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Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation

Marc S. Sabatine, M.D., M.P.H., Christopher P. Cannon, M.D., C. Michael Gibson, M.D., Jose L. López-Sendón, M.D., Gilles Montalescot, M.D., Pierre Theroux, M.D., Marc J. Claeys, M.D., Ph.D., Frank Cools, M.D., Karen A. Hill, B.A., Allan M. Skene, Ph.D., Carolyn H. McCabe, B.S., and Eugene Braunwald, M.D., for the CLARITY–TIMI 28 Investigators*

ABSTRACT

BACKGROUND

A substantial proportion of patients receiving fibrinolytic therapy for myocardial infarction with ST-segment elevation have inadequate reperfusion or reocclusion of the infarct-related artery, leading to an increased risk of complications and death.

METHODS

We enrolled 3491 patients, 18 to 75 years of age, who presented within 12 hours after the onset of an ST-elevation myocardial infarction and randomly assigned them to receive clopidogrel (300-mg loading dose, followed by 75 mg once daily) or placebo. Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin (dispensed according to body weight) and were scheduled to undergo angiography 48 to 192 hours after the start of study medication. The primary efficacy end point was a composite of an occluded infarct-related artery (defined by a Thrombolysis in Myocardial Infarction flow grade of 0 or 1) on angiography or death or recurrent myocardial infarction before angiography.

RESULTS

The rates of the primary efficacy end point were 21.7 percent in the placebo group and 15.0 percent in the clopidogrel group, representing an absolute reduction of 6.7 percentage points in the rate and a 36 percent reduction in the odds of the end point with clopidogrel therapy (95 percent confidence interval, 24 to 47 percent; P<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20 percent (from 14.1 to 11.6 percent, P=0.03). The rates of major bleeding and intracranial hemorrhage were similar in the two groups.

CONCLUSIONS

In patients 75 years of age or younger who have myocardial infarction with ST-segment elevation and who receive aspirin and a standard fibrinolytic regimen, the addition of clopidogrel improves the patency rate of the infarct-related artery and reduces ischemic complications.

From the TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., C.P.C., C.M.G., C.H.M., E.B.); Hospital Universitario Gregorio Marañon, Madrid (J.L.L.-S.); Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris (G.M.); the Montreal Heart Institute, Montreal (P.T.); the Department of Cardiology, University Hospital Antwerp, Edegem, Belgium (M.J.C.); Academisch Ziekenhuis Klina, Brasschaat, Belgium (F.C.); and Nottingham Clinical Research Group, Nottingham, United Kingdom (K.A.H., A.M.S.). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at msabatine@partners.org.

*The participants in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 study are listed in the Appendix.

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THE BENEFIT OF FIBRINOLYTIC THERAPY for myocardial infarction with ST-segment elevation is limited by inadequate reperfusion or reocclusion of the infarct-related artery in a sizable proportion of patients. Initial reperfusion fails to occur in approximately 20 percent of patients[1-3] and is associated with a doubling of mortality rates.[4] The artery becomes reoccluded in an additional 5 to 8 percent of patients during their index hospitalization, and this event is associated with an increase in mortality rates by a factor of nearly three.[5]

Platelet activation and aggregation play a key role in initiating and propagating coronary-artery thrombosis. In the Second International Study of Infarct Survival, conducted in patients with acute myocardial infarction, aspirin reduced the odds of death from vascular causes by 23 percent and the odds of reinfarction by 46 percent.[6] Aspirin has also been shown to reduce the rate of angiographic reocclusion by 22 percent, as compared with placebo.[7]

Clopidogrel is an adenosine diphosphate–receptor antagonist, a class of oral antiplatelet agents that block the $P2Y_{12}$ component of the adenosine diphosphate receptor and thus inhibit the activation and aggregation of platelets.[8] Clopidogrel has been shown to prevent death and ischemic complications in patients with symptomatic atherosclerotic disease, patients who have undergone percutaneous coronary intervention, and patients with unstable angina or myocardial infarction without ST-segment elevation.[9-11] A major remaining question is whether the addition of clopidogrel is beneficial in patients who have myocardial infarction with ST-segment elevation and who are receiving a standard fibrinolytic regimen, including aspirin.

METHODS

PATIENT POPULATION

Between February 10, 2003, and October 31, 2004, 3491 patients were enrolled at 319 sites in 23 countries (listed in the Appendix). As described previously,[12] men and women 18 to 75 years of age were eligible if they had begun to have ischemic discomfort at rest within 12 hours before randomization and it had lasted more than 20 minutes; if they had ST-segment elevation of at least 0.1 mV in at least two contiguous limb leads, ST-segment elevation of at least 0.2 mV in at least two contiguous precordial leads, or left bundle-branch block that was not known to be old; and if they were scheduled to receive a fibrinolytic agent, an anticoagulant (if a fibrin-specific lytic agent was prescribed), and aspirin.

Exclusion criteria were as follows: treatment with clopidogrel within seven days before enrollment or planned treatment with clopidogrel or a glycoprotein IIb/IIIa inhibitor before angiography; contraindications to fibrinolytic therapy (including documented stroke, intracranial hemorrhage, and intracranial neoplasm); a plan to perform angiography within 48 hours in the absence of a new clinical indication; cardiogenic shock; prior coronary-artery bypass grafting; and a weight of 67 kg or less and receipt of more than a 4000-U bolus of unfractionated heparin, a weight of more than 67 kg and receipt of more than a 5000-U bolus of unfractionated heparin, or receipt of more than a standard dose of low-molecular-weight heparin.

The protocol was approved by the institutional review board at each participating center. Written informed consent was obtained from all patients.

STUDY PROTOCOL

Patients were randomly assigned in a 1:1 ratio to receive either clopidogrel (Plavix, Sanofi-Aventis and Bristol-Myers Squibb; a 300-mg loading dose followed by 75 mg once daily) or placebo in a double-blind fashion by means of a central, computerized system of randomization. Patients were to receive study medication daily up to and including the day of coronary angiography. For patients who did not undergo angiography, study drug was to be administered up to and including day 8 or hospital discharge, whichever came first.

All patients were to be treated with a fibrinolytic agent (selected by the treating physician), aspirin (recommended dose, 150 to 325 mg on the first day and 75 to 162 mg daily thereafter), and for those receiving a fibrin-specific lytic agent, heparin for 48 hours. The recommended dose of unfractionated heparin was a bolus of 60 U per kilogram of body weight given intravenously (maximum, 4000 U), followed by infusion at a rate of 12 U per kilogram per hour (maximum, 1000 U per hour).[13] The use of low-molecular-weight heparin instead of unfractionated heparin and the use of heparin in patients receiving streptokinase were at the discretion of the treating physician. Unless clinically indicated, the use of glycoprotein IIb/IIIa inhibitors was permitted only after coronary angiography.

Coronary angiography was to be performed according to the protocol during the index hospitalization, 48 to 192 hours after the start of study

medication, to assess for late patency of the infarct-related artery. Angiography was permitted before 48 hours had elapsed only if clinically indicated.[12,13] For patients who underwent coronary stenting, it was recommended that open-label clopidogrel be administered after angiography, with the use of a loading dose of at least 300 mg, followed by a daily dose of 75 mg. Patients were to undergo electrocardiography at baseline and 90 and 180 minutes after the administration of the loading dose of study drug.

Patients were followed for clinical end points and adverse events during their index hospitalization. Telephone follow-up was performed at 30 days to identify clinical end points or adverse events, which were verified by means of medical records. Vital status was ascertained in 3487 of the 3491 patients (99.9 percent).

END POINTS

The primary efficacy end point was the composite of an occluded infarct-related artery (defined by a Thrombolysis in Myocardial Infarction [TIMI] flow grade of 0 or 1) on angiography, death from any cause before angiography could be performed, or recurrent myocardial infarction before angiography — the last two of which served as surrogates for failed reperfusion or reocclusion of the infarct-related artery. For patients who did not undergo angiography, the primary end point was death or recurrent myocardial infarction by day 8 or hospital discharge, whichever came first. The TIMI flow grade[1] in the infarct-related artery was determined in a blinded fashion by the TIMI Angiographic Core Laboratory. The definitions of recurrent myocardial infarction and other efficacy end points have been described previously.[12]

The primary safety end point was the rate of major bleeding (according to TIMI criteria[14]) by the end of the calendar day after angiography or, if angiography was not performed, by day 8 or hospital discharge, whichever came first. Other safety end points included the rates of intracranial hemorrhage and minor bleeding (according to TIMI criteria). All ischemic and any clinically significant bleeding events were adjudicated in a blinded fashion by members of an independent clinical-events committee.

STATISTICAL ANALYSIS

We estimated that the enrollment of 3500 patients would provide the study with a statistical power of

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Clopidogrel (N=1752)	Placebo (N=1739)
Age — yr	57.7±10.3	57.2±10.3
Male sex — no. (%)	1400 (79.9)	1403 (80.7)
White race — no. (%)†	1569 (89.6)	1556 (89.5)
Weight — kg	80.1±14.7	80.1±14.6
Hypertension — no. (%)	750 (42.8)	764 (43.9)
Hyperlipidemia — no. (%)	564 (32.2)	574 (33.0)
Current smoker — no. (%)	887 (50.7)	865 (49.9)
Diabetes mellitus — no. (%)	289 (16.5)	286 (16.4)
Prior myocardial infarction — no. (%)	159 (9.1)	159 (9.1)
Prior percutaneous coronary intervention — no. (%)	84 (4.8)	85 (4.9)
Anterior myocardial infarction — no. (%)	722 (41.2)	697 (40.1)
Fibrinolytic agent — no. (%)‡		
Tenecteplase	838 (47.8)	822 (47.3)
Reteplase	209 (11.9)	214 (12.3)
Alteplase	159 (9.1)	155 (8.9)
Streptokinase	542 (30.9)	543 (31.2)
None	4 (0.2)	6 (0.3)
Initial aspirin — no. (%)	1726 (98.5)	1715 (98.6)
Initial heparin — no. (%)§		
Unfractionated heparin	808 (46.1)	792 (45.5)
Low-molecular-weight heparin	528 (30.1)	506 (29.1)
Both	85 (4.9)	90 (5.2)
Neither	331 (18.9)	351 (20.2)
Time from onset of symptoms to start of fibrinolytic therapy — hr		
Median	2.7	2.6
Interquartile range	1.8–4.2	1.7–4.0
Angiography — no. (%)	1645 (93.9)	1638 (94.2)
Time to angiography — hr		
Median	84	84
Interquartile range	55–123	50–124
Cardiac medications during index hospitalization — no. (%)		
Beta-blockers	1554 (88.7)	1559 (89.6)
Statins	1408 (80.4)	1410 (81.1)
ACE inhibitors or angiotensin-receptor blockers¶	1273 (72.7)	1254 (72.1)
Open-label clopidogrel after completion of study drug	954 (54.5)	967 (55.6)
Ticlopidine after completion of study drug	62 (3.5)	50 (2.9)

* Plus–minus values are means ±SD. None of the differences between groups were statistically significant. Data on weight were missing for 61 patients (31 in the clopidogrel group and 30 in the placebo group), and data on smoking status were missing in 7 patients (2 and 5, respectively).
† Race was self-reported.
‡ One patient in the placebo group was treated with both reteplase and streptokinase.
§ Initial heparin includes any heparin that was given immediately before or during the first two hours after randomization.
¶ ACE denotes angiotensin-converting enzyme.

Table 2. Efficacy Outcomes.*

Outcome	Clopidogrel (N=1752)	Placebo (N=1739)	Odds Ratio (95% CI)	P Value
Primary efficacy end point — no. of patients (%)†	262 (15.0)	377 (21.7)	0.64 (0.53 to 0.76)	<0.001
TIMI flow grade 0 or 1	192 (11.7)	301 (18.4)	0.59 (0.48 to 0.72)	<0.001
Death	45 (2.6)	38 (2.2)	1.17 (0.75 to 1.82)	0.49
Recurrent myocardial infarction	44 (2.5)	62 (3.6)	0.70 (0.47 to 1.04)	0.08
Other angiographic measurement — no. of patients (%)				
TIMI flow grade 3	1112 (67.8)	993 (60.8)	1.36 (1.18 to 1.57)	<0.001
TIMI myocardial-perfusion grade 3	885 (55.8)	817 (51.2)	1.21 (1.05 to 1.40)	0.008
Intracoronary thrombus	697 (43.0)	822 (50.8)	0.73 (0.64 to 0.84)	<0.001
Mean stenosis — %	68.4	70.8	−2.3 (−3.8 to −0.9)‡	0.001
Mean minimal luminal diameter — mm	0.82	0.75	0.07 (0.03 to 0.11)‡	0.001

* Data on the Thrombolysis in Myocardial Infarction (TIMI) flow grade were available for 1640 patients in the clopidogrel group and 1634 patients in the placebo group; data on TIMI myocardial-perfusion grade were available for 1585 and 1596 patients, respectively; data on thrombus were available for 1622 and 1619 patients, respectively; and data on stenosis and the minimal luminal diameter were available for 1560 and 1559 patients, respectively. CI denotes confidence interval.

† The primary efficacy end point was ascertained through the start of coronary angiography (at a median of 3.5 days) or, among patients who did not undergo angiography, at hospital discharge or day 8, whichever came first.

‡ This value is the mean difference between groups, rather than the odds ratio.

95 percent to detect a relative reduction in the rate of the primary end point of 24 percent (from 19.0 to 14.4 percent) with the use of a two-sided test at the 5 percent level. All efficacy analyses were based on the intention-to-treat principle. The prospectively defined analyses of the primary and secondary end points involved a logistic-regression model that included terms for the treatment group, the type of fibrinolytic agent used, the type of heparin used, and the location of the infarct. For continuous variables, differences between the treatment groups were assessed by analysis of variance. Safety analyses were performed according to the treatment actually received by each patient. The rates of the safety end points and stroke were compared with the use of Fisher's exact test.

An independent data and safety monitoring board monitored the incidence of the safety end points after the enrollment of every 500 patients, with one formal interim analysis after 50 percent of the patients had been enrolled. No stopping rules were specified; therefore, the overall significance levels were not adjusted as a result of the formal interim analysis.

The study was an investigator-initiated clinical trial by the TIMI Study Group, which designed the trial and had free and complete access to the data. Data were coordinated by the Nottingham Clinical Research Group. Members of the TIMI Study Group and of the Nottingham group carried out the prespecified analyses, and the sponsors independently validated them.

RESULTS

A total of 3491 patients underwent randomization, and the two groups were well matched with regard to baseline characteristics (Table 1). Their average age was 57 years, 80.3 percent were men, 50.3 percent were current smokers, and 9.1 percent had a history of myocardial infarction. A total of 99.7 percent of the patients received a fibrinolytic agent, of whom 68.8 percent received a fibrin-specific agent. The median time from the onset of symptoms to the administration of a fibrinolytic agent was 2.7 hours. A total of 98.6 percent of the patients received aspirin. For initial anticoagulation, 45.8 percent received unfractionated heparin, 29.6 percent low-molecular-weight heparin, 5.0 percent both, and 19.5 percent neither.

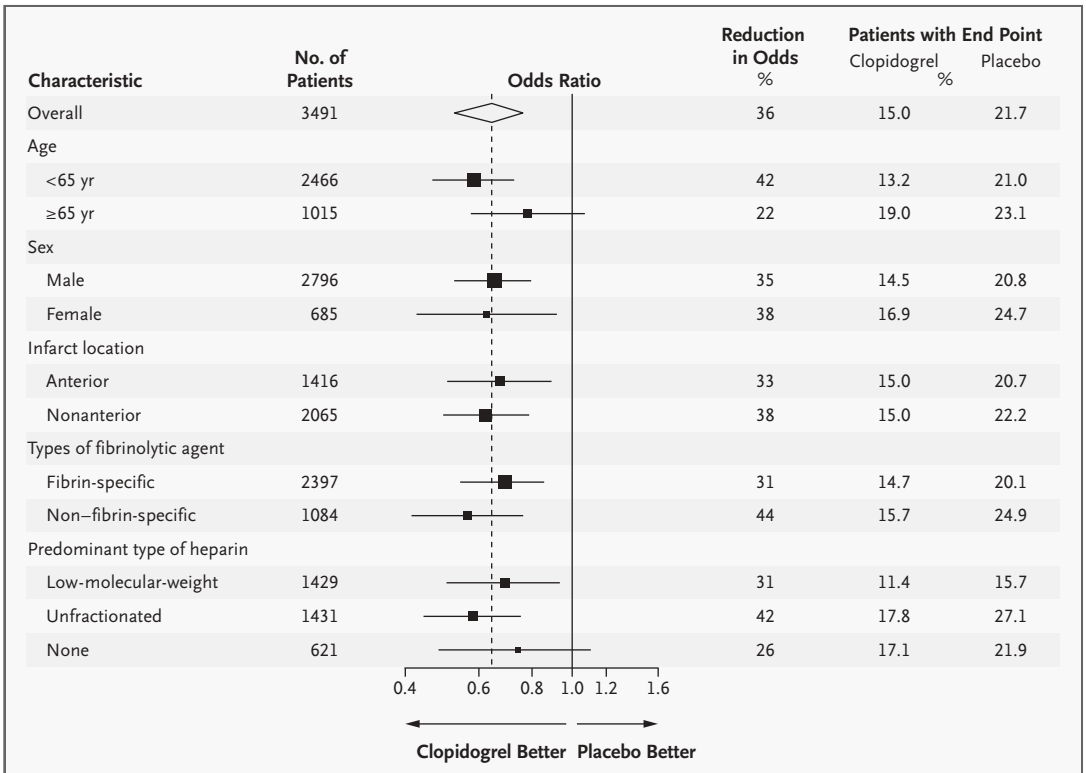


Figure 1. Rates of and Odds Ratios for the Primary Efficacy End Point Overall and in Various Subgroups.

The primary efficacy end point was a composite of a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 or 1 on angiography or death or recurrent myocardial infarction before angiography. For the logistic-regression models to converge correctly, the 10 patients who did not receive a fibrinolytic agent were excluded from the subgroup analyses. The analysis of subgroups according to the type of heparin used was based on the predominant heparin used from randomization to the time of angiography. All P values for interactions were not significant. The overall treatment effect is represented by the diamond, the left and right borders of which indicate the 95 percent confidence interval. The dotted line represents the point estimate of the overall treatment effect. For subgroups, the size of each box is proportional to the number of patients in the individual analyses. The horizontal lines represent the 95 percent confidence intervals.

In all, 98.9 percent of the patients received study medication. The median time from the administration of a fibrinolytic agent to the administration of study medication was 10 minutes (interquartile range, 5 to 25). Patients received a median of four doses of study medication. The rate of use of other cardiac medications was high and similar in the two groups (Table 1). Angiography was performed in 93.9 percent of the patients in the clopidogrel group and 94.2 percent of those in the placebo group, at a median of 84 hours after randomization in each group. Percutaneous coronary intervention and coronary-artery bypass grafting were performed in 57.2 percent and 5.9 percent, respectively, of the patients in the clopidogrel group and in 56.6 percent and 6.0 percent, respectively, of those in the placebo group. After angiography and ascertainment of the primary end point, open-label clopidogrel or ticlopidine was given to 56.7 percent of the patients in the clopidogrel group and 57.4 percent of those in the placebo group.

EFFICACY END POINTS

The rates of the prespecified primary efficacy end point were 21.7 percent in the placebo group and 15.0 percent in the clopidogrel group, representing an absolute reduction of 6.7 percentage points in the rate and a 36 percent reduction in the odds of the end point in favor of treatment with clopidogrel (95 percent confidence interval, 24 to 47 percent; $P<0.001$). Among the individual components of the primary end point (Table 2), clopidogrel had the greatest effect on the rate of an occluded infarct-related artery (reducing it from 18.4 percent

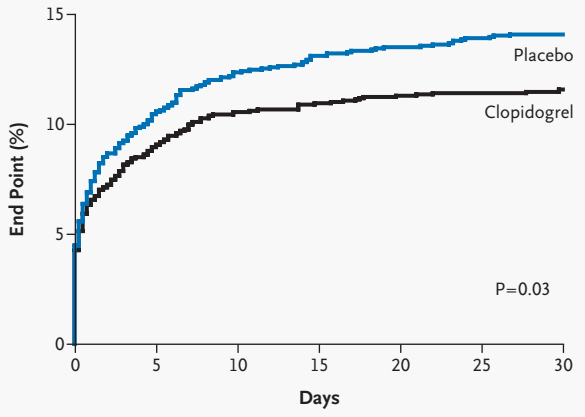


Figure 2. Cumulative Incidence of the End Point of Death from Cardiovascular Causes, Recurrent Myocardial Infarction, or Recurrent Ischemia Leading to the Need for Urgent Revascularization.

The odds ratio for this end point was significantly lower in the clopidogrel group than in the placebo group at 30 days (11.6 percent vs. 14.1 percent; odds ratio, 0.80 [95 percent confidence interval, 0.65 to 0.97]; P=0.03).

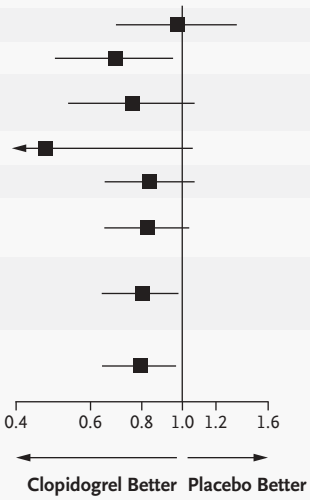
to 11.7 percent; 41 percent reduction in the odds; P<0.001) and the rate of recurrent myocardial infarction (reducing it from 3.6 to 2.5 percent; 30 percent reduction in the odds; P=0.08), but it had no significant effect on the rate of death from any cause (2.2 percent in the placebo group vs. 2.6 percent in the clopidogrel group, P=0.49). The beneficial effect of clopidogrel on the incidence of the primary end point was consistent across the prespecified subgroups, as defined on the basis of age, sex, the type of fibrinolytic agent used, the type of heparin used, and the location of the infarct (Fig. 1).

Clopidogrel improved all angiographic measurements (Table 2). Specifically, as compared with placebo, treatment with clopidogrel increased the odds of achieving optimal epicardial flow (defined by a TIMI flow grade of 3) by 36 percent (P<0.001) and the odds of achieving optimal myocardial reperfusion (defined by a TIMI myocardial-perfusion grade of 3) by 21 percent (P=0.008) and reduced the odds of intracoronary thrombus by 27 percent (P<0.001). As compared with placebo, treatment with clopidogrel also resulted in less severe stenosis (P=0.001) and a larger minimal luminal diameter of the infarct-related artery (P=0.001). Clopidogrel therapy had no significant effect on the mean degree of resolution of ST-segment elevation by 180 minutes: the degree of resolution was 59 percent (median, 73 percent) with clopidogrel, as compared with 61 percent (median, 72 percent) with placebo (P=0.22). As compared with placebo, clopidogrel therapy was associated with a 21 percent reduction in the odds of the need for early angiography (i.e., within 48 hours after randomization) for clinical indications (15.4 percent vs. 18.6 percent, P=0.01) and a 21 percent reduction in the odds of the need for revascularization on an urgent basis during the index hospitalization, as assessed by local investigators (19.5 percent vs. 23.3 percent, P=0.005). Among the patients who underwent percutaneous coronary intervention, the rates of use of glycoprotein IIb/IIIa were 29.3 percent in the clopidogrel group and 33.0 percent in the placebo group (P=0.07). By the time of the ascertainment of the primary end point (median, 3.5 days), the rate of the composite end point of death, recurrent myocardial infarction, or recurrent myocardial ischemia was 8.3 percent in the clopidogrel group and 9.3 percent in the placebo group (reduction in the odds, 12 percent; P=0.27).

By 30 days, clopidogrel therapy had reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20 percent (from 14.1 to 11.6 percent, P=0.03) (Fig. 2). In terms of the individual end points (Fig. 3), there were the following: no difference in the rate of death from cardiovascular causes; a statistically significant, 31 percent reduction in the odds of recurrent myocardial infarction in the clopidogrel group as compared with the placebo group (P=0.02); a 24 percent reduction in the odds of recurrent myocardial ischemia leading to the need for urgent revascularization (P=0.11); and a 46 percent reduction in the odds of stroke (P=0.052).

SAFETY END POINTS

The rates of the primary safety end point, TIMI-defined major bleeding through the day after angiography, were 1.3 percent in the clopidogrel group and 1.1 percent in the placebo group (P=0.64) (Table 3). There were no significant increases in the risk of major bleeding with clopidogrel in any of the subgroups prespecified according to the type of fibrinolytic agent used, the type of heparin used, age, sex, or weight (data not shown). The rates of TIMI-defined major bleeding or the need for the transfusion of at least 2 units of blood were 1.8



End Point	Odds Ratio	Reduction in Odds %	Patients with End Point Clopidogrel %	Placebo %
Death from CV causes		3	4.4	4.5
Recurrent MI		31	4.1	5.9
Recurrent ischemia leading to urgent revascularization		24	3.5	4.5
Stroke		46	0.9	1.7
Death from CV causes or recurrent MI		17	8.4	9.9
Death from CV causes, recurrent MI, or stroke		18	9.1	10.9
Death from CV causes, recurrent MI, or recurrent ischemia leading to urgent revascularization		20	11.6	14.1
Death from CV causes, recurrent MI, stroke, or recurrent ischemia leading to urgent revascularization		21	12.3	15.0

Figure 3. Odds Ratios for Individual and Composite Clinical End Points through 30 Days in the Clopidogrel Group as Compared with the Placebo Group.

The horizontal lines represent the 95 percent confidence intervals. CV denotes cardiovascular, and MI myocardial infarction.

percent in the clopidogrel group and 1.3 percent in the placebo group (P=0.28), and the rates of TIMI-defined minor bleeding through the day after angiography were 1.0 percent and 0.5 percent, respectively (P=0.17) (Table 3). The rates of intracranial hemorrhage were 0.5 percent in the clopidogrel group and 0.7 percent in the placebo group (P=0.38). At 30 days, there were no significant differences in the rates of major or minor bleeding between the two groups (Table 3). Among the 136 patients who underwent coronary-artery bypass grafting during the index hospitalization, treatment with clopidogrel was not associated with a significant increase in the rate of major bleeding through 30 days of follow-up (7.5 percent in the clopidogrel group, as compared with 7.2 percent in the placebo group; P=1.00), even among those who underwent coronary-artery bypass grafting within 5 days after the discontinuation of study medication (9.1 percent and 7.9 percent, respectively; P=1.00).

DISCUSSION

Our study demonstrates the benefit of adding clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. Treatment with a loading dose of 300 mg of clopidogrel followed by a daily dose of 75 mg resulted in a 36 percent reduction in the odds of an occluded infarct-related artery or death or recurrent myocardial infarction by the time of angiography. The benefit was consistent across a broad range of subgroups, including those categorized according to the type of fibrinolytic agent used and the type of heparin used. By 30 days, clopidogrel therapy led to a significant, 20 percent reduction (from 14.1 to 11.6 percent) in the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization. Treatment with clopidogrel was not associated with an increased rate of major bleeding or intracranial hemorrhage.

Arterial thrombi that are rich in platelets are relatively resistant to fibrinolysis and prone to induce reocclusion after initial reperfusion.[15] Despite the inhibition of cyclooxygenase by aspirin, platelet activation can still occur through thromboxane A_2–independent pathways, leading to the aggregation of platelets and the formation of thrombin.[16] Clopidogrel is a potent antiplatelet agent that has a synergistic antithrombotic effect when combined with aspirin.[17] Clopidogrel has been shown to benefit patients with documented atherosclerosis (re-

Table 3. Safety Outcomes.*

Outcome	Clopidogrel (N=1733)	Placebo (N=1719)	P Value
	no. of patients (%)		
Through the day after angiography			
Major bleeding	23 (1.3)	19 (1.1)	0.64
Minor bleeding	17 (1.0)	9 (0.5)	0.17
Major or minor bleeding	40 (2.3)	28 (1.6)	0.18
Intracranial hemorrhage	8 (0.5)	12 (0.7)	0.38
At 30 days			
Major bleeding	33 (1.9)	30 (1.7)	0.80
Minor bleeding	27 (1.6)	16 (0.9)	0.12
Major or minor bleeding	59 (3.4)	46 (2.7)	0.24

* Safety end points were assessed in the treated population. The incidence of bleeding was ascertained through the calendar day after angiography and at 30 days. For patients who did not undergo angiography, the incidence of bleeding was ascertained through day 8 or hospital discharge, whichever came first. The prespecified primary bleeding end point was major bleeding, according to Thrombolysis in Myocardial Infarction (TIMI) criteria,[14] through the calendar day after angiography. TIMI-defined major bleeding includes intracranial hemorrhage.

cent myocardial infarction, recent stroke, or established peripheral arterial disease), patients who have undergone percutaneous coronary intervention, and patients with unstable angina or myocardial infarction that is not associated with ST-segment elevation.[9-11] We now extend those findings to patients with the most severe manifestation of atherosclerotic coronary artery disease: myocardial infarction that is associated with ST-segment elevation.

Since the use of aspirin, heparin, and fibrin-specific lytic therapy became established for myocardial infarction with ST-segment elevation in the late 1980s and early 1990s,[6,18,19] there have been many attempts to improve on this regimen, with little success. Newer fibrinolytic agents are equivalent but not superior to older fibrin-specific agents.[20,21] Aggressive antiplatelet therapy with glycoprotein IIb/IIIa inhibitors improves the rate of patency and reduces the risk of reinfarction, but at the cost of doubling the rates of major bleeding and, in patients older than 75 years of age, intracranial hemorrhage.[22,23] Low-molecular-weight heparin has emerged as an attractive alternative to unfractionated heparin in patients who have myocardial infarction with ST-segment elevation,[24] and the efficacy and safety of enoxaparin are currently being tested in a large clinical trial.[25] The benefit we observed with clopidogrel was equally apparent in patients treated with unfractionated heparin and patients who received low-molecular-weight heparin.

The trial was not powered to detect a survival benefit, and none was seen. However, we did observe consistent effects of clopidogrel in improving multiple angiographic outcomes and reducing ischemic events, all of which have been shown to be associated with improved long-term survival after myocardial infarction.[2,4,5,26-28] The use of protocol-driven angiography and its attendant high rate of revascularization in our trial may have attenuated the translation of the angiographic benefit into an immediate reduction in mortality. Whether a mortality benefit would emerge in the setting of fibrinolysis without mandatory angiography is the subject of a separate study specifically powered to assess mortality.[29]

We excluded patients who presented more than 12 hours after the onset of symptoms, those older than 75 years of age, and those with a history of coronary-artery bypass grafting. The efficacy and safety of adding treatment with clopidogrel to aspirin and fibrinolytic therapy in these groups remain to be established. There was a low rate of bleeding complications in our trial, most likely because of our emphasis on adherence to weight-based guidelines for heparin dosing.[13,30] Still, the administration of a fibrinolytic agent in conjunction with heparin and two antiplatelet agents must be performed with caution. As with any clinical trial, application of the results to a different population outside the setting of the trial should be done carefully.

In conclusion, we found that, in patients 75 years of age or younger who have myocardial infarction with ST-segment elevation and who receive fibrinolytic therapy, aspirin, and (when appropriate) weight-based heparin, clopidogrel offers an effective, simple, inexpensive, and safe means by which to improve the rate of patency of the infarct-related artery and to reduce the rate of ischemic complications.

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APPENDIX

The participants in the CLARITY–TIMI 28 study were as follows: *Operations Committee* — E. Braunwald (chair), C. Cannon (principal investigator), M. Sabatine (co–principal investigator), C. McCabe, A. McCagg, B. Job, C. Gaudin, I. Thizon-de Gaulle, M. Blumenthal, R. Saini, I. Delaet, L. Townes, D. Anhalt, K. van Holder, A. Skene, K. Hill; *Steering Committee* — E. Braunwald, C. Cannon, M. Sabatine, C. McCabe, B. Job, C. Gaudin, I. Thizon-de Gaulle, M. Blumenthal, R. Saini, I. Delaet, L. Townes, A. Skene, D. Ardissino, P. Aylward, M. Bertrand, C. Bode, A. Budaj, M. Claeys, M. Dellborg, R. Ferreira, A. Gershlick, K. Huber, M. Keltai, N. Kleiman, B. Lewis, J. Lopez-Sendon, J. Marx, G. Montalescot, J. Nicolau, Z. Ongen, E. Paolasso, J. Leiva Pons, M. Ruda, P. Theroux, F. Van de Werf, F. Verheugt, R. Wilcox, U. Zeymer; *TIMI Study Group* — E. Braunwald, C. Cannon, M. Sabatine, M. Gibson, C. McCabe, A. McCagg; *Sponsors*: Sanofi-Aventis (Paris) — B. Job, C. Gaudin, I. Thizon-de Gaulle; Bristol-Myers Squibb (Princeton, N.J.) — M. Blumenthal, R. Saini, J. Froehlich, I. Delaet, L. Townes, D. Anhalt, K. van Holder, A. Pieters; *Data Coordinating Center* (Nottingham Clinical Research Group, Nottingham, United Kingdom) — A. Skene, K. Hill, A. Charlesworth, M. Goulder, S. Stead; *Clinical Events Committee* — S. Wiviott (chair); *Physician Reviewers* — J. Aroesty, C. Berger, L. Garcia, D. Greer, D. Leeman, H. Lyle, G. Philippides, L. Schwamm; *TIMI Angiographic Core Laboratory* (Brigham and Women's Hospital, Boston) — M. Gibson (director), S. Marble, J. Aroesty, J. Buros, L. Ciaglo, A. Kirtane, A. Shui, A. Wilson; *TIMI Static Electrocardiographic (ECG) Core Laboratory* (Brigham and Women's Hospital, Boston) — B. Scirica (director), D. Morrow, R. Giugliano, S. Wiviott; *Biomarker Core Laboratory* (Brigham and Women's Hospital, Boston) — D. Morrow, P. Ridker, N. Rifai; *Genetics Core Laboratory* (Harvard–Partners Center for Genetics and Genomics, Cambridge, Mass.) — M. Sabatine, R. Kucherlapati, D. Kwiatkowski; *Continuous ECG Core Laboratory* (Brigham and Women's Hospital, Boston) — P. Stone (director), G. Maccallum, M. Lucier, A. Garriga; J. Anderson (chair), K. Fox, S. Kelsey; *Clinical Centers (grouped by countries, which are listed in order of number of patients enrolled)*: **Spain:** A. Batalla; E. Lopez de Sa y Areses; M. Fiol, A. Bethencourt; I. Lozano; J. Figueras; J. Guiterrez Cortés, A. Garcia Jimenez; A. Rivera Fernandez; I. Ferreira Montero, J. Casasnovas; F. Ortigosa Aso; R. Carbonell de Blas; J. Audicana; I. Echanove Errazti; J. Sala Montero, I. Rohlfs; C. Piñero; M. Martinez Rodriguez; L. Velasco Alvarez; A. Castro Belras, S. Barros; J. Diaz Fernández, A. Tobaruela; **France**: A. Bonneau, L. Soulat; Y. Lambert, J. Caussanel, B. Livareck, C. Ramaut, J. Ricome; F. Lapostolle, A. Beruben; F. Thieleux; J. Martelli, Etori; M. Martelet, J. Mouallem; F. Ahmed; D. Galley, S. Alhabaj, Strateman; D. Doucos; E. Bearez, S. Spetebroodt; C. Gully; J. Dujardin, B. Averland; B. Emmonot; D. Pollet, P. Vallet; R. Mossaz, A. Marquand; A. Kermarrec, C. Le Lay, R. Douillet; L. Olliver, O. Matas; **Canada:** S. Kassam, F. Halperin, P. Parsons, B. Bovak, B. Hart; B. Sussex, S. Newman; G. Gosselin, M. David; K. Sidhar, D. Wiseman; C. Lefkowitz, M. Thornley; R. Bhargava, A. McCullum; D. Grandmond, D. Carignan; S. Kouz, M. Roy; P. Polasek, V. Stedham; K. Lai, B. Paquette; D. Raco, M. Sayles; K. Sridhar, D. Wiseman; B. Tremblay, C. Darveau; B. Sussex, S. Newman; M. Senaratne, M. Holland; I. Bata, M. Hulan; C. Constance, S. Pouliot; D. Gossard, L. Day; A. Glanz, C. Vilag; W. Hui, L. Kvill; D. Dion, A. Morisette; F. Sandrin, S. Mitges; **Belgium:** F. Cools, S. Vanhagendoren; A. De Meester, O. Marcovitch; E. Allaf, F. Gits; J. Verrostte; J. Thoeng; M. Quinonez, H. Appeltants; G. D'Hooghe; M. Eycken, I. Swennen; G. Hollanders; E. Michaël; P. Decroly; E. Rombaut, D. Carlaire; D. Vermander; *St.* F. Marenne, C. Gavray; P. Michel, A. Poth; J. Paquay, S. Lutasu; D. Dirk; J. Vermeulen, E. Govaerts; **Russia**: S. Boldueva; A. Sherenkov; M. Ruda; V. Kostenko; S. Tereschenko; G. Zalevsky; M. Boyarkin; B. Tankhilevitch; M. Glezer; N. Gratsiansky; E. Shlyakhto; B. Sidorenko; V. Zadiontchenko; N. Perepech; A. Gruzdev; S. Chernov; **Germany**: B. Pollock; D. Andresen, S. Hoffmann; D. Andresen; H. Arntz; H. Klein; H. Neuss; E. Wilhelms; R. Henzgen, H. Kuckuck; H. Darius, C. Hausdorf; H. Ochs; H. Olbrich; R. Willenbrock; A. Hepp, P. Wucherpfennig; H. Wiechmann, H. Schmidtendorf; B. Kohler; W. Sehnert; A. Ueberreiter; R. Uebis, M. Stockmann; U. Rommele; A. Meissner; L. Schneider; **United Kingdom**: J. Adgey, T. McAllister; D. McEneaney, A. Mackin; N. Sulke, R. Dixon; R. Wilcox, S. Congreave; A. Flapan, L. Flint; J. Purvis, G. McCorkell; P. Stubbs, C. Steer, P. McKee; R. Senior, L. Chester; T. Levy, S. Kennard; A. Bishop, S. Hlaing; M. de Belder, N. Cunningham; T. Gilbert, J. Young; R. Henderson, D. Falcoln-Lang; A. Gershlick, K. Fairbrother; **Israel**: T. Rosenfeld, S. Atar; B. Lewis, R. Yuval; S. Meisel, I. Alony; Y. Rozenman, S. Logrineuko; E. Goldhammer, S. Harel; D. David, N. Erez; J. Jafari, O. Tubul; A. Marmor, L. Pritulo; A. Caspi, N. Roitberg; E. Kaluski, R. Amar; D. Tzivoni, A. Rojanski, S. Yedid-Am; A. Keren, L. Datiashvily; **Brazil:** J. Kerr Saraiva, C. Travaini Garcia; M. Markman, A. Chaves; R. Cecin Vaz, O. Dutra; O. Rizzi Coelho, R. Sciampaglia; C. Pereira da Cunha, M. Ribas de Brito; P. Lotufo, E. Ribeiro; A. Cicogna; Y. Lage Michalaros, C. Eduardo Ornellas; S. Carlos de Moreas Santos, P. Rosatelli; W. Pimentel Filho, M. Grudzinski; F. Guimaraes Filho, C. Gustavo; M. Moreira, J. Gosmao; **the Netherlands:** D. Hertzberger, A. Schut; C. van der Zwaan, H. Havenaar; J. van Wijngaarden, H. Verheij; E. Wajon, M. Bosschaart; A. Oomen; M. Daniëls, A. Coppes; F. Vergeught, H. Dieker; D. Jochemsen, I. Fijlstra; C. Leenders, T. Gelder; **United States:** D. Janicke, J. Bass; G. Hamroff, K. Keeler; M. Chandra, B. Van Hoose; S. Minor, P. Mock; M. Chandra, M. Olliges; A. Unwala, C. Fisher; W. French, O. Barillas; H. Chandna, D. Holly; H. Chandna, D. Holly; G. Grewal, L. Gurnsey; P. Mehta, A. Cruse; R. Perlman, D. Palazzo; J. Puma, C. Payne; J. Torres, L. Patten; L. Lefkovic, N. Viswanathan; A. Rees, A. Yoches; L. Rodriguez-Ospina, J. Santos; A. Chohan, A. Kemp; R. Perlman, D. Palazzo; R. Weiss, B. Brennan; Y. Aude, P. Harrison; G. Brogan, J. Ayan; D. Cragg, A. Murawka; M. Garg, J. McKelvy; A. Hulyalkar, C. Kuchenrither; S. Jackson, J. Whitaker, J. Richardson; R. Vicari, M. Howard; Y. Aude, P. Harrison; H. Chadow, R. Hauptman; J. Gelormini, T. Giambra; N. Lakkis, S. Jiang; **Mexico:** I. Hernandez, A. Vazquez; E. Lopez Rosas; J. Cortes Lawrenz, F. Bustamante; C. Arean Martinez; M. Antonio Alcocer, E. Garcia Hernandez; C. Wabi Dogre, M. de Los Reyes Barrera Bustillos; R. Alvarado, M. Casares Ramirez; P. Hinojosa, O. Omar Rivera; J. Leiva Pons, J. Carrillo; J.A. Velasco, F. Quintana; F. Petersen, R. Palomera; M. Ibarra, C. Jerjes Sanchez; L. Delgado, E. Bayram; G. Mendez Machado; **Argentina:** M.A. Berli, J.C. Vinuela; O. Allall, V. Fuentealba, M. Reguero; G. Covelli, E. San Martin, E. Francia; F. Gadaleta, M. Haehnel; R. Iglesias, S. Blumberg; A. Alves de Lima, R. Henquin; J. Navarro Estrada, D. de Arenaza; R. Fernandez, M. Abud, C. Becker; R. Milesi, R. Schamuck, J. Manuel Doyharzabal; D.G. Caime, L.C. Teresa; E. Kuschnir, H. Sgammini, J. Sgammini, J. David; C.H. Sosa, E. Redcozub, V. Avalos; D. Nul, S. Ramos, P. T. Castro; A. Rodriguez, C. Sosa; J. Gant Lopez,

F. Novo; F. Diez; R. Piraino, G. Godoy, C. Weller; J. Pomposiello; A. Sanchez; **Sweden**: J. Karlsson, K. Collberg; K. Malmqvist, E. Cedergren; M. Dellborg, G. Coops; A. Kallryd, P. Laudon; S. Bandh, C. Andersson; S. Soome, H. Classon; J. Lugnegard, H. Ahlmark; M. Risenfors, L. Ortgren; B. Fjelstad, S. Osberg; J. Frisell, M. Sandstrom; **Italy**: O. Silvestri, A. Sasso; A. Rolli, G. Paoli; F. Chiarella, L. Olivotte; B. Doronzo, A. Coppolino; G. Pivoccari, A. Pesaresi; G. Ambrosio, M. Del Pinto; I. De Luca, M. Laico; G. De Ferrari, E. Baldini; U. Guiducci, G. Tortorella; M. Romano, R. Villani; F. Casazza, A. Capozi; L. Moretti, M. Del Pinto; S. Perelli; G. Sinagra, P. Maras; M. Porcu, G. Scorcu; F. Proietti; S. Severi; **Poland:** J. Gessek, L. Pawlowicz; R. Szelemej, M. Gorski; M. Janion, J. Sielski; A. Kleinrok, J. Rodzik; J. Hiczkiewicz; M. Mikulicz Pasler, M. Soltsiak; J. Gorny; **Austria:** K. Huber, N. Jordanova; M. Heigert, K. Kopp; H. Frank; A. Laggner, W. Schreiber; W. Weihs; M. Heinz Drexel; **South Africa:** A. Doubell, L. Burgess; J. Bennett, F. Snyders; I. Ebrahim, C. Bobak; J. Marx, M. deBeer; S. Schmidt, H. Cyster; P. van der Berg, W. Groenewald; L. Herbst, A. Britz; M. Snyman, M. Schonken; J. Badenhorst, P. Blomerus; M. Mpe, C. Bobak; J. Mynhardt, C. Groenewald; C. van Dyk, J. Meiring; L. Steingo, L. Glaeser; **Australia:** A. Whelan, G. Tulloch; B. Gunalingham, B. Conway; A. Soward, S. Hales; J. Lefkovits, M. Sallaberger; D. Owesby, J. Kesby; J. Amerena, K. Fogarty; D. Chew, M. Austin, S. Kovaricek; N. Banham, G. Tulloch; **Hungary**: L. Jobbagy; J. Dinnyes; J. Lippai; B. Oze; I. Szakal; G. Bartal, A. Foldi; **Ireland**: D. Foley, F. McGrath; B. Meany, M. Geraghty; K. Daly, S. Henessey; N. Mulvihill, C. Schilling; P. Kearney, P. Kelly; P. Kearney, P. Kelly; **Turkey**: Z. Ongen, A. Vura; O. Kozan, E. Ozaydin; H. Kultursay, M. Kayikcioglu; M. Degertekin, B. Mutlu; **Portugal**: F. Monteiro; D. Ferreira; M. Carrageta.

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