior to lower-dose aspirin (75 to 100 mg daily) in patients with acute coronary syndromes referred for an early invasive strategy.

METHODS

STUDY DESIGN AND OVERSIGHT

This international randomized trial was conducted between June 2006 and July 2009.[25] The trial protocol and amendments are available with the full text of this article at NEJM.org. The statistical analysis plan is included in the Supplementary Appendix, also available at NEJM.org. The trial was coordinated by the investigators at the Population Health Research Institute at McMaster University and Hamilton Health Sciences, who independently managed the database and performed the primary data analyses. The trial was sponsored by Sanofi-Aventis and Bristol-Myers Squibb. An operations committee, with assistance from an international steering committee, was responsible for the study design and conduct, manuscript preparation, and the decision to submit the manuscript for publication. An independent data and safety monitoring committee periodically reviewed unblinded data. The study was approved by all appropriate national regulatory authorities and the ethics committees at the participating centers, and all patients provided written informed consent. All authors vouch for the accuracy and completeness of the data and the analyses.

PATIENTS

Trial participants were 18 years of age or older and presented with a non–ST-segment elevation acute coronary syndrome or an ST-segment elevation myocardial infarction. Either electrocardiographic changes compatible with ischemia or elevated levels of cardiac biomarkers were required for eligibility. An additional requirement was coronary angiographic assessment, with a plan to perform PCI as early as possible but no later than 72 hours after randomization. Major exclusion criteria were an increased risk of bleeding or active bleeding and a known allergy to clopidogrel or aspirin. Details of the eligibility criteria are described in the Supplementary Appendix.

PROCEDURES

The trial had a 2-by-2 factorial design. In the first component of the factorial design, patients were randomly assigned in a double-blind fashion to a double-dose regimen of clopidogrel or to the standard-dose regimen. In the second component of the factorial design, patients were randomly assigned in an open-label fashion to higher-dose aspirin or lower-dose aspirin. Permuted-block randomization, stratified according to study center, was performed with the use of a 24-hour, computerized, automated voice-response system located at the Population Health Research Institute.

Immediately after randomization and before coronary angiography, patients randomly assigned to double-dose clopidogrel received a loading dose of 600 mg on day 1, followed by 150 mg once daily on days 2 through 7. Patients assigned to standard-dose clopidogrel received a 300-mg loading dose on day 1 before angiography, followed by 75 mg once daily on days 2 through 7. On days 8 through 30, both the double-dose and standard-dose groups received 75 mg of clopidogrel once daily.

All patients received a loading dose of aspirin (≥300 mg) on day 1, regardless of the aspirin dose assignment. Patients randomly assigned to lower-dose aspirin received 75 to 100 mg daily on days 2 through 30, and those randomly assigned to higher-dose aspirin received 300 to 325 mg daily on days 2 through 30. Locally approved preparations of aspirin were used. The protocol allowed for the use of either enteric-coated or non–enteric-coated aspirin preparations.

The use of other therapies, including antithrombin therapy and glycoprotein IIb/IIIa antagonists, was left to the discretion of the attending physician. The use of vitamin K antagonists was prohibited during the first 7 days of the trial.

PERCUTANEOUS CORONARY INTERVENTION

All patients were to undergo early angiography and PCI, if appropriate, no later than 72 hours after randomization. Levels of creatine kinase, the creatine kinase MB fraction, and levels of troponin were measured 4 to 8 hours after randomization. In patients who underwent PCI, the level of creatine kinase and the creatine kinase MB fraction were measured immediately before and 2, 6, and 12 hours after PCI.

OUTCOMES

The primary outcome was the time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first, up to day 30. The secondary outcomes included the composite of death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia; the individual components of the primary outcome; and death from any cause. Definite or probable stent thrombosis, as defined by the Academic Research Consortium,[26] was a prespecified secondary outcome in the subgroup of patients who underwent PCI. The main safety outcome was major bleeding, defined according to a set of prespecified criteria specific to the trial. Bleeding was also assessed according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. A central committee that was unaware of the treatment assignments adjudicated all primary and secondary outcomes, recurrent ischemia, stent thromboses, and major bleeding events. Events are defined in the Supplementary Appendix.

STATISTICAL ANALYSIS

According to the original sample-size calculations, which were based on a primary-outcome event rate of 11% at 30 days with either standard-dose clopidogrel or lower-dose aspirin, we estimated that 14,000 patients would be required for the study to have 90% power to detect a 16.1% reduction in this event rate with the higher dose of either study drug. Because of a lower-than-expected overall blinded event rate for the primary outcome, the sample size was increased during the trial from 14,000 to 25,000 patients. With 25,000 patients, the trial had 80% power to detect a relative hazard reduction of 15.8% with double-dose clopidogrel, assuming an event rate in the standard-dose group of 4.5%. The assumptions and calculations were identical for the aspirin dose comparison. No interaction between the two study-drug comparisons was anticipated.

The relative efficacy of the double-dose regimen of clopidogrel versus the standard-dose regimen of clopidogrel was assessed with respect to the primary outcome by a comparison of the survival curves (estimated with the use of the Kaplan–Meier method) for the two treatments. We used the log-rank test, stratified according to aspirin dose and qualifying condition (i.e., non–ST-segment elevation acute coronary syndrome or ST-segment elevation myocardial infarction). The treatment effect was estimated from a Cox proportional-hazards model, stratified according to aspirin dose and qualifying condition. An analogous approach, stratified according to clopidogrel dose and qualifying condition, was taken for the aspirin dose comparison. The treatment effect was also examined in a set of prespecified subgroup analyses (details are provided in the Supplementary Appendix).

RESULTS

CHARACTERISTICS OF THE PATIENTS AND COMPLIANCE WITH STUDY REGIMENS

We enrolled 25,086 patients. Of these patients, 24,835 underwent coronary angiography and

Table 1. Baseline Characteristics of the Patients.*

Variable	Clopidogrel		Aspirin	
	Double Dose (N=12,520)	Standard Dose (N=12,566)	Higher Dose (N=12,507)	Lower Dose (N=12,579)
Age				
Mean (yr)	61.3	61.4	61.5	61.2
>75 yr (%)	13.3	13.0	13.4	13.0
Female sex (%)	27.3	27.5	28.0*	26.8
Diagnosis at admission (%)				
Unstable angina or NSTEMI (%)	70.7	70.9	70.8	70.8
STEMI	29.3	29.1	29.2	29.2
Interval between randomization and intervention (hr)				
Unstable angina or NSTEMI				
Median	3.4	3.4	3.4	3.4
Interquartile range	1.0–19.1	1.0–19.3	1.0–19.3	1.0–19.1
STEMI				
Median	0.6	0.5	0.6	0.5
Interquartile range	0.3–1.2	0.3–1.2	0.3–1.2	0.3–1.1
Race or ethnic group (%)†				
White	62.6	62.5	62.4	62.6
Black	1.4	1.3	1.5	1.2
South Asian	10.7	10.9	10.9	10.7
East Asian	12.3	12.0	12.1	12.2
Other	13.0	13.3	12.9	13.3
Medical history (%)				
Current tobacco use	33.6	33.2	33.2	33.6
Hypertension	60.5	60.2	60.4	60.2
Dyslipidemia	41.2	41.1	41.4	40.9
Diabetes mellitus	23.4	23.5	23.8	23.1
Myocardial infarction	18.0	17.7	17.8	17.9
PCI	14.9	14.8	15.1	14.6
CABG	6.2	6.7	6.3	6.6
Electrocardiographic findings (%)				
ST-segment elevation	27.2	27.3	27.2	27.3
New left bundle-branch block	0.4	0.3	0.3	0.4
ST-segment depression	24.3	24.2	24.1	24.3
T-wave inversion	19.5	19.7	19.7	19.4
Transient ST-segment elevation	5.9	5.6	6.0	5.5
Elevated biomarker level (%)	64.7	65.8	65.2	65.4

* CABG denotes coronary-artery bypass grafting, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† Race or ethnic group was self-reported.

17,263 underwent PCI. Of the 7823 patients who did not undergo PCI, 3520 (45.0%) had no clinically significant coronary artery disease (either angiographically normal coronary arteries or all lesions with <70% stenosis), 1859 (23.8%) underwent coronary-artery bypass grafting (CABG), and 2444 (31.2%) were not candidates for any type of revascularization.

Baseline characteristics were well balanced among the randomized clopidogrel and aspirin dose groups (Table 1). The use of medications and invasive procedures was also well balanced

Table 2. Major Outcomes at 30 Days, According to Dose of Clopidogrel.*

Outcome	Double Dose (N=12,520)	Standard Dose (N=12,566)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary outcome: death from cardiovascular causes, myocardial infarction, or stroke	522 (4.2)	557 (4.4)	0.94 (0.83–1.06)	0.30
Secondary outcomes				
Death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia	564 (4.5)	606 (4.8)	0.93 (0.83–1.05)	0.25
Death from cardiovascular causes	267 (2.1)	281 (2.2)	0.95 (0.81–1.13)	0.57
Myocardial infarction	237 (1.9)	277 (2.2)	0.86 (0.72–1.02)	0.09
Stroke	64 (0.5)	65 (0.5)	0.99 (0.70–1.40)	0.95
Recurrent ischemia	51 (0.4)	55 (0.4)	0.93 (0.64–1.36)	0.72
Death from any cause	287 (2.3)	300 (2.4)	0.96 (0.82–1.13)	0.61
Safety outcome: bleeding				
Major				
Study criteria	313 (2.5)	255 (2.0)	1.24 (1.05–1.46)	0.01
Requiring red-cell transfusion ≥2 units	267 (2.2)	210 (1.7)	1.28 (1.07–1.54)	0.01
CABG-related	123 (1.0)	114 (0.9)	1.09 (0.84–1.40)	0.53
Severe	236 (1.9)	195 (1.6)	1.22 (1.01–1.47)	0.04
Leading to decrease in hemoglobin level ≥5 g/dl	130 (1.0)	107 (0.9)	1.22 (0.95–1.58)	0.13
Symptomatic intracranial	4 (0.03)	6 (0.05)	0.67 (0.19–2.37)	0.53
Fatal	16 (0.1)	15 (0.1)	1.07 (0.53–2.16)	0.85
TIMI criteria	210 (1.7)	168 (1.3)	1.26 (1.03–1.54)	0.03
Minor	631 (5.1)	538 (4.3)	1.18 (1.05–1.33)	0.01

* The percentages are Kaplan–Meier estimates of the event rates at 30 days. CABG denotes coronary-artery bypass grafting, and TIMI Thrombolysis in Myocardial Infarction.

(Table 3 in the Supplementary Appendix), except that after randomization there was a higher rate of use of proton-pump inhibitors among patients assigned to higher-dose aspirin than among those assigned to lower-dose aspirin. The median time from randomization to catheterization or PCI was 3.4 hours for patients with a non–ST-segment elevation acute coronary syndrome and 0.5 hours for patients with an ST-segment elevation myocardial infarction. A total of 61.6% of patients in the standard-dose group and 61.8% of patients in the double-dose clopidogrel group received enteric-coated aspirin preparations. A total of 60.3% of patients in the lower-dose aspirin group and 63.2% of patients in the higher-dose aspirin group received enteric-coated aspirin preparations.

During the first 7 days (i.e., the period when the clopidogrel dose differed between the double-dose and standard-dose groups), the median duration of compliance with the clopidogrel dose regimen among patients who underwent PCI was 7 days. Among patients who did not undergo PCI, the median duration was only 1 day for those who underwent CABG and was 7 days for those without clinically significant coronary artery disease and those who were not candidates for revascularization. The median duration of compliance with the assigned aspirin dose between day 2 and day 30 (i.e., the period when the aspirin dose differed between the higher-dose and lower-dose groups) was 29 days in both groups. Follow-up was complete in 99.9% of patients who were enrolled in the study.

CLOPIDOGREL DOSE COMPARISON

The primary outcome occurred in 4.2% of patients in the double-dose clopidogrel group at

30 days, as compared with 4.4% in the standard-dose group (hazard ratio, 0.94, 95% confidence interval [CI], 0.83 to 1.06; P=0.30) (Table 2 and Fig. 1A). Consistent results were observed for each component of the primary outcome, as well as for the expanded composite outcome, consisting of the primary outcome plus recurrent ischemia (Table 2). The rate of death from any cause did not differ significantly between the double-dose and standard-dose groups (2.3% and 2.4%, respectively; hazard ratio with the double dose, 0.96; 95% CI, 0.82 to 1.13; P=0.61).

Major bleeding occurred in 2.5% of patients in the double-dose clopidogrel group as compared with 2.0% of patients in the standard-dose clopidogrel group (hazard ratio, 1.24; 95% CI, 1.05 to 1.46; P=0.01). The incidence of major bleeding as defined according to the TIMI criteria and the incidence of severe bleeding were also higher among patients who received double-dose clopidogrel (Table 2). The increased incidences of major and severe bleeding were accounted for mainly by a higher rate of red-cell transfusion among patients in the double-dose group. The use of double-dose clopidogrel did not increase the incidence of fatal or intracranial bleeding, nor did it significantly increase the incidence of bleeding that was related to CABG (Table 2). There were no reports of neutropenia in either clopidogrel group.

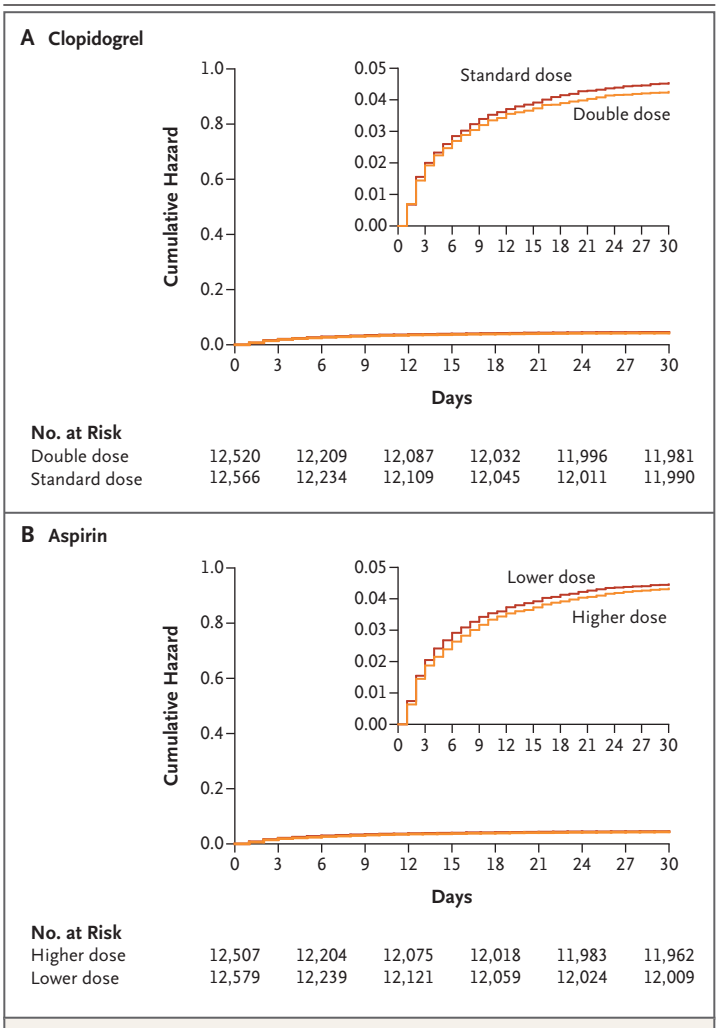

Figure 1. Cumulative Hazard Ratios for the Primary Outcome at 30 Days, According to Treatment Group.

Data for the primary outcome of death from cardiovascular causes, myocardial infarction, or stroke are shown for patients who received clopidogrel (Panel A) and aspirin (Panel B). Hazard ratios were calculated with the use of a Cox proportional-hazards model.

ASPIRIN DOSE COMPARISON

Overall, 4.2% of patients in the higher-dose aspirin group had a primary outcome event at 30 days, as compared with 4.4% of patients in the lower-dose aspirin group (hazard ratio, 0.97; 95% CI, 0.86 to 1.09; P=0.61) (Table 3 and Fig. 1B). Consistent results were observed for each component of the primary outcome and for the expanded composite of the primary outcome plus recurrent ischemia (Table 3). A nominally significant reduction in recurrent ischemia alone was associated with higher-dose aspirin as compared with lower-dose aspirin (0.3% vs. 0.5%; hazard ratio, 0.63; 95% CI, 0.43 to 0.94; P=0.02). Death from any cause occurred in 2.2% of patients in the higher-dose aspirin group, as compared with 2.5% of patients in the lower-dose aspirin group (hazard ratio, 0.87; 95% CI, 0.74 to 1.03; P=0.10).

The aspirin dose groups did not differ significantly with respect to major bleeding, as defined according to the study criteria or the TIMI criteria, or severe bleeding (Table 3). There was a nominally significant increase in the incidence of minor bleeding among patients who received higher-dose aspirin (hazard ratio, 1.13; 95% CI, 1.00 to 1.27; P=0.04). There was a small increase in the incidence of major gastrointestinal bleeding among patients who received higher-dose aspirin, as compared with those who received lower-dose aspirin (47 patients [0.4%] vs. 29 patients [0.2%], P=0.04). Six patients in each aspirin dose group had intracranial bleeding.

Table 3. Major Outcomes at 30 Days, According to Dose of Aspirin.*

Outcome	Higher Dose (N=12,507)	Lower Dose (N=12,579)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary outcome: death from cardiovascular causes, myocardial infarction, or stroke	530 (4.2)	549 (4.4)	0.97 (0.86–1.09)	0.61
Secondary outcomes				
Death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia	563 (4.5)	608 (4.8)	0.93 (0.83–1.04)	0.21
Death from cardiovascular causes	259 (2.1)	289 (2.3)	0.90 (0.76–1.06)	0.22
Myocardial infarction	253 (2.0)	261 (2.1)	0.97 (0.82–1.16)	0.76
Stroke	70 (0.6)	59 (0.5)	1.19 (0.84–1.68)	0.32
Recurrent ischemia	41 (0.3)	65 (0.5)	0.63 (0.43–0.94)	0.02
Death from any cause	273 (2.2)	314 (2.5)	0.87 (0.74–1.03)	0.10
Bleeding				
Major				
Study criteria	282 (2.3)	286 (2.3)	0.99 (0.84–1.17)	0.90
Requiring red-cell transfusion ≥2 units	239 (1.9)	238 (1.9)	1.01 (0.84–1.21)	0.93
CABG-related	111 (0.9)	126 (1.0)	0.88 (0.68–1.14)	0.34
Severe	216 (1.7)	215 (1.7)	1.01 (0.84–1.22)	0.93
Leading to decrease in hemoglobin level ≥5 g/dl	115 (0.9)	122 (1.0)	0.95 (0.73–1.22)	0.67
Symptomatic intracranial	6 (0.05)	4 (0.03)	1.51 (0.42–5.33)	0.53
Fatal	16 (0.1)	15 (0.1)	1.07 (0.53–2.17)	0.85
TIMI criteria	197 (1.6)	181 (1.4)	1.09 (0.89–1.34)	0.39
Minor	618 (5.0)	551 (4.4)	1.13 (1.00–1.27)	0.04

* The percentages are Kaplan–Meier estimates of the event rates at 30 days. CABG denotes coronary-artery bypass grafting, and TIMI Thrombolysis in Myocardial Infarction.

CLOPIDOGREL AND ASPIRIN DOSE INTERACTION

We found a nominally significant interaction between the clopidogrel dose comparison and the aspirin dose comparison for the primary outcome (P=0.04 for interaction). Among patients assigned to higher-dose aspirin, the primary outcome occurred in 3.8% of patients in the double-dose clopidogrel group, as compared with 4.6% of patients in the standard-dose clopidogrel group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98; P=0.03). Among patients assigned to lower-dose aspirin, there was no significant difference between the double-dose and standard-dose clopidogrel groups (4.5% and 4.2%, respectively; hazard ratio, 1.07; 95% CI, 0.90 to 1.26; P=0.46) (Fig. 2).

PRESPECIFIED SUBGROUPS

Our analyses showed a consistent treatment effect of double-dose versus standard-dose clopidogrel and of higher-dose versus lower-dose aspirin with respect to the primary outcome in most of the prespecified subgroups (Fig. 3 and 4). There was nominally significant heterogeneity (P=0.03 for interaction) in the treatment effect of double-dose versus standard-dose clopidogrel with respect to the primary outcome in the 17,263 patients who underwent PCI, as compared with the 7823 patients who did not undergo PCI. In the subgroup of patients who underwent PCI, double-dose clopidogrel was associated with a significant reduction in the rate of the prespecified secondary outcome of stent thrombosis (1.6% vs. 2.3%; hazard ratio, 0.68; 95% CI, 0.55 to 0.85; P<0.001). In the aspirin dose comparison, there was no evidence of heterogeneity according to whether patients underwent PCI. In addition, we found no heterogeneity in the outcome according to whether patients received enteric-coated aspirin tablets.

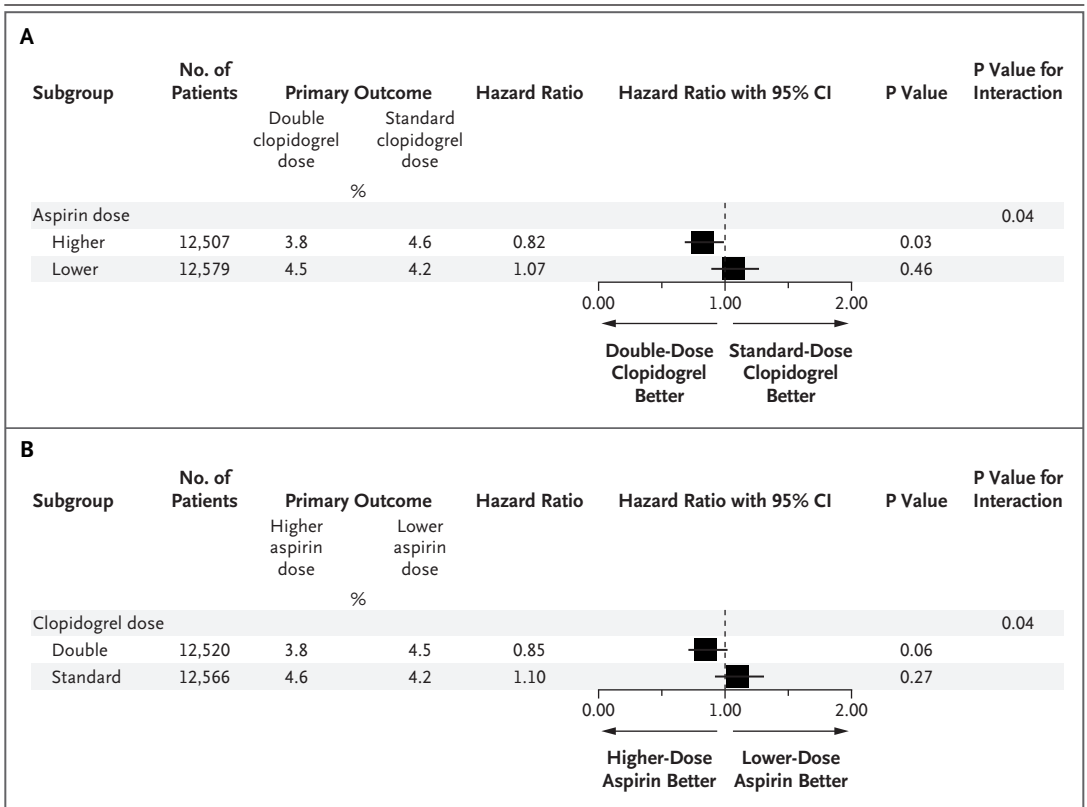

Figure 2. Hazard Ratios for the Primary Outcome in the Clopidogrel and Aspirin Dose Groups According to the Factorial Design.

Panel A shows the comparison of double-dose clopidogrel with standard-dose clopidogrel, according to aspirin dose, and Panel B shows the comparison of higher-dose aspirin with lower-dose aspirin, according to clopidogrel dose. P values were calculated with the use of the log-rank test. Hazard ratios were calculated with the use of a Cox proportional-hazards model. The size of the squares is proportional to the number of patients and represents the point estimate of the treatment effect. The horizontal line through each square spans the 95% confidence interval.

DISCUSSION

We compared double-dose clopidogrel with standard-dose clopidogrel, and higher-dose aspirin with lower-dose aspirin, in patients presenting with acute coronary syndromes for whom early coronary angiography was planned. We found that the use of a double dose of clopidogrel for 7 days, as compared with the standard dose, did not reduce the incidence of the primary outcome of cardiovascular death, myocardial infarction, or stroke at 30 days. Similarly, we found that higher-dose aspirin, as compared with lower-dose aspirin, was not associated with a reduction in the incidence of the same primary outcome at 30 days. In addition, for both the clopidogrel dose comparison and the aspirin dose comparison, we found no significant difference in the expanded secondary composite outcome that included recurrent ischemia.

A nominally significant reduction in the primary outcome was associated with the use of higher-dose clopidogrel in the subgroup of 17,263 study participants who underwent PCI after randomization (69%). Because a test for interaction between the patients who underwent PCI and those who did not undergo PCI (P=0.03) did not meet our prespecified threshold of a P value of 0.01 or less for subgroup interactions, and since 13 prespecified subgroup analyses were performed for the clopidogrel dose comparison, this result could have been due to the play of chance. However, this result is consistent with the results of previous studies[1,11-18] and a meta-analysis[27] evaluating a 600-mg loading dose of clopidogrel, and patients undergoing PCI were

Subgroup	No. of Patients	Primary Outcome: Double clopidogrel dose (%)	Primary Outcome: Standard clopidogrel dose (%)	Hazard Ratio	Hazard Ratio with 95% CI	P Value	P Value for Interaction
Overall	25,086	4.2	4.4	0.94		0.31	
PCI after randomization							0.03
Yes	17,263	3.9	4.5	0.85		0.04	
No	7823	4.9	4.3	1.14		0.22	
ST-segment deviation							0.61
Unstable angina or non-STEMI	17,759	4.0	4.1	0.96		0.58	
STEMI	7327	4.7	5.2	0.90		0.32	
Diabetes							0.32
Yes	5880	5.2	6.1	0.86		0.16	
No	19,203	3.9	3.9	0.98		0.77	
GRACE score							0.09
<140	17,410	2.5	3.0	0.84		0.06	
≥140	6317	7.7	7.4	1.04		0.64	
Age							0.29
≤65 yr	15,765	2.9	2.9	1.01		0.88	
>65 yr	9321	6.3	7.1	0.89		0.15	
Sex							0.17
Female	6871	4.5	5.4	0.83		0.09	
Male	18,213	4.1	4.1	1.00		0.95	
Clopidogrel before randomization							0.16
No	19,626	4.3	4.4	0.98		0.78	
<300 mg	4524	3.8	4.7	0.81		0.15	
≥300 mg	936	3.3	4.4	0.73		0.35	
Weight <60 kg, age ≥75 yr, or prior stroke							0.98
Yes	5826	7.2	7.7	0.94		0.49	
No	19,260	3.3	3.5	0.94		0.42	
Current tobacco use							0.14
Yes	8373	2.9	3.6	0.80		0.07	
No	16,701	4.8	4.8	0.99		0.89	
Proton-pump inhibitor before randomization							0.31
Yes	3215	3.9	5.0	0.78		0.14	
No	15,215	4.1	4.4	0.94		0.43	
Race or ethnic group							0.51
South Asian	2711	4.6	3.7	1.24		0.25	
East Asian	3050	4.1	4.8	0.85		0.36	
Black African	260	3.8	5.4	0.70		0.55	
European	15,688	4.0	4.5	0.90		0.17	
Other	3377	4.5	4.3	1.04		0.83	
Clinically significant coronary artery disease							0.06
Yes	21,340	4.5	4.8	0.92		0.21	
No	3746	1.7	1.0	1.67		0.09	
Glycoprotein IIb/IIIa inhibitor after randomization							0.71
Yes	5873	5.3	5.8	0.91		0.39	
No	19,195	3.8	4.0	0.95		0.51	
Proton-pump inhibitor after randomization							0.50
Yes	7752	4.6	5.3	0.87		0.16	
No	10,678	3.7	3.9	0.95		0.63	

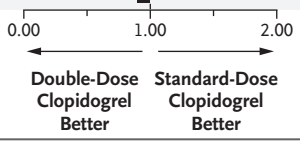

Figure 3 (facing page). Hazard Ratios for the Primary Outcome According to the Clopidogrel Dose in Selected Subgroups.

The Global Registry of Acute Coronary Events (GRACE) risk score (ranging from 0 to 372, with a score ≥140 considered to indicate high risk) is derived from baseline clinical variables and is used to estimate the risk of in-hospital death. Clinically significant coronary artery disease was defined as at least one lesion with stenosis of 70% or more on angiography. The percentages are Kaplan–Meier estimates of the rate of the primary outcome at 30 days. The size of the squares is proportional to the number of patients and represents the point estimate of the treatment effect. The horizontal line through each square spans the 95% confidence interval. NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

the intended patient population for the current trial. More notably, double-dose clopidogrel significantly reduced the secondary outcome of stent thrombosis, including angiographically confirmed definite stent thrombosis, in the subgroup of patients who underwent PCI. Although this result is a secondary outcome in a subgroup, such an effect is plausible in that it is consistent with the expectation that the risk of stent thrombosis is likely to be reduced with more potent platelet inhibition. The magnitude of the reduction in stent thrombosis in this trial is similar to the magnitude observed with newer, more potent, ADP-receptor blockers.[19,20]

Our trial was designed with the intention of administering the study drug as early as possible, mainly to take advantage of the benefits of clopidogrel treatment before cardiac catheterization.[6,8] This early-treatment strategy is consistent with the recommendations of an expert committee,[22,23,28-30] and the steering committee did not consider it appropriate or ethical to withhold antiplatelet therapy until after the coronary anatomy was defined. A consequence of this approach, however, is that a substantial proportion of the patients who were enrolled in the trial were found to have no clinically significant coronary artery disease, and in other patients, clopidogrel was discontinued early (median of only 1 dose received) because of referral for CABG. These two groups reduced the power of the trial to show a beneficial effect of double-dose clopidogrel.

In addition, the 1-week duration of treatment with double-dose clopidogrel was relatively short. The rationale for choosing a 1-week treatment period was to optimize the benefit–risk balance by targeting the higher dose during the period of highest risk, shortly after the acute coronary event (or shortly after PCI), while minimizing the risk of longer-term bleeding complications. Two recent trials evaluating a short duration of treatment with an intravenous ADP-receptor antagonist, as compared with placebo or clopidogrel, also did not show a significant benefit with respect to the primary outcome.[31,32] Recent trials evaluating longer-term therapy with more potent ADP-receptor inhibition have shown a benefit with respect to major cardiovascular events.[19,20]

The use of double-dose clopidogrel, as compared with the standard dose, was associated with an increase in the risk of major bleeding that led to an increase in the requirement for transfusion of at least 2 units of red cells; there was no significant difference in intracranial, CABG-related, or fatal bleeding.

Although doses of aspirin as low as 30 mg completely block the effects of cyclooxygenase-1,[33] international variations in aspirin dosing remain large, with most centers in Europe using lower-dose aspirin and most centers in North America using higher-dose aspirin. In a randomized comparison, we found that no added benefit was associated with increasing the dose of aspirin beyond 75 to 100 mg daily in patients with an acute coronary syndrome, and there was no significant difference between higher-dose and lower-dose aspirin with respect to the incidence of major bleeding. Accordingly, treatment with either lower-dose or higher-dose aspirin for the first 30 days appears to be acceptable in such patients.

There was a nominally significant interaction between the clopidogrel and aspirin dose comparisons with respect to the primary outcome. This finding was unexpected because although clopidogrel and aspirin have been associated with additive benefits in patients with acute coronary syndromes,[3-5] an interaction between these two antiplatelet drugs has not been demonstrated. The interaction also lacks a known biologic mechanism. Thus, it is possible that the interaction was due to the play of chance.

In conclusion, we found that in patients with an acute coronary syndrome who were referred

Subgroup	No. of Patients	Primary Outcome (%) Higher aspirin dose	Primary Outcome (%) Lower aspirin dose	Hazard Ratio	Hazard Ratio with 95% CI	P Value	P Value for Interaction
Overall	25,086	4.2	4.4	0.97		0.61	
PCI after randomization							0.93
Yes	17,263	4.1	4.2	0.97		0.73	
No	7823	4.5	4.7	0.96		0.72	
ST-segment deviation							0.49
Unstable angina or non-STEMI	17,759	3.9	4.2	0.94		0.41	
STEMI	7327	5.0	4.8	1.03		0.79	
Diabetes							0.62
Yes	5880	5.7	5.6	1.01		0.93	
No	19,203	3.8	4.0	0.95		0.46	
GRACE score							0.98
<140	17,410	2.7	2.8	0.95		0.60	
≥140	6317	7.4	7.7	0.96		0.62	
Age							0.19
≤65 yr	15,765	2.7	3.1	0.88		0.17	
>65 yr	9321	6.8	6.6	1.03		0.69	
Sex							0.99
Female	6871	4.9	5.0	0.97		0.75	
Male	18,213	4.0	4.1	0.97		0.95	
Clopidogrel before randomization							0.14
No	19,626	4.4	4.3	1.01		0.91	
<300 mg	4524	4.0	4.5	0.88		0.40	
≥300 mg	936	3.0	4.7	0.63		0.18	
Weight <60 kg, age ≥75 yr, or prior stroke							0.50
Yes	5826	7.1	7.7	0.92		0.37	
No	19,260	3.4	3.4	1.00		0.96	
Current tobacco use							1.00
Yes	8373	3.2	3.3	0.97		0.82	
No	16,701	4.7	4.9	0.97		0.66	
Proton-pump inhibitor before randomization							0.42
Yes	3215	4.7	4.2	1.14		0.44	
No	15,215	4.2	4.3	0.99		0.87	
Race or ethnic group							0.85
South Asian	2711	3.6	4.8	0.75		0.12	
East Asian	3050	4.7	4.2	1.12		0.50	
Black African	260	5.0	4.2	1.18		0.78	
European	15,688	4.3	4.2	1.03		0.73	
Other	3377	3.9	4.9	0.78		0.14	
Clinically significant coronary artery disease							0.45
Yes	21,340	4.6	4.7	0.97		0.62	
No	3746	1.5	1.2	1.21		0.52	
Glycoprotein IIb/IIIa inhibitor after randomization							0.57
Yes	5873	5.6	5.5	1.02		0.84	
No	19,195	3.8	4.0	0.95		0.46	
Proton-pump inhibitor after randomization							0.40
Yes	7752	5.2	4.8	1.07		0.52	
No	10,678	3.7	3.9	0.95		0.60	

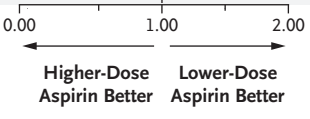

Figure 4 (facing page). Hazard Ratios for the Primary Outcome According to the Aspirin Dose in Selected Subgroups.

The Global Registry of Acute Coronary Events (GRACE) risk score (ranging from 0 to 372, with a score ≥140 considered high risk) is derived from baseline clinical variables and is used to estimate the risk of in-hospital death. Clinically significant coronary artery disease was defined as at least one lesion with stenosis of 70% or more on angiography. The percentages are Kaplan–Meier estimates of the rate of the primary outcome at 30 days. The size of the squares is proportional to the number of patients and represents the point estimate of the treatment effect. The horizontal line through each square spans the 95% confidence interval. NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

for an early invasive strategy, there was no significant difference between a 7-day double-dose regimen of clopidogrel and standard-dose clopidogrel with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke. There was also no significant difference between aspirin doses of 300 to 325 mg daily and doses of 75 to 100 mg daily with respect to the same outcome.

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

APPENDIX

The CURRENT–OASIS 7 committee members are as follows: **Steering Committee:** (asterisk denotes member of the operations committee, and dagger denotes member of the events adjudication committee): S.R. Mehta* (principal investigator), S. Yusuf* (steering committee chair), S. Chrolavicius* (project manager), A.E. Ajani, A. Avezum,† J.P. Bassand,* W.E. Boden, A. Budaj,† E.G. Cardona-Muñoz,† J. Col, P.J. Commerford,† G. Di Pasquale, R. Diaz,*† J. Eha, J.W. Eikelboom, D.P. Faxon, M. Flather, D. Foley, K.A.A. Fox,* M.G. Franzosi, C.B. Granger,* M. Gupta, S. Jolly,*† C. Joyner*† (events adjudication committee chair), N. Karatzas,† A. Kastrati, J.H. Kim,† T.H. Koh, F. Lanas,† B. Lewis,† C. Macaya,† T. Moccetti, G. Montalescot, K.O. Niemelä, Z. Öngen, A. Orlandini,† P. Pais, R.J.G. Peters, L. Piegas,† J. Probstfield, J.M. Rankin, M. Ruda, Z. Rumboldt,† H.J. Rupprecht,* P.G. Steg,† J.F. Tanguay, V. Valentin,† J. Varigos, H.D. White, P. Widimsky,*† D. Xavier, J. Zhu, J.R. Zhu; **Sponsors:** Sanofi-Aventis: C. Gaudin, C. Marchese, C. Bouancheau; Bristol-Myers Squibb: M. Blumenthal, P. Hornick, R. Saini; **Events Adjudication Committee:** The above-listed persons whose names are indicated by daggers and M. Atra, K. Bainey, A. Barsan, I. Benedek, G. Borislav, N. Bornstein, Y. Cottin, A. Czepiel, H. DeRaedt, M. Dorobantu, G. Fodor, E. Gardinale, B. Gross, H. Guimaraes, D. Halon, O. Happola, J. Hartikainen, D. Himbert, Q. Hua, S.S. Iyengar, P. Kalvach, B. Kies, C.J. Kim, M. Laine, S. Lang, A. Maggioni, A. Massaro, C. Morillo, J. Narendra, U. Naslund, Y. Nisanci, T. Okay, A. Peeters, M. Penicka, A. Perakis, A. Piplis, G. Pizzolato, S. Polic, J. Renkin, M. Rokoss, N. Runev, A. Siva, E. Sorokin, B. Stockins, F. Turrazza, N. Valettas, Y. Yang, J. Zaborski, R. Zimlichman; **Data and Safety Monitoring Committee:** P. Sleight (chair), J.L. Anderson, D.L. DeMets, J. Hirsh, D.R. Holmes Jr., D.E. Johnstone; **Project Office:** B. Jedrzejowski (research coordinator), A. Robinson (research coordinator), M. Lawrence (event adjudication coordinator), J. Pogue (statistician), R. Afzal (statistician), L. Blake, W. Chen, S. Di Diodato, R. Manojlovic, L. Mastrangelo, A. Mead, E. Pasadyn, T. Sovereign, L. Wasala.

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