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

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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.

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*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.

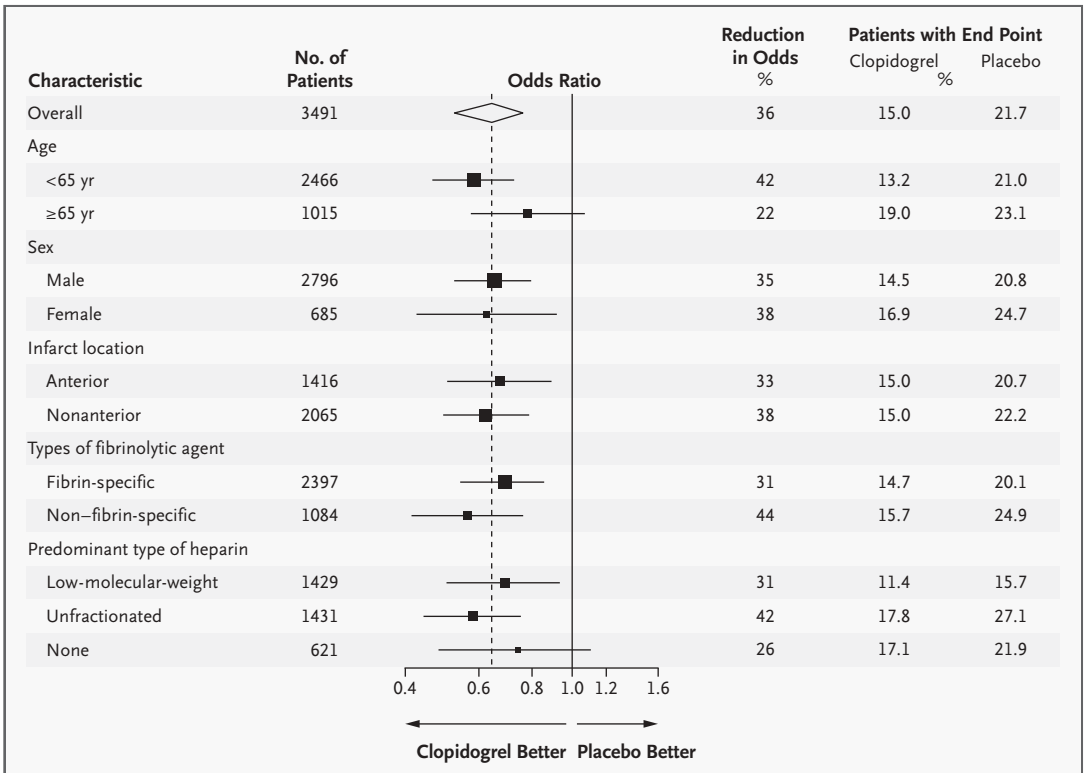


Figure 1. Rates of and Odds Ratios for the Primary Efficacy End Point Overall and in Various Subgroups.

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

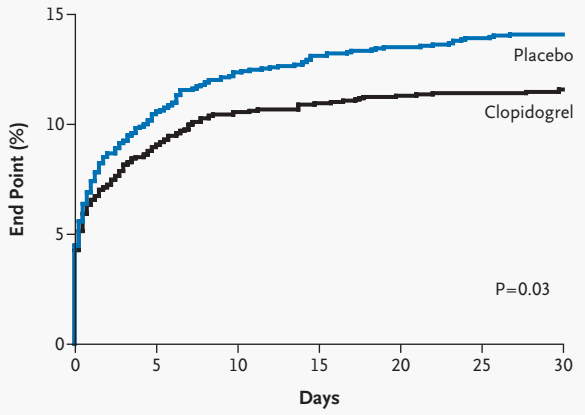


Figure 2. Cumulative Incidence of the End Point of Death from Cardiovascular Causes, Recurrent Myocardial Infarction, or Recurrent Ischemia Leading to the Need for Urgent Revascularization.

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).

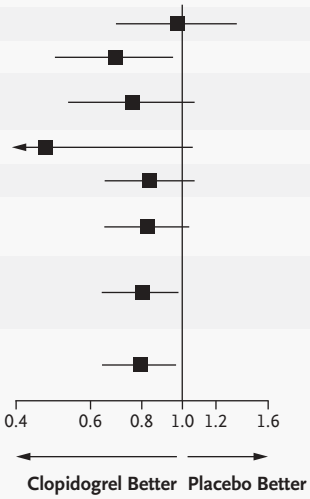
to 11.7 percent; 41 percent reduction in the odds; P<0.001) and the rate of recurrent myocardial infarction (reducing it from 3.6 to 2.5 percent; 30 percent reduction in the odds; P=0.08), but it had no significant effect on the rate of death from any cause (2.2 percent in the placebo group vs. 2.6 percent 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

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REFERENCES

1. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: Phase I findings. N Engl J Med 1985;312:932-6.

2. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-22. [Erratum, N Engl J Med 1994;330:516.]

3. Braunwald E. The open-artery theory is alive and well — again. N Engl J Med 1993;329:1650-2.

4. Dalen JE, Gore JM, Braunwald E, et al. Six- and twelve-month follow-up of the phase I Thrombolysis in Myocardial Infarction (TIMI) trial. Am J Cardiol 1988;62:179-85. [Erratum, Am J Cardiol 1988;62:1151.]

5. Ohman EM, Califf RM, Topol EJ, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. Circulation 1990;82:781-91.

6. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349-360.

7. Meijer A, Verheugt FW, Werter CJ, Lie KI, van der Pol JM, van Eenige MJ. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study: results of the APRICOT Study. Circulation 1993;87:1524-30.

8. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999;100:1667-72.

9. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.

10. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20. [Erratum, JAMA 2003;289:987.]

11. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. [Erratum, N Engl J Med 2001;345:1506, 1716.]

12. Sabatine MS, McCabe CH, Gibson CM, Cannon CP. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 trial. Am Heart J 2005;149:227-33.

13. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for the Management of Patients with Acute Myocardial Infarction. Circulation 2004;110:e82-e292.

14. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. Ann Intern Med 1991;115:256-65.

15. Yasuda T, Gold HK, Leinbach RC, et al. Lysis of plasminogen activator-resistant platelet-rich coronary artery thrombus with combined bolus injection of recombinant tissue-type plasminogen activator and antiplatelet GPIIb/IIIa antibody. J Am Coll Cardiol 1990;16:1728-35.

16. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:234S-264S.

17. Herbert JM, Dol F, Bernat A, Falotico R, Lale A, Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. Thromb Haemost 1998;80:512-8.

18. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397-402.

19. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.

20. The Global Use of Strategies to Open Occluded Coronary Arteries. (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med 1997;337:1118-23.

21. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.

22. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial. Circulation 1999;99:2720-32.

23. Topol EJ, GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001;357:1905-14.

24. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001; 358:605-13.

25. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST elevation MI: design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction–Study 25 (ExTRACT–TIMI 25). Am Heart J 2005;149:217-26.

26. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125-30.

27. Mueller HS, Forman SA, Menegus MA, Cohen LS, Knatterud GL, Braunwald E. Prognostic significance of nonfatal reinfarction during 3-year follow-up: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II clinical trial. J Am Coll Cardiol 1995;26:900-7.

28. Cannon CP, Sharis PJ, Schweiger MJ, et al. Prospective validation of a composite end point in thrombolytic trials of acute myocardial infarction (TIMI 4 and 5): Thrombosis in Myocardial Infarction. Am J Cardiol 1997; 80:696-9.

29. Second Chinese Cardiac Study (CCS-2) Collaborative Group. Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. J Cardiovasc Risk 2000;7: 435-41.

30. Giugliano RP, McCabe CH, Antman EM, et al. Lower-dose heparin with fibrinolysis is associated with lower rates of intracranial hemorrhage. Am Heart J 2001;141: 742-50.

Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial

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Summary

Background Despite improvements in the emergency treatment of myocardial infarction (MI), early mortality and morbidity remain high. The antiplatelet agent clopidogrel adds to the benefit of aspirin in acute coronary syndromes without ST-segment elevation, but its effects in patients with ST-elevation MI were unclear.

Methods 45 852 patients admitted to 1250 hospitals within 24 h of suspected acute MI onset were randomly allocated clopidogrel 75 mg daily (n=22 961) or matching placebo (n=22 891) in addition to aspirin 162 mg daily. 93% had ST-segment elevation or bundle branch block, and 7% had ST-segment depression. Treatment was to continue until discharge or up to 4 weeks in hospital (mean 15 days in survivors) and 93% of patients completed it. The two prespecified co-primary outcomes were: (1) the composite of death, reinfarction, or stroke; and (2) death from any cause during the scheduled treatment period. Comparisons were by intention to treat, and used the log-rank method. This trial is registered with ClinicalTrials.gov, number NCT00222573.

Findings Allocation to clopidogrel produced a highly significant 9% (95% CI 3–14) proportional reduction in death, reinfarction, or stroke (2121 [9·2%] clopidogrel *vs* 2310 [10·1%] placebo; p=0·002), corresponding to nine (SE 3) fewer events per 1000 patients treated for about 2 weeks. There was also a significant 7% (1–13) proportional reduction in any death (1726 [7·5%] *vs* 1845 [8·1%]; p=0·03). These effects on death, reinfarction, and stroke seemed consistent across a wide range of patients and independent of other treatments being used. Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel, either overall (134 [0·58%] *vs* 125 [0·55%]; p=0·59), or in patients aged older than 70 years or in those given fibrinolytic therapy.

Interpretation In a wide range of patients with acute MI, adding clopidogrel 75 mg daily to aspirin and other standard treatments (such as fibrinolytic therapy) safely reduces mortality and major vascular events in hospital, and should be considered routinely.

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Introduction

About 10 million people have heart attacks every year worldwide and the incidence of myocardial infarction (MI) is rising in many developing countries.[1] Although considerable improvements have been made in the emergency treatment of acute MI, appreciable risks of early mortality and morbidity remain, especially in populations with limited health resources. If simple and widely practicable treatments for acute MI can be shown reliably to produce even moderate improvements in outcome, then the worldwide benefits could be substantial.

Platelet activation and aggregation, which can be mediated by thromboxane or by ADP, play a key part in initiating and propagating coronary thrombosis, and are raised during MI (particularly after fibrinolytic therapy). Aspirin started soon after acute MI and continued for a few weeks has been shown to reduce 1-month mortality by about a quarter and the risks of non-fatal reinfarction and stroke by about half.[2] Platelet aggregation is only inhibited in part by aspirin, which acts mainly by blocking the thromboxane-mediated aggregation pathway. Clopidogrel (like its predecessor ticlopidine) acts mainly by inhibiting the ADP-mediated aggregation pathway,[3,4] and has also been shown to be effective at preventing ischaemic events in patients with symptomatic atherothrombotic disease.[5] Simultaneous inhibition of both of these pathways with the combination of clopidogrel (or ticlopidine) and aspirin should produce greater antiplatelet effects than either agent alone.[6,7]

Compared with aspirin alone, results of randomised trials have shown that clopidogrel plus aspirin reduces the risk of ischaemic events in patients undergoing percutaneous coronary intervention (PCI), and in those with non-ST-elevation acute coronary syndromes.[8,9] More recently, the findings of a randomised trial of about 3500 patients with ST-elevation MI showed that adding clopidogrel to aspirin improved the patency of the infarct-related coronary artery after fibrinolytic therapy, and suggested some reduction in clinical events.[10] But substantial uncertainty remained regarding the net effects on mortality and major morbidity of adding clopidogrel to aspirin in this setting. The aim of this study was to address these issues.

Methods

COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial; also Second Chinese Cardiac Study [CCS-2]) is a randomised placebo-controlled trial of the emergency treatment of patients with suspected acute MI. It used a 2×2 factorial design to allow separate assessment of the efficacy and safety of adding oral clopidogrel to aspirin and of using intravenous then oral metoprolol. Details of the study objectives, design, and methods have been reported previously,[11] and are summarised below. (Results for the metoprolol comparison are reported separately.[12])

Patients

Recruitment took place between August, 1999, and February, 2005. Patients who presented with ST elevation, left-bundle branch block, or ST depression within 24 h of the onset of the symptoms of suspected acute MI were potentially eligible for the study, provided that their responsible physician did not consider them to have clear indications for, or contraindications to, any of the study treatments. Patients scheduled for primary PCI were to be excluded because the combined use of aspirin plus clopidogrel (or ticlopidine) was likely to be considered indicated. Otherwise, the exact reasons for excluding patients were determined by the responsible physician based on general guidance in the protocol, and included: either small likelihood of worthwhile benefit in hospital (eg, other life-threatening disease or unconvincing history of MI) or high risk of adverse effects with the study treatments. Criteria for a high risk of adverse effects with antiplatelet therapy would generally have included previous allergy to aspirin, active bleeding, or history of a haemostatic disorder (whereas for metoprolol they would generally have included persistently low blood pressure or heart rate, high-degree heart block, or cardiogenic shock[12]).

Written or witnessed oral informed consent was obtained from potentially eligible patients, and no payments to patients were made for participation. Before the start of the study, approval was obtained from the Chinese Ministry of Health, the Chinese State Food and Drug Administration, and the central ethics committee of the Chinese Academy of Medical Sciences. All collaborating hospitals also obtained approval from a local ethics committee or institutional research review board. Collaborating hospitals were reimbursed only nominally for recruitment of eligible patients.

Procedures

Random allocation of the study treatments at participating hospitals was achieved by use of sealed study treatment cases, each containing eight sequentially numbered packs of randomly allocated study treatments, which were prepared centrally by the coordinating centres in Oxford and Beijing. To randomise a patient, the next available treatment pack in the sequence was removed from an opening at the bottom of the treatment case, and the one-page entry form attached to the outside of that pack completed and returned to the national coordinating centre in Beijing (along with the presenting ECG, which was reviewed by a cardiologist). This treatment pack was then opened and the 4-week calendar pack of aspirin tablets plus clopidogrel or placebo tablets removed (along with three metoprolol or placebo ampoules for intravenous injection and a 4-week calendar pack of metoprolol or placebo tablets[12]). The first two antiplatelet tablets (aspirin 162 mg plus either clopidogrel 75 mg or matching placebo) were to be given immediately. Subsequently, two more such tablets were to be given once daily for up to 4 weeks (or, if earlier, until hospital discharge or death), unless some definite contra-indication was thought to have arisen. All other aspects of the patients' management were entirely at the discretion of their responsible doctors, except that non-study antiplatelet therapy (and non-study β blocker[12]) was to be avoided during the scheduled treatment period unless it was believed that some strong indication had developed (eg, elective PCI). For patients receiving fibrinolytic therapy, treatment was generally started before randomisation.

At the first discharge from hospital or at day 28 (whichever came first), a single-sided follow-up form was to be completed and returned to the national coordinating centre in Beijing. This form provided brief details of compliance with the study treatments, use of other concomitant therapies in hospital, possible side-effects of the study treatments, major clinical events, and, if dead before discharge, the probable main cause of death. After the first hospital discharge (or day 28), no further follow-up was sought. Post-discharge use of aspirin, β blocker, and other established therapies for the secondary prevention of major vascular events was encouraged but not monitored.

The two prespecified co-primary outcomes for assessment of the efficacy of clopidogrel were: the composite of death, reinfarction, or stroke; and death from any cause during the scheduled treatment period (ie, until first discharge or day 28). Strokes were categorised according to their likely type (probably haemorrhagic; or ischaemic or unknown) and residual handicap (none; minor or moderate; or severe). For assessment of the safety of clopidogrel, haemorrhagic stroke and major non-cerebral bleeding (defined as bleeding that required transfusion or was fatal) were grouped together as life-threatening bleeding (although haemorrhagic stroke and fatal non-cerebral bleeding were already included in the co-primary efficacy outcomes). All the main efficacy and safety outcomes were reviewed and, if necessary, additional information sought to allow adjudication (without knowledge of the study treatment allocation) by clinical staff in the coordinating centres. Confirmation of reinfarction

within the first 24 h after the initial MI required evidence of recurrent typical chest pain and persistent ischaemic ECG changes; subsequent reinfarction required recurrent typical chest pain with characteristic new ECG changes or a further increase in enzyme levels. Suspected ECG changes were to be sent to the trial office in Beijing for central review, blind to the treatment allocation, by a cardiologist who accepted only those that involved new Q-waves or ST-segment elevation. (Enzyme changes were not, in general, reviewed centrally unless the ECG evidence was ambiguous.) New ECG evidence was available for 95% of 600 unrefuted non-fatal reinfarctions and 91% of 432 fatal reinfarctions. CT scans or MRI were available for 77% of 269 unrefuted non-fatal strokes and for 36% of 198 fatal strokes. Irrespective of the diagnostic criteria, any relevant event that was reported and not refuted was included in the analyses.

The main prespecified subsidiary comparisons were to be of the effects of clopidogrel on the co-primary outcomes during days 0–1, 2–7, and day 8 to the end of the scheduled treatment period. Other prespecified subsidiary comparisons were of the effects on the primary composite outcome in certain subgroups (eg, age, delay from symptom onset, use of fibrinolytic therapy, prognostic index defined from baseline characteristics during the final analyses).[11] For the many further analyses that might be undertaken, due allowance was to be made for their exploratory (and, perhaps, data-dependent) nature.

Statistical analysis

The original aim was to recruit 20 000–40 000 patients, depending on what proved practicable.[11] Based on a previous study in similar patients in China,[13] the placebo-group event rate for the primary composite outcome had been anticipated to be about 14% (10% death plus 4% non-fatal reinfarction or stroke), and a reduction of one tenth in this risk was hoped for.[11] During the study, however, the event rate in both treatment groups combined was only 10% (8% fatal plus 2% non-fatal). Hence, to have at least 95% statistical power to detect a reduction of one tenth with a two-sided p value of 0·05, at least 45 000 patients needed to be recruited. In 2003, therefore, the decision was made (blind to any interim treatment differences) that full recruitment would continue until the start of the Chinese spring festival in February, 2005. By that time, 45 852 patients had been randomised.

The data analysis plan was prespecified in the original protocol[11] and in amendments made by the principal investigator and study co-chairs before any analyses of the effects of the study treatments were available to them. All analyses involve comparisons based on the randomly allocated treatments (ie, intention-to-treat[14]) of outcomes occurring after randomisation and before first discharge from hospital (or day 28, if earlier). The main comparisons involve log-rank analyses of the two co-primary endpoints, some of which are illustrated by Kaplan-Meier survival curves. These graphs show, for the first 28 days after randomisation, the proportions of patients who had a relevant event before first discharge. The statistical analyses do not censor patients at discharge, because discharged patients cannot, by definition, have a trial endpoint thereafter. Because there are two co-primary endpoints, the protocol specified that if the overall p value was more extreme for death than for the composite outcome, then only the p value for the composite would be used in assessing the significance of the effects on mortality.[11]

During the study period, interim analyses of efficacy and safety were done yearly for the independent data monitoring committee. In the light of those analyses and the results of any other relevant studies, that committee was to advise the steering committee if, in their view, the randomised comparisons in the study had provided both: (1) proof beyond reasonable doubt that, either for all patients or for some specific type of patient, use of clopidogrel was clearly indicated or clearly contra-indicated in terms of a net difference in all-cause mortality; and (2) evidence that might reasonably be expected to affect materially the management of patients by many clinicians who were already aware of any other relevant study results then available. In general, the data monitoring committee would have required a difference of at least 3 SD in an interim analysis of mortality to justify halting or modifying such a study prematurely.[11] (This condition means that these multiple interim analyses would have no material effect on a moderate p value for mortality,[14] and no effect at all on any other p values.) Since the study was not stopped prematurely, the investigators (except those doing the confidential analyses) and the funding agencies remained unaware of the results on mortality and major morbidity until completion of the study.

Quality control procedures

During the trial, central destructive testing (for laboratory analysis of the study medication) was undertaken on the contents of one study case chosen at random at least once every other month, as well as on

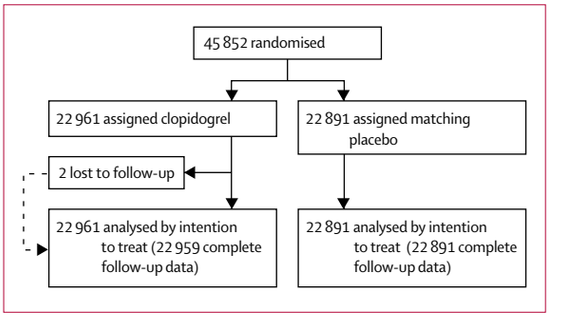


Figure 1: **Trial profile**

See http://www.commit-ccs2.org

	Clopidogrel (n=22 961)	Placebo (n=22 891)
Age at entry (years)		
<60	9624 (41·9%)	9463 (41·3%)
60–69	7361 (32·1%)	7470 (32·6%)
⩾70	5976 (26·0%)	5958 (26·0%)
Mean (SD)	61·3 (11·9)	61·4 (11·8)
Sex		
Female	6366 (27·7%)	6393 (27·9%)
Time since onset (h)		
<6	7745 (33·7%)	7707 (33·7%)
6 to <13	7567 (33·0%)	7505 (32·8%)
13–24	7649 (33·3%)	7679 (33·5%)
Mean (SD)	10·3 (6·7)	10·3 (6·7)
Systolic blood pressure (mm Hg)		
<120	7690 (33·5%)	7709 (33·7%)
120–139	8092 (35·2%)	8108 (35·4%)
140–159	4549 (19·8%)	4471 (19·5%)
⩾160	2630 (11·5%)	2603 (11·4%)
Mean (SD)	128·2 (22·6)	128·2 (22·5)
Heart rate (bpm)		
<70	5094 (22·2%)	5043 (22·0%)
70–89	11 101 (48·3%)	11 161 (48·8%)
90–109	5140 (22·4%)	5069 (22·1%)
⩾110	1626 (7·1%)	1618 (7·1%)
Mean (SD)	82·2 (17·2)	82·1 (17·2)
ECG abnormality at entry		
ST elevation	19 877 (86·5%)	19 878 (86·9%)
Bundle branch block	1505 (6·6%)	1423 (6·2%)
ST depression (without ST elevation)	1579 (6·9%)	1590 (6·9%)
Killip class		
I	17 320 (75·4%)	17 283 (75·5%)
II or III	5641 (24·6%)	5608 (24·5%)
Previous disease and drug use		
Previous MI	1972 (8·6%)	1846 (8·1%)
Previous hypertension	9935 (43·3%)	9903 (43·3%)
Aspirin before admission	4214 (18·4%)	4230 (18·5%)
β blocker before admission	1457 (6·3%)	1533 (6·7%)
Fibrinolytic agent before randomisation	11 407 (49·7%)	11 387 (49·7%)
Non-trial treatment during hospital stay		
Non-trial antiplatelet	2305 (10·0%)	2280 (10·0%)
Fibrinolytic agents before or after entry	12 468 (54·3%)	12 499 (54·6%)
Anticoagulant	17 022 (74·1%)	17 157 (75·0%)
Antiarrhythmic	5150 (22·4%)	5093 (22·2%)
ACE inhibitor	15 649 (68·2%)	15 638 (68·3%)
Nitrate (oral or intravenous)	21 615 (94·1%)	21 590 (94·3%)
Diuretic	5344 (23·3%)	5344 (23·3%)
Calcium antagonist	2701 (11·8%)	2705 (11·8%)

Data are number (%) unless otherwise indicated.

Table 1: **Baseline characteristics and concomitant treatment in hospital**

two drug packs from each of the four treatment groups during each of the six drug packaging cycles; no problems were identified with the 312 study drug packs so tested (each contained what it should have). Extensive checks and central monitoring of the data took place throughout the course of the trial. All forms were registered and checked manually before being double-entered at the national coordinating centre in Beijing, and queries or missing items were reported back to the relevant hospital for clarifications. The data were transmitted on a weekly basis to the international coordinating centre in Oxford for computerised checks, coding, and central monitoring. The clinical coordinator in Oxford reviewed any queries generated by these checks, and those that could not be resolved centrally were returned to the relevant hospital for correction or confirmation.

On-site audits were done at 300 hospitals selected on the basis of either the large number recruited or central statistical monitoring, and at 44 other randomly selected hospitals. In every hospital, the coordinating centre chose about ten randomised patients (about half of whom had had relevant events) for review. For the 3237 patients audited, no material discrepancies were noted between the study records and the hospital notes in terms of patients' characteristics and the main clinical events; in particular, mortality (1035 deaths) was always correctly reported, and about 98% of reported reinfarctions or strokes (384 cases) were also identified in the notes. Although these audited patients accounted for only 7% of all randomised patients, the 344 audited hospitals together randomised 66% of all study patients, and so suffice to show that the study was generally well done. Two hospitals required special investigation because central monitoring identified unusually low event rates and rapid increases in the recruitment rate, and these were found to have deliberately entered some non-cardiac patients or invented some patients. No deaths, no strokes, and only one reinfarction were recorded in the 189 entries from these two hospitals; all data from them have been excluded from the study analyses. This trial is registered with Clinical Trials.gov, number NCT00222573.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The writing committee had final responsibility for the decision to submit for publication.

Results

45 852 patients with suspected acute MI were randomised from 1250 hospitals in China to receive aspirin 162 mg daily plus either clopidogrel 75 mg daily (n=22 961) or matching placebo (n=22 891) for up to 28 days in hospital. Follow-up to first hospital discharge or day 28 was available for all but two patients (figure 1). The qualifying MI was confirmed by the local investigators in 95·8% (n=22 002 clopidogrel and n=21 946 placebo) of randomised patients, with a further 1·8% (410 and 404) diagnosed as possible MI, 1·3% (288 and 308) as unstable angina, and 1·1% (259 and 233) as other vascular or non-vascular conditions. Irrespective of the final diagnosis, all randomised patients were included in intention-to-treat comparisons of outcome.

Patients' characteristics

The large sample size ensured good balance between the two treatment groups with respect to baseline

characteristics (table 1). Mean age was 61 years, with 11 934 (26%) patients aged 70 years or older at entry, and 12 759 (28%) women enrolled. Mean time from symptom onset was 10 h, with 15 452 (34%) patients randomised within 6 h. The presenting ECG showed ST elevation in 39 755 (87%) patients and bundle branch block in 2928 (6%), with the remainder having ST depression alone. Previous MI was recorded in 3818 (8%) patients and hypertension in 19 838 (43%). Aspirin had been used before hospital admission by 8444 (18%) patients. Fibrinolytic therapy (chiefly urokinase) had been received by 22 794 (50%) patients just before randomisation, and by a total of 24 967 (54%) at some time before or after randomisation. During the hospital stay, 4585 (10%) patients received non-study antiplatelet therapy, and 34 179 (75%) received anticoagulant therapy (chiefly heparin). No significant differences were noted between the patients allocated clopidogrel and those allocated matching placebo in the use of these or other non-study treatments recorded during the hospital stay.

There was no significant difference between the treatment groups in the number of patients who completed their allocated study antiplatelet treatment (table 2), and the mean treatment duration in survivors in both groups was 14·9 days (quartiles: 9, 14, and 21 days). The two most common reasons for discontinuation of treatment were bleeding or other possible side-effects and elective angioplasty, but there were no significant differences between the treatment groups in these or other reasons for stopping (table 2).

	Clopidogrel (n=22 961)	Placebo (n=22 891)
Compliance		
Not started at all	109 (0·5%)	116 (0·5%)
First pair of tablets taken	22 441 (97·7%)	22 355 (97·7%)
Treatment completed	21 243 (92·5%)	21 210 (92·7%)
Main reason for discontinuation		
Not MI	103 (0·4%)	90 (0·4%)
Bleeding or other side-effects	549 (2·4%)	494 (2·2%)
Elective PCI	684 (3·0%)	713 (3·1%)
Patient wishes	40 (0·2%)	35 (0·2%)
Other	233 (1·0%)	233 (1·0%)
Any	1609 (7·0%)	1565 (6·8%)
Mean (SD) scheduled treatment duration (days)*	14·9 (7·9)	14·9 (7·8)

Data are number (%) unless otherwise indicated. *Restricted to those discharged alive before day 28, or still alive and not discharged by day 28.

Table 2: **Compliance and reasons for discontinuation of trial treatment**

Primary and other efficacy outcomes

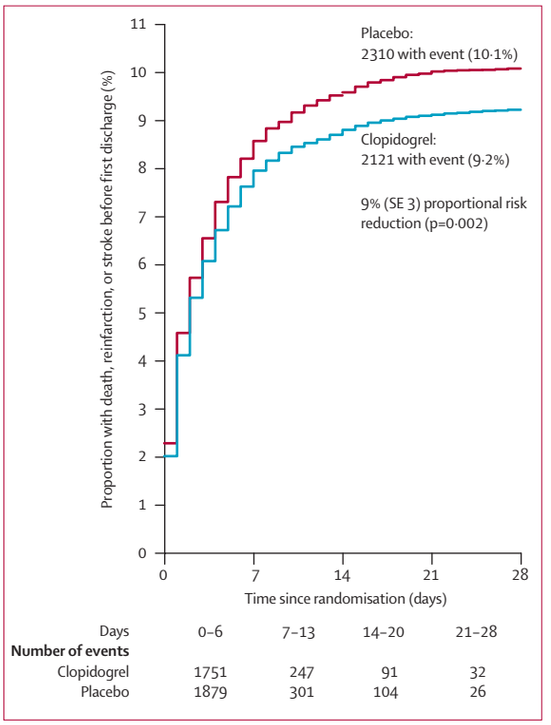
Both of the co-primary outcomes were significantly reduced during the scheduled treatment period by allocation to clopidogrel. For the primary composite outcome of death, reinfarction, or stroke, 2121 (9·2%) patients had at least one such event among the 22 961 clopidogrel-allocated patients compared with 2310 (10·1%) among the 22 891 allocated matching placebo, which corresponds to a highly significant 9% (95% CI 3–14; p=0·002) proportional reduction with clopidogrel (table 3 and figure 2). For the co-primary outcome of death alone, there were 1726 (7·5%) events in the clopidogrel group versus 1845 (8·1%) in the placebo group, corresponding to a significant 7% (1–13; p=0·03) proportional reduction (table 3 and figure 3). The flatness of the right-hand ends of the graphs is because any events after discharge were not recorded; if information on events after discharge had been sought and included, the absolute 28-day risks would have been bigger than those shown. In absolute terms, about 2 weeks of clopidogrel 75 mg daily was associated with nine (SE 3) fewer patients with death, reinfarction, or stroke in hospital per 1000 allocated treatment (figure 4).

Allocation to clopidogrel produced a significant 14% (95% CI 3–24) proportional reduction in the risk of any (fatal or not) reinfarction during the scheduled treatment period (table 3). Although the proportional reduction seemed to be somewhat greater for non-fatal reinfarction (19% [SE 7]) than for fatal reinfarction (7% [SE 9]), the difference between these effects was not significant (heterogeneity p=0·28). Clopidogrel was associated with a non-significant 14% (SE 9) proportional reduction in the risk of stroke (217 [0·9%] *vs* 250 [1·1%]; p=0·11). This finding reflected a 16% (SE 10) reduction

	Clopidogrel (n=22 961)	Placebo (n=22 891)	Odds ratio (95% CI)	p
Primary outcome				
Death, reinfarction, or stroke	2121 (9·2%)	2310 (10·1%)	0·91 (0·86–0·97)	0·002
Death, any cause*	1726 (7·5%)	1845 (8·1%)	0·93 (0·87–0·99)	0·03
Arrhythmia	432 (1·9%)	454 (2·0%)		
Asystole	642 (2·8%)	697 (3·0%)		
Cardiac rupture	188 (0·8%)	210 (0·9%)		
Cardiogenic shock	503 (2·2%)	562 (2·5%)		
Reinfarction	113 (0·5%)	101 (0·4%)		
Stroke	72 (0·3%)	87 (0·4%)		
Other	92 (0·4%)	103 (0·4%)		
Secondary outcome				
Reinfarction				
Died, any cause	209 (0·9%)	223 (1·0%)	0·93 (0·77–1·13)	0·46
Survived†	270 (1·2%)	330 (1·4%)	0·81 (0·69–0·95)	0·01
All	479 (2·1%)	553 (2·4%)	0·86 (0·76–0·97)	0·02
Stroke				
Ischaemic (or unknown)	164 (0·7%)	194 (0·8%)	0·84 (0·68–1·03)	0·10
Haemorrhagic	55 (0·2%)	56 (0·2%)	0·98 (0·67–1·42)	0·90
Died, any cause	90 (0·4%)	108 (0·5%)	0·83 (0·63–1·10)	0·19
Survived†	127 (0·6%)	142 (0·6%)	0·89 (0·70–1·13)	0·33
All‡	217 (0·9%)	250 (1·1%)	0·86 (0·72–1·03)	0·11
Other outcome				
Cardiogenic shock	983 (4·3%)	1043 (4·6%)	0·94 (0·86–1·02)	0·15
Heart failure	3033 (13·2%)	3093 (13·5%)	0·97 (0·92–1·03)	0·34
Presumed cardiac rupture	209 (0·9%)	224 (1·0%)	0·93 (0·77–1·12)	0·45
Ventricular fibrillation	624 (2·7%)	655 (2·9%)	0·95 (0·85–1·06)	0·35
Other cardiac arrest	867 (3·8%)	913 (4·0%)	0·94 (0·86–1·04)	0·24
Pulmonary embolus	32 (0·1%)	33 (0·1%)	0·97 (0·59–1·57)	0·89

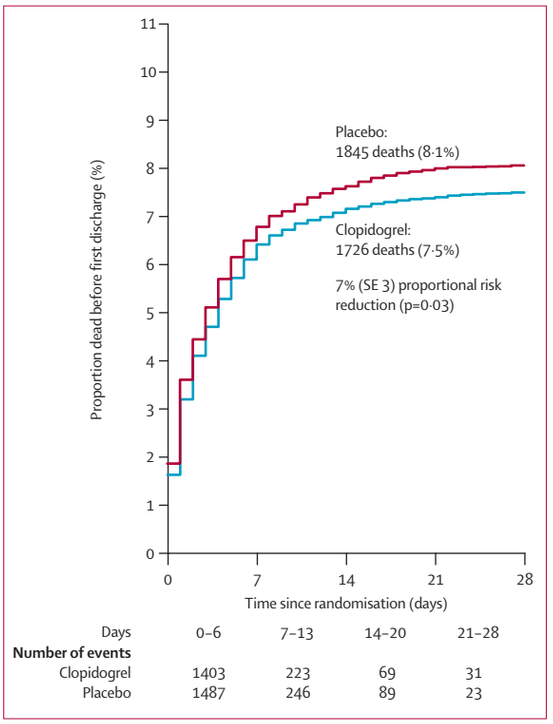
Data are number (%) unless otherwise indicated. *652 patients (301 clopidogrel *vs* 351 placebo) had more than one cause reported (including 530 patients with two, 111 with three, and 11 with four), all of which are tabulated as possible causes (ie, some deaths included in more than one row). †Nine patients (two clopidogrel *vs* seven placebo) had both a non-fatal reinfarction and a non-fatal stroke. ‡Two patients (both in clopidogrel group) had both an ischaemic and a haemorrhagic stroke.

Table 3: **Effects of clopidogrel on primary and other clinical outcomes during scheduled treatment period in hospital**



Days	0–6	7–13	14–20	21–28
Number of events				
Clopidogrel	1751	247	91	32
Placebo	1879	301	104	26

Figure 2: **Effects of clopidogrel allocation on death, reinfarction, or stroke before first discharge from hospital**
Time-to-event analyses based on first relevant event during scheduled treatment period. Mean treatment duration in survivors was 14·9 days. Flatness of right-hand ends of graph is because events after discharge were not included.



Days	0–6	7–13	14–20	21–28
Number of events				
Clopidogrel	1403	223	69	31
Placebo	1487	246	89	23

Figure 3: **Effects of clopidogrel allocation on death before first discharge from hospital**
Conventions as in figure 2.

in strokes attributed to ischaemic or unknown type (164 [0·7%] *vs* 194 [0·8%]; p=0·10), with similar trends for non-fatal (112 [0·49%] *vs* 127 [0·55%]) and fatal (52 [0·23%] *vs* 67 [0·29%]) presumed ischaemic strokes. No apparent difference was noted in strokes attributed to haemorrhage, either overall (55 [0·2%] *vs* 56 [0·2%]; p=0·90: table 3) or when non-fatal (16 [0·07%] *vs* 15 [0·07%]) and fatal haemorrhagic strokes (39 [0·17%] *vs* 41 [0·18%]: table 4) were considered separately.

Allocation to clopidogrel produced no significant effects on any of the other major outcomes that were to be recorded systematically during the scheduled treatment period (table 3), which included: cardiogenic shock, heart failure, presumed cardiac rupture, ventricular fibrillation, other cardiac arrest, and pulmonary embolus. Apart from heart failure, most of these events resulted in death during the scheduled treatment period, and so were already included in the primary efficacy outcomes. Analyses restricted to patients who were discharged alive did not find any significant differences between the treatment groups in the rates of these non-fatal outcomes.

Subsidiary analyses

Although the overall proportional reduction of 9% (SE 3) in the composite outcome of death, reinfarction, or stroke is highly significant (p=0·002), the corresponding χ^2 statistic is only 9·6, which is not big enough for subgroup analyses to be reliable. Nevertheless, the main subsidiary analyses specified in the protocol are reported. Figure 5 shows the effects of clopidogrel allocation on the primary composite outcome of death, reinfarction, or stroke by time after randomisation. The benefits of clopidogrel 75 mg daily seemed to emerge

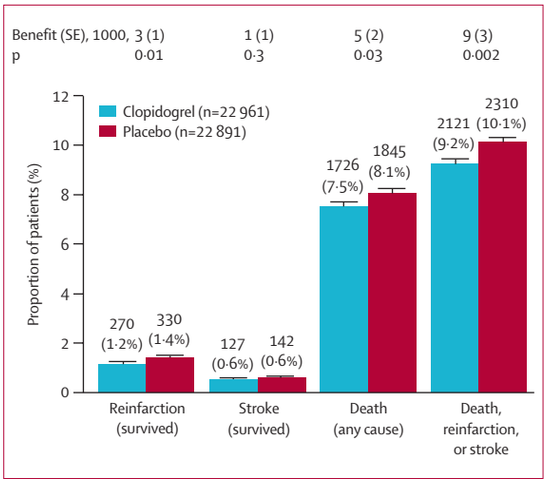


Figure 4: **Absolute effects of clopidogrel on death, reinfarction, or stroke**

rapidly (despite a loading dose not having been used), with an 11% (99% CI 0 to 20; p=0·014) proportional reduction during the prespecified period of days 0–1; this included a 12% (SE 6; p=0·05) reduction on day 0 (which lasted for an average of only about 12 h after initiation of treatment). The early benefit during days 0–1 was due mainly to an 11% (99% CI –1 to 22; p=0·019) proportional reduction in death (736 [3·2%] clopidogrel *vs* 825 [3·6%] placebo) during that period, and did not differ significantly from the risk reduction in each subsequent period (heterogeneity p=0·6).

Overall, the proportional reductions in the primary composite outcome did not differ significantly from each other in the different prespecified subcategories of patient studied (figure 6; global heterogeneity p=0·4). In particular, there were apparently similar proportional risk reductions in different age groups: 7% (SE 6) at ages younger than 60 years; 10% (SE 5) at ages 60–69 years; and 9% (SE 4) at ages 70 years or older (heterogeneity p=0·9). But since the absolute risk of the composite outcome was higher in the 11 934 patients aged at least 70 than in the 19 087 aged younger than 60 years (16·2% *vs* 5·4% in the placebo group), the absolute reduction in risk also seemed, if anything, to be somewhat greater (13 [SE 6] and four [SE 4] fewer events per 1000 treated, respectively, in these older and younger patients). Similar proportional reductions with clopidogrel were also noted irrespective of the use of fibrinolytic therapy before randomisation: 11% (SE 4) with fibrinolytic *vs* 7% (SE 4) without it (heterogeneity p=0·4). Nor was the effect of clopidogrel significantly modified by the random allocation to metoprolol (heterogeneity p=0·1). When the subgrouping by hours from symptom onset was considered in isolation (and without adjustment for multiple comparisons), the proportional reductions in the composite outcome seemed to be larger when clopidogrel was started earlier after the onset of symptoms: 16% (SE 5) for less than 6 h; 10% (SE 5) for 6 h to less than 13 h; and –1% (SE 6) for 13 h to 24 h (trend p=0·02 before adjustment for multiple comparisons). A similar trend was noted for mortality, but not for reinfarction. Given the number of subgroups examined and the lack of significance after correction for multiple comparisons, this apparent trend cannot be trusted (particularly since no such trend was noted with aspirin alone versus placebo in the ISIS-2 trial[2]).

Allocation to clopidogrel did not produce any significant differences in the use of other concomitant therapies in hospital. So, although such information was not recorded before randomisation, analyses of outcome in participants subdivided according to their use of other treatments in hospital might still be approximately valid. Apparently similar proportional reductions in the risk of the composite outcome were noted with clopidogrel in the presence or absence of: any fibrinolytic therapy in hospital, including any received after randomisation (11% [SE 4] *vs* 7% [SE 4]); any anticoagulant therapy (10% [SE 4] *vs* 9% [SE 5]); or any angiotensin converting enzyme (ACE) inhibitor therapy (11% [SE 4] *vs* 7% [SE 4]).

	Clopidogrel (n=22 961)	Placebo (n=22 891)	Excess per 1000 (SE)	p
Fatal	73 (0·32%)	74 (0·32%)	–0·1 (0·5)	0·92
Cerebral	39 (0·17%)	41 (0·18%)		
Non-cerebral	36 (0·16%)	37 (0·16%)		
Non-fatal	61 (0·27%)	51 (0·22%)	0·4 (0·5)	0·35
Cerebral	16 (0·07%)	15 (0·07%)		
Transfused	46 (0·20%)	36 (0·16%)		
Any*	134 (0·58%)	125 (0·55%)	0·4 (0·7)	0·59

Data are number (%) unless otherwise indicated. *Three patients in clopidogrel and four in placebo group had both cerebral and non-cerebral bleeding during scheduled treatment period in hospital. In those given fibrinolytic therapy before randomisation, there were 0·65% clopidogrel versus 0·63% placebo major bleeds: 28 versus 31 fatal cerebral; 17 versus 18 other fatal; nine versus nine non-fatal cerebral; and 23 versus 16 other non-fatal.

Table 4: **Effects of clopidogrel on cerebral and major non-cerebral bleeding during scheduled treatment period in hospital**

Bleeding

Overall, when all transfused, fatal, or cerebral bleeds were considered together, there was no significant excess risk associated with the use of clopidogrel during the scheduled treatment period (134 [0·58%] clopidogrel *vs* 125 [0·55%] placebo; p=0·59: table 4). Nor was there any excess of such bleeds in the 22 794 patients who had been given fibrinolytic therapy before randomisation (74 [0·65%] *vs* 72 [0·63%]; p=0·88), or in the 11 934 aged 70 years or older (50 [0·84%] *vs* 43 [0·72%]; p=0·48). About three-quarters of the people who had cerebral bleeds, and half of those who had non-cerebral major bleeds, died in hospital and so are already included in the primary efficacy outcomes. There was no apparent excess of fatal bleeds (73 clopidogrel *vs* 74 placebo), and the excess of major non-fatal bleeds was not significant (61 *vs* 51; p=0·35). Clopidogrel was, however, associated with a small, but significant, excess of 4·7 (SE 1·7) reported minor bleeds (including dental bleeding or skin bruising) per 1000 patients

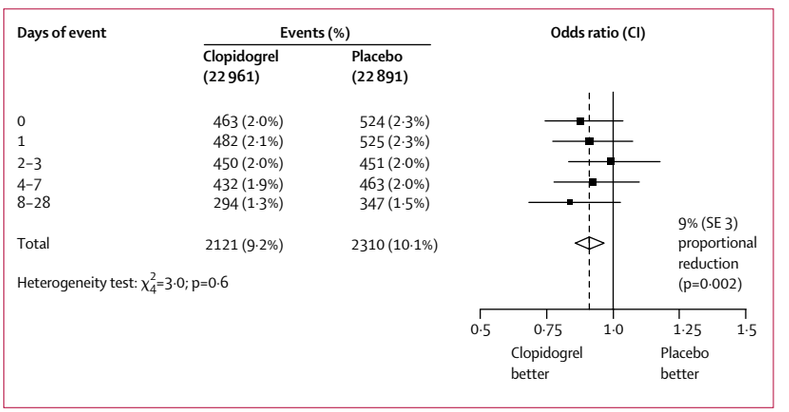
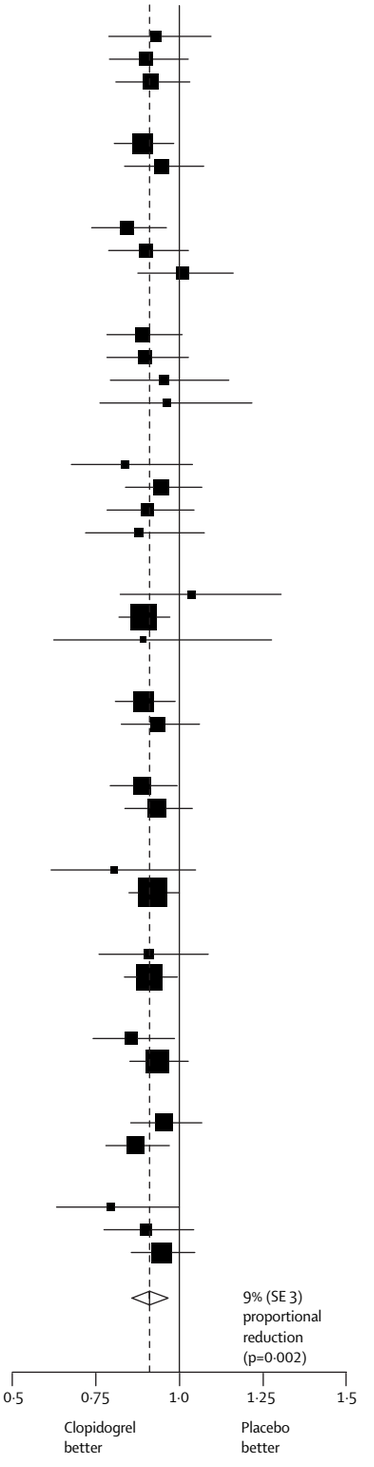


Figure 5: **Effects of clopidogrel allocation on death, reinfarction, or stroke by day of event**
Odds ratio in each period (black square with area proportional to number of events) and 99% CI (horizontal line). Broken vertical line indicates overall result, and diamond indicates its 95% CI.

Figure 6: **Effects of clopidogrel allocation on death, reinfarction, or stroke in different categories of patient**

Conventions as in figure 5. Summation of 13 separate χ^2 heterogeneity test statistics (one for each baseline characteristic) yields a global test for heterogeneity between 34 subgroups (χ^2_{21}=22·6, p=0·4). When a value was missing for some variable in a particular patient, then that patient was included in most common category for that variable (so each subgroup analysis includes all patients). Eligibility criteria for CLARITY trial were age up to 75 years; ST-segment elevation or bundle branch block within 12 h of symptom onset; and received fibrinolytic therapy before randomisation. Three similar-sized prognostic index groups were based on absolute risk of primary composite outcome for each patient calculated from baseline prognostic variables (excluding allocated treatments) with a Cox regression model.

Baseline categorisation	Events (%)		Heterogeneity or trend test χ^2 (p)
	Clopidogrel (22 961)	Placebo (22 891)	
Age at entry (years)			
<60	485 (5·0%)	512 (5·4%)	0·0 (0·9)
60–69	745 (10·1%)	835 (11·2%)	
⩾70	891 (14·9%)	963 (16·2%)	
Sex			
Male	1274 (7·7%)	1416 (8·6%)	1·0 (0·3)
Female	847(13·3%)	894 (14·0%)	
Time since onset (h)			
<6	709 (9·2%)	830 (10·8%)	5·7 (0·02)
6 to <13	738 (9·8%)	808 (10·8%)	
13–24	674 (8·8%)	672 (8·8%)	
Systolic blood pressure (mm Hg)			
<120	797 (10·4%)	892 (11·6%)	1·0 (0·3)
120–139	693 (8·6%)	770 (9·5%)	
140–159	388 (8·5%)	399 (8·9%)	
⩾160	243 (9·2%)	249 (9·6%)	
Heart rate (bpm)			
<70	268 (5·3%)	315 (6·2%)	0·0 (1·0)
70–89	898 (8·1%)	952 (8·5%)	
90–109	632 (12·3%)	683 (13·5%)	
⩾110	323 (19·9%)	360 (22·2%)	
ECG at entry			
Bundle branch block	270 (17·9%)	247 (17·4%)	1·8 (0·2)
ST elevation	1753 (8·8%)	1952 (9·8%)	
ST depression	98 (6·2%)	111 (7·0%)	
Killip class			
I	1273 (7·3%)	1415 (8·2%)	0·6 (0·5)
II/III	848 (15·0%)	895 (16·0%)	
Fibrinolytic agent given			
Yes	1003 (8·8%)	1122 (9·9%)	0·7 (0·4)
No	1118 (9·7%)	1188 (10·3%)	
Previous MI			
Yes	177 (9·0%)	204 (11·1%)	1·6 (0·2)
No	1944 (9·3%)	2106 (10·0%)	
Previous aspirin use			
Yes	399 (9·5%)	439 (10·4%)	0·0 (1·0)
No	1722 (9·2%)	1871 (10·0%)	
Eligible for CLARITY trial			
Yes	612 (8·2%)	717 (9·6%)	1·8 (0·2)
No	1509 (9·7%)	1593 (10·4%)	
Metoprolol allocation			
Yes	1063 (9·3%)	1110 (9·7%)	2·4 (0·1)
No	1058 (9·2%)	1200 (10·5%)	
Prognostic index (3 equal groups)			
Good	228 (3·0%)	282 (3·7%)	3·1 (0·08)
Average	574 (7·5%)	636 (8·3%)	
Poor	1319 (17·3%)	1392 (18·2%)	
Total	2121 (9·2%)	2310 (10·1%)	
Heterogeneity test: χ^2_{21}=22·9; p=0·3			



treated (831 [3·6%] *vs* 721 [3·1%]; p=0·005). Taking major and minor bleeds together, there was no apparent trend with respect to age in the excess risk: 302 (3·1%) *vs* 263 (2·8%) at ages younger than 60 years; 304 (4·6%) *vs* 284 (3·8%) at ages 60–69 years; and 292 (4·9%) *vs* 275 (4·6%) at older ages.

Discussion

The findings of this large randomised trial show that addition of clopidogrel to aspirin reduces mortality and major morbidity in a wide range of patients with suspected acute MI, and these benefits seem to be largely independent of, and hence additional to, those of other standard treatments (such as fibrinolytic and anticoagulant therapy). The findings also show that such treatment is safe, with no apparent increase in life-threatening bleeds even when given with fibrinolytic therapy, or to older patients. Although done only in China, there is no good reason to expect materially different results in other populations.

Death, reinfarction, and stroke

Aspirin has been shown previously to be effective both for the emergency treatment of acute MI and for long-term secondary prevention.[2,15] Compared with placebo in the ISIS-2 trial, up to 1 month of aspirin 162 mg daily after suspected acute MI prevented about 40 deaths, non-fatal reinfarctions, or strokes per 1000 patients treated[2] (and these early benefits persisted for at least 10 years[16]). The results of the COMMIT trial now show that adding clopidogrel 75 mg daily to aspirin (as well as other standard therapies) in the emergency treatment of acute MI prevents about another ten deaths, reinfarctions, or strokes per 1000 treated for about 2 weeks. Consequently, compared with no antiplatelet treatment, it can be inferred that the combination of clopidogrel plus aspirin prevents an average of about 50 major vascular events per 1000 treated for just a few weeks soon after the onset of acute MI. Evidence from long-term trials of aspirin use after MI and other vascular conditions,[15] and of the addition of clopidogrel to aspirin in patients with acute coronary syndromes,[9] suggests that more prolonged use of this combined antiplatelet regimen after acute MI would produce even greater absolute benefits than aspirin alone. This question is being studied in the ongoing CHARISMA trial.[17]

The results of COMMIT are generally consistent with those from other studies of adding clopidogrel to aspirin in patients with non-ST-elevation acute coronary syndromes[9] and with ST-elevation MI,[10] although no previous trial was large enough to show a significant mortality benefit. Aspirin might be more effective at preventing recurrent clinical events than at maintaining coronary artery patency.[18] Clopidogrel might exert its effects in acute MI chiefly by preventing re-occlusion or by limiting the microvascular effects of platelet activation, rather than by enhancing fibrinolysis. In the CLARITY study of adding clopidogrel to aspirin in 3491 patients with ST-elevation MI given fibrinolytic therapy, clopidogrel (300 mg loading dose then 75 mg daily) produced a highly significant 41% proportional reduction in the probability of the infarct-related artery being occluded (TIMI flow grade 0 or 1) at a median of 84 h, but there was no apparent effect on the rate of resolution of ST-segment elevation (as a surrogate for reperfusion) at 180 min after the initiation of treatment.[10] In the present trial, the risk reduction with clopidogrel seemed to be somewhat greater when treatment was initiated earlier after symptom onset. This finding would be consistent with at least part of the benefit of clopidogrel being related to myocardial salvage through improved coronary patency.[18] But since no such time-dependent effect on reinfarction or mortality was noted in the ISIS-2 trial of aspirin[2] (or, indeed, on patency with clopidogrel in CLARITY:[10] Sabatine MS, Brigham and Women's Hospital, Harvard, personal communication), this apparent time-dependent effect could be largely or wholly a consequence of the play of chance in one of the many subgroups examined in figure 6.

No loading dose of clopidogrel was used in the present study, in part because of previous concerns about the potential for bleeding in this setting. Even so, some of the clinical benefit of clopidogrel seemed to emerge rapidly, with a marginally significant 12% (SE 6; p=0·05) proportional reduction in death, reinfarction, or stroke on day 0 (ie, within an average of 12 h of starting treatment) and a somewhat more significant 11% (99% CI 0–20%, p=0·01) benefit when the results on days 0 and 1 were combined. Although it generally takes days rather than hours to achieve maximal antiplatelet effects without an initial loading dose, partial antiplatelet effects do emerge within a few hours after administering 75 mg clopidogrel orally.[19] When platelet activity has already been substantially reduced by aspirin, even a moderate further reduction might significantly alter the threshold of platelet aggregation, and so reduce the risk of thrombotic complications. The addition of an initial loading dose of clopidogrel could, however, produce more rapid antithrombotic effects.[19,20] For example, in the CLARITY trial among 3491 ST-elevation MI patients given fibrinolytic therapy plus aspirin, initiation of clopidogrel with a 300 mg loading dose was associated with a 30% proportional reduction in the risk of reinfarction at a median of 3·5 days, although this difference was not significant (p=0·08).[10] Likewise, in the CURE trial among 12 562 patients with non-ST-elevation acute coronary syndromes given aspirin, an initial 300 mg loading dose of clopidogrel was associated with a 20% proportional reduction in the risk of major vascular events within 24 h of the initiation of treatment, although this early trend was also not significant.[9,21] Even higher loading doses of clopidogrel could produce even greater antiplatelet effects more

rapidly,[20] although the bleeding risk would need to be monitored, especially in older patients who are at somewhat greater risk of bleeding (but also at somewhat greater risk of an occlusive vascular event).

Major bleeding

Although the present study did not involve a loading dose of clopidogrel, it did involve sufficiently large numbers of patients for the safety of the clopidogrel regimen used to be shown in various subgroups. For example, among the 23 000 patients who had been given fibrinolytic therapy or the 12 000 patients aged 70 years or older, adding clopidogrel 75 mg daily for about 2 weeks was not associated with any apparent increase in major bleeding. Although the fairly low proportion of CT and MRI scans in patients with fatal stroke could have led to some underascertainment of fatal intracranial haemorrhage (as bleeds are more likely to be fatal than infarcts), the lack of any apparent excess of confirmed (fatal or not) haemorrhagic stroke was reassuring, as was the apparent reduction in total stroke. Among the largely middle-aged patients (mean age 57 years) with ST-elevation MI in the CLARITY trial, a 300 mg loading dose of clopidogrel followed-up by 75 mg daily for 3–4 days also did not seem to produce a significant increase in the risk of major bleeding. But that trial involved only a few cases of serious bleeding (33 [1·9%] clopidogrel *vs* 30 [1·7%] placebo). The CURE trial involved somewhat older patients (mean age 64 years), and a 300 mg loading dose followed-up by 75 mg daily of clopidogrel for an average of 9 months increased the overall risk of major bleeding by about a third (231 [3·7%] clopidogrel *vs* 169 [2·7%] placebo; of which only seven *vs* five involved cerebral haemorrhage and 11 *vs* 15 were fatal).[9,21] The proportional increases in major bleeding were similar at all ages (49 [2·4%] *vs* 37 [1·8%] at age younger than 60 years; 65 [3·3%] *vs* 50 [2·5%] at ages 60–69 years; 117 [5·2%] *vs* 82 [3·7%] at older ages), but little of this excess risk was noted during the first week of treatment, even in older patients (Yusuf S, McMaster University and Hamilton Health Sciences, personal communication).

Conclusions

COMMIT took place in a wide range of specialist and non-specialist hospitals throughout China, the selection of suitable patients did not involve any great change in the normal patterns of investigation or diagnosis, and the study treatment had little effect on the use of other treatments. Patients who were undergoing primary PCI were explicitly excluded (because other studies have shown that clopidogrel is beneficial during such procedures),[7,8] but the trial did not exclude the use of various interventional procedures after randomisation. As with aspirin, the use of clopidogrel in acute MI does not require careful monitoring and, given the short treatment duration and fairly low cost, it could be used widely not only in developed countries but also in many populations with more limited resources. Although the absolute benefits of adding a few weeks of clopidogrel to aspirin (and other standard treatments) are only moderate, it has definite benefits and no significant hazards. As such, clopidogrel (probably starting with a loading dose) should be considered for almost all patients presenting in hospital with suspected acute MI, irrespective of their age, sex, and the use of other treatments (provided that there are no strong contraindications). If, based on the results of COMMIT and CLARITY,[10] early clopidogrel therapy was given in hospital to just 1 million of the 10 million patients who have an MI every year[1] then it would, on present evidence, prevent about 5000 deaths and 5000 non-fatal reinfarctions and strokes (probably with no great increase in major bleeding). Moreover, continued treatment with clopidogrel after hospital discharge (as in CURE[9]) could lead to further net gains, although the benefits and hazards of more long-term therapy are still under investigation.[17]

Contributors

All members of the writing committee contributed to the study design, its undertaking, data analysis, and interpretation of the study results, as well as to the writing of the manuscript.

Conflict of interest statement

The Clinical Trial Service Unit (writing committee members: Z M Chen, H C Pan, Y P Chen, R Peto, and R Collins) has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. Other members of the writing committee (L X Jiang, J X Xie, and L S Liu) have accepted honoraria from the pharmaceutical industry for lecturing in China.

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Hebei—Cangzhou people's hospital (378) Y Hu; Leting county hospital (185) K Shang, J Zhao; Yanshan county hospital (156) Z Liu; Zunhua people's hospital (129) X Yang; Renqiu people's hospital (112) N Huang, J Fu; Wenan county hospital (103) J Gao, T Han; Beijing Xiaotangshan hospital (96) W Wang; She county hospital (75) Z Li; Bethune international peace hospital (72) Y Wei; Anguo city hospital (72) S Zhang; Qianxi hospital (71) C Gao; Hejian people's hospital (64) B Du; Xinji second hospital (63) J Liu; Xinji first hospital (59) J Chen; Cang county hospital (57) F Xu; Jize county hospital (57) Q Guo; Hebei medical university third hospital (53) X Zhang; China railway bureau Gaobeidian hospital (53) B Zhang; Baoding first aid centre (52) W Zhao; Baoding second central hospital (49) Y Wang; Gaobeidian hospital (49) Y Xu; Yutian county hospital (49) X Kang; Beidaihe hospital (48) X Xing; Mancheng county hospital (46) C Yan; Nanpi county hospital (44) J Cao; Lulong county hospital (44) S Liu; Qinhuangdao second hospital (42) L Zhang; Tang Hai county hospital (40) J Han; Gaoyi county hospital (40) Z Shang; Raoyang county hospital (40) Z Zhao; Xingtai people's hospital (32) Q Wei; Haixing county hospital (31) X Liang; Linxi county hospital (28) F Ma; Kailuan mining bureau hospital (28) S Wu; Chengan county hospital (28) F Geng; Julu county hospital (27) J Yang; Kangbao county hospital (27) J Yin; Nangong people's hospital (26) C Shi; Pingshan county hospital (26) Q Lu; Cangzhou railway hospital (25) S Geng; Quyang county hospital (24) B Ding; Dingzhou people's hospital (24) L Guo; Xinglong people's hospital (24) J Gao; Chengde central hospital (23) Y Jia; Hebei provincial people's hospital (23) Y Han; Wuqiang county hospital (23) B Liu; Handan first hospital (23) Y Wu; Tianjin railway bureau Tangshan hospital (23) Y Shen; Zhangjiakou medical college first hospital (23) F Li; Ci county hospital (23) S Miao; Hengshui fourth people's hospital (22) J Feng; PLA Baoding 252 hospital (22) X Mu; Chengde PLA 266 hospital (22) X Li; Ministry of Communications Qinhangdao harbor hospital (22) Q Han; Wuqiao county hospital (21) G Liu; Xuanhua county hospital (21) W Shen; Dongguang county hospital (20) Z Zhang; Qinglong county hospital (19) Q Fan; Jingxing mining district hospital (19) Y Gu; Chengde medical college affiliated hospital (19) C Li; Hebei medical university fourth hospital (18) X Li; Hengshui second people's hospital (18) G Zhang; Weichang county hospital (17) G Zhang; Zhengding county hospital (16) Z Liu; Zhangbei county hospital (16) G Geng; Shijiazhuang third hospital (16) G Ma; Guyuan county hospital (16) D Zuo; Hebei medical university second hospital (16) B Wang; Chengde county hospital (16) J Yu; Quzhou county hospital (16) S Zhu; Shijiazhuang railway central hospital (16) W Dou; Funing people's hospital (16) B Du; Zanhuang county hospital (15) L Wang; Neiqiu

people's hospital (15) G Li; Qianan people's hospital (13) R Xue; Tangshan new district hospital (13) X Zhou; Qinghe second hospital (12) Y Sun; Xinhe county hospital (12) H Zhang; Huabei petroleum industry general hospital (11) B Wu; Wei county hospital (11) J Zhang; Handan third hospital (11) J Zhang; Qiu county second hospital (10) Y Liu; Chongli county hospital (10) W Xue; Longyao county hospital (9) L Zhang; Beijing steel corporation mining hospital (9) J Wang; Gaocheng county hospital (9) Q Guo; Xingtai steel corporation hospital (9) S Guo; Handan fourth hospital (8) Y Yi; Huanghua people's hospital (8) J Yu; PLA 251 hospital (8) D An.

Heilongjiang—Jixi mining bureau general hospital (263) W Du, J Nan; Yichun forestry central hospital (172) Y Zhang; Mishan people's hospital (130) Z Yu, Y Zhao; Shuangyashan mining corporation general hospital (108) L Tian, P Ji; Acheng people's hospital (106) H Yu; Mudanjiang first people's hospital (100) J Wang, M Zhang; Heilongjiang provincial people's hospital (93) H Wu; Daqing first hospital (86) D Liu; Haerbin 242 hospital (73) Y Zhou; Haerbin fourth hospital (68) F Xu; PLA 211 hospital (66) Z Peng; Qiqihaer medical college second hospital (60) Y Wang; Nahe people's hospital (54) Z Niu; PLA 224 hospital (52) W Liu; Shuangyashan mining bureau general hospital (48) T Dai; Longnan hospital of Daqing Oil Field (46) P Wang; Wangkui people's hospital (43) G Li; Sunwu county hospital (40) L Ding; Mudanjiang medical college second hospital (36) L Wang; Jiansanjiang central hospital (35) X Yu; Fuyu county hospital (35) H Cheng; Yichun first people's hospital (35) F Ni; Longjiang first people's hospital (31) Y Wang; Heihe second people's hospital (24) H Li; Haerbin medical university first teaching hospital (23) W Li; Shuangyashan people's hospital (21) X Qin; Luobei people's hospital (20) Y Zheng; Hailun people's hospital (19) L Luan; Forestry administrative bureau central hospital (18) C Zhu; Mudanjiang medical college Red flag hospital (18) W Li; Hulin people's hospital (17) S Ming; PLA Heilongjiang 203 hospital (15) A Li; Haerbin tenth hospital (15) G Wang; Mudanjiang second people's hospital (14) J Liu; Qiqihaer second hospital (14) L Hou; Jiamusi medical college first hospital (12) C Lu; Chinese people's armed police units hospital (11) M Cao; Wudalianchi first people's hospital (11) H Wan; Ningan people's hospital (9) Y Bai.

Henan—Qinyang people's hospital (446) X Ma; Zhenping County hospital (303) Y Zhang; Xinmi first people's hospital (229) B Wu, J Meng; Puyang Zhongyuan oilfield general hospital (162) D Si, G Bai; Changyuan county hospital (143) Y Dun; Gongyi people's hospital (139) T Du; Zhengzhou university first hospital (127) Z Huang; Wen county hospital (112) S Cui, J Gao; Xuchang central hospital (111) S Chen, M Guo; Qi county hospital (110) W Feng; Lingbao first people's hospital (109) W Li; Zhoukou central hospital (107) L Tian, Y Shi; Yongcheng people's hospital (106) C Tian, J Wang; Shangqiu fourth people's hospital (105) G Huang, Y Wang; Puyang people's hospital (96) L Ma; Henan university of science and technology first hospital (90) P Dong; Dancheng county hospital (87) J Yu; Jun county hospital (85) J Li; Yuanyang county hospital (83) S Wang; Yanshi people's hospital (80) C Li; Yuzhou people's hospital (80) Y Huang; Shangshui county hospital (75) Z Zhu; Hebi first people's hospital (70) W Guo; Pingdingshan coal corporation general hospital (66) F Shao; Sanmenxia people's hospital (64) Q Yang; Luoyang railway central hospital (63) M Sun; Neihuang county hospital (62) H Shen; Luoyang first people's hospital (60) G Ren; Huojia county hospital (60) H Jia; Nanyang medical school affiliated hospital (53) L Wang; Dengfeng people's hospital (49) F Gao; Xiangcheng county Chinese and Western medicine hospital (49) Q Zhang; China Great Wall aluminium company general hospital (49) S Guo; Shangqiu third people's hospital (47) J Qu; Anyang Chinese medicine hospital (46) Q Li; Zhengzhou second people's hospital (44) P Fan; Qingfeng county hospital (43) J Chen; Yanjin county hospital (40) S Ren; Pingyu county central hospital (40) Z Wang; Fan county hospital (40) J Hao; PLA Zhengzhou 153 hospital (38) C Hao; Xinxiang medical college first affilated hospital (37) S Zhang; Kaifeng first people's hospital (37) B Zhang; Xinyang central hospital (37) J Liu; Hui county hospital (36) K Jiang; Queshan county hospital (36) G Fan; Yiyang county hospital (35) Y Li, J Li; Ningling county hospital (33) M Liu; Xinxiang second people's hospital (31) P He; Shan county hospital (27) X Chen; Xiuwu county hospital (26) X Xu; Jiaozuo people's hospital (25) X Zhao; Neihuang county second people's hospital (24) H Yang; Xiayi central hospital (24) G Yang; Hebi coal corporation general hospital (24) M Li; Nanle county hospital (23) A Li; Mengjin county hospital (23) Y Lu; Xixia county hospital (22) Q Li; Henan university Huaihe hospital (22) G Cheng; Luoyang PLA 202 hospital (22) Y Liu; Xinxiang railway centre hospital (21) W Gu; Shangqiu Changzheng hospital (21) Y Tian; Anyang third people's hospital (20) H Si; Nanyang second people's hospital (20) H Zhou; Xinye county hospital (19) Q Liu; Wen county Chinese medicine hospital (19) B Song; Xinxiang first people's hospital (19) J Ren; Xinan county hospital (19) C Chen; Zhumadian central people's hospital (19) F Zhang; Jiyuan people's hospital (18) J Zhao; Shangcai county hospital (18) D Wang; Zhengzhou fifth people's hospital (18) H Yu; Anyang district hospital (18) Y Hu; Pingdingshan second people's hospital (18) Q Du; Wugang people's hospital (17) X Yang; Luoning county hospital (16) X Kang; PLA Henan 152 central hospital (16) C Li; Ruyang county hospital (15) Z Wang; Zhengzhou traditional Chinese medical hospital (14) S Shang; PLA 371 hospital (14) S Zhang; Fugou county hospital (14) X Chen; Huanghe central hospital (12) L Jin; Neixiang county hospital (12) Z Li; Baofeng county hospital (12) C Fan; Wen county second People's hospital (11) S Wang; Lushan county hospital (11) D Ding; Fengqiu people's hospital (11) R Shao; Kaifeng second people's hospital (11) L Wang; Zhumadian central hospital (10) L Guan; Shenqiu county hospital (10) Y Yan; Ju county hospital (10) W Wang; Jia county hospital (9) J Zhao.

Hubei—Tongji medical college hospital (91) D Wang; Guangshui first people's hospital (59) G Wang; Tianmen first people's hospital (56) S Wan; Zhongxiang people's hospital (49) F Liu; Zhijiang people's hospital (46) J Zhou; Jianghan university affiliated hospital (36) K Chou; Huangshi central hospital (32) Z Chen; Huangshi second hospital (27) L Zou; Dongxihu district hospital (27) H Wang; Wuhan steel company first hospital (26) Y Li; Wuhan Puai hospital (25) Y Gu; Hanchuan people's hospital (22) Y Wang; Guangzhou military region Wuhan general hospital (22) S Ding; PLA 161 central hospital (21) Y Ding; Daye people's hospital (20) X Dong; Yichang central hospital (19) C Zhang; Wuhan fifth hospital (18) Q Kang; Wuhan seventh hospital (17) J Wang; Danjiangkou first hospital (16) Z Zhang; Wuhan railway central hospital (16) H Han; Yunxi people's hospital (15) S Li; Tongcheng county hospital (15) T Cai; Jianghan oilfield central hospital (14) C Chen; Yingshan county hospital (14) Z Wang; Chongyang people's hospital (11) A Wang; Yicheng people's hospital (10) Y Li; Qianjiang central hospital (9) S Yang; Wuhan commercial industry hospital (8) Y Huang; Jingshan county hospital (8) Y Chen; Hubei Yiye construction company hospital (8) S Liang; Yangtze shipping company general hospital (8) G Xie.

Hunan—Taojiang county hospital (68) J Luo; Liuyang people's hospital (60) J Liu; Yueyang first hospital (47) X Xu; Xiangtan second people's hospital (44) X Zhou; Changsha first hospital (41) X Yang; Xiangxiang people's hosptal (34) C Zhou; Yongzhou third people's hospital (32) X Li; PLA Changsha 163 hospital (25) D Yang; Anhua county hospital (20) J Xia; Ningxiang county hospital (19) Z Chen; Hengnan county hospital (18) Y Tao; Yiyang second people's hospital (18) G Cao; Xinhuang county hospital (16) Q Zhang; Lianyuan people's hospital (15) Z Yang; Linxiang people's hospital (14) X Zhao; Suining county hospital (12) G Yu; Dao county hospital (11) S Zhou; Jin first people's hospital (9) M Chen; Hunan Xianggang hospital (9) N Lan; Baojing county hospital (8) Y Yao.

Inner Mongolia—Baotou central hospital (544) R Zhao; Baotou steel corporation hospital (183) X Chen; Hulunbier people's hospital (148) G Wang; Wuhai people's hospital (104) T Wang; Baotou medical college second hospital (93) G Sun; Baotou railway hospital (85) Y Shi; Wu Lan Charbu Central hospital (77) M Liu; Inner Mogolia university of science and technology third hospital (72) T Liu; Liangcheng county hospital (65) L Zhang; Inner Mongolia medical college affilated hospital (64) S Zhang; Dalateqi people's hospital (56) Y Bai; Hangjinhouqi hospital (53) H Zhang; Linhe first people's hospital (45) J Ao; Alashan central hospital (45) Z Li; Inner Mongolia People's hospital (41) L Dou; Chifeng medical college affiliated hospital (31) K Wang; Xinganmeng hospital (31) Q Wang; Baotou fourth hospital (29) G Wang; Inner Mongolia first machinery hospital (28) H Ma; Inner Mongolia railway hospital (28) X Liu; Huhehaote first hospital (27) D Li; Zhungerqi people's hospital (26) Y Hao; Xilinguole Meng hospital (24) X Zhao; PLA 253 hospital

(24) H Zhen; Taipusiqi hospital (24) X Lin; Inner Mogolia armed police forces headquarters hospital (22) H Liu; Zhenglanqi people's hospital (22) M Te; Erdos Emergency medical center (20) Z Wang; Balinzuoqi second hospital (16) M Yi; Dalateqi people's hospital (10) C Bai; Shangdou county hospital (10) Z Xu; Baotou seventh hospital (8) X Li.
Jiangsu—Xuzhou fourth hospital (207) Q Fu, Y Wang; Xuzhou medical college second hospital (98) W Wu; Xuzhou medical college affiliated hospital (81) D Li; Ganyu people's hospital (67) F Wang; Jiangyin people's hospital (51) D Wang; Xishan people's hospital (47) X Li; Dafeng people's hospital (41) Y Wang; Shuyang people's hospital (38) C Zhou; Jianhu County hospital (32) C Cai; Funing people's hospital (30) B Ding; Wuxi second hospital (26) Y Zheng; Donghai county hospital (26) S Wang; Nanjing Liuhe people's hospital (24) Z Xie; Lianyungang first people's hospital (23) Q Yang; Wujiang first people's hospital (23) H You; Nanjing Gulou hospital (22) G Shi; Suqian people's hospital (22) Y Cheng; Jiangdu people's hospital (21) Z Li; Pizhou people's hospital (21) Y Zhang; Yizheng people's hospital (20) X Qian; Xuzhou railway hospital (20) J Li; Feng county hospital (18) C Wang; Suzhou university second hospital (18) X Hong; Bin Hai people's hospital (18) A Liu; Suzhou third people's hospital (17) W Liu; Xiangshui county hospital (17) Y Song; Baoying county hospital (16) G Zhu; Taizhou Chinese medicine hospital (15) X Wang; Wuxi first hospital (14) X Wu; Wuxi fourth people's hospital (13) C Chen; Nanjing first hospital (12) J Huang; Wuxi third people's hospital (12) W Jin; Jiangyan people's hospital (11) S Shen; Jiangsu Haigang cardiology institute (11) X He; Jiangsu university affiliated hospital (10) J Hou; Nanjing Pukou district central hospital (10) H Mei; Zhangjiagang first people's hospital (9) Y Wu; Rugao people's hospital (9) Z Guo; Xuzhou first people's hospital (9) W Nie; Taizhou Gaogang people's hospital (8) Y Qian; Nanjing railway central hospital (8) J Zhuang.
Jiangxi—Jingdezhen second hospital (60) S Wan; Xingguo county hospital (44) Z Xu; Jiujiang first people's hospital (23) Y Luo; Wanzai people's hospital (15) S Yu; Yifeng people's hospital (14) P He; Shangrao people's hospital (13) L Ye; Xinyu people's hospital (12) R Yan; Gannan medical college affiliated hospital (11) W Liao; Jiangxi medical college third hospital (11) J Zhao; Pingxiang people's hospital (9) J Ye.
Jilin—Jilin chemical corporation second general hospital (208) F Wang; Siping central people's hospital (190) J Wang, H Wang; Jilin chemical industry corporation first hospital (156) Y Jin; Shenyang military 208 hospital (145) L Zheng; Jilin central hospital (143) F Lou, J Wang; Liaoyuan mining bureau general hospital (142) M Li, S Shi; Da'an first people's hospital (101) Z Wang; Jilin railway central hospital (87) J Yang; Gongzhuling central hospital (87) X Cui, L Yu; Lishu county first people's hospital (86) X Wang; Yanbian university medical college affiliated hospital (85) L Cui; Longjing hospital (68) J Jiang; Tumen railway hospital (68) Z Zhang; Tonghua people's hospital (68) G Hou, L Chen, L Tao; Yongji county hospital (65) X Jin; Jilin oilfield central hospital (64) H Jia; Jilin provincial people's hospital (63) X Wang, Y Liu; Shuangliao people's hospital (48) G Zhou; Jilin second people's hospital (41) Q Zhuang; Guowen hospital (40) G Li; Changchun Chinese first automobile corporation hospital (38) H Pan; Jilin hospital of Chinese and western medicine (36) X Li; Jilin electric power hospital (35) M Fang; Huichun hospital (35) L Yu; Liuhe people's hospital (34) J Wang; Tonghua iron & steel corporation hospital (34) Y Wang; Linjiang hospital (32) Z Wang; Yanji hospital (32) M Cui; Jian hospital (29) T Liu; Jiaohe people's hospital (28) X Liu; Changchun second hospital (21) M Li; Qianguo Chinese medicine hospital (16) J Mi; Gongzhuling air force hospital (16) F Sun; Tumen hospital (13) J Lu; Jilin university China-Japan union hospital (13) X Zhou; Changling people's hospital (12) Y Wang; Beihua university affiliated hospital (10) T Liu; Changchun Chinese medicine affiliated hospital (8) S Zhao; Bai Qiuen medical college second hospital (8) S Li; Jilin hospital (8) Y Jiang.
Liaoning—Liaoning PLA cardiology institute (689) Y Han, M Dong; Liaoning provincial people's hospital (544) Z Li, N Ju; Shenyang fourth people's hospital (542) Y Li, X Zhou; Angang Lishan hospital (482) X Li, R Wu; Anshan central hospital (392) W Gao, G Wang, W Gao; Fushun second hospital (270) H Jiang; Angang Tiedong hospital (258) W Zhao; Fuxin mining bureau general hospital (231) T Zhang; Xinmin people's hospital (216) B Jiang, W Zhang; Anshan Tiexi hospital (200) J Li, L Liu; Jinzhou medical college third hospital (192) J Wang, L Dong; Liaoyang second people's hospital (184) C Wang; Liaoning air force Shenyang hospital (152) H Liu; Fushun central hospital (134) S Sun; Liaoyang third people's hospital (132) A Huang; Shenyang Sujiatun district central hospital (131) Z Lin, H Che; Wafangdian central hospital (129) T Zhao, J Lang; Benxi first people's hospital (123) Y Fu, Y Li; Xingcheng people's hospital (120) G Wang; Dalian municipal central hospital (116) H Lin, L Qiu; Chaoyang third people's hospital (116) F Zheng, H Yao; Zhuanghe people's hospital (96) Y Sui; Anshan steel corporation Shuguang hospital (94) H Wang; Dalian railway hospital (91) S Zhou; Dandong central hospital (87) X Fan; Fushun mining industry general hospital (85) Q Cui; Benxi central hospital (83) Y Zhao, H Wang; Shenyang seventh people's hospital (82) Y Xu; Shenyang emergency center (81) S Zhang; Shenyang medical college affiliated hospital (72) S Wang; Dalian second people's hospital (70) F Yao; Chaoyang second hospital (62) H Li; Shenyang first people's hospital (59) Z Liu; Liaoyang central hospital (58) S Fan; PLA 201 hospital (56) L Liu; Fushun third hospital (52) Z Xie; Liaoning Zhongxiyi treatment for thrombotic disease (52) B Zhao; Fuxin second people's hospital (51) Z Lan; Beipiao first people's hospital (45) J Liu; Jinzhou second hospital (40) H Wang; Tiexi district central hospital (39) F Zhang; Dalian fourth people's hospital (37) Q Liu; Liaoyang petrochemical fiber company hospital (37) F Wang; Angang Qidashan hospital (37) D Lu; Shenyang 157 hospital (36) L Li; China medical university second hospital (35) X Li; Jinzhou central hospital (33) Y Li; Dalian sea fishery corporation hospital (33) F Zhang; Dalian friendship hospital (30) X Liu; Benxi Jinshan hospital (29) G Xiu; Dalian port hospital (28) X Zhang; Jinzhou medical college first hospital (28) J Cai; Dalian medical university second hospital (28) P Qu; Kangping people's hospital (27) X Wang; Liaoyang first people's hospital (25) Z Yu; Chaoyang central hospital (21) G Ren; Shenyang railway central hospital (20) F Yao; Lingyuan prison bureau central hospital (20) D Wang; Wafangdian third people's hospital (15) W Li; Beining people's hospital (14) Y Liu; Shenyang medical college second hospital (13) Q Pei; Tieling central hospital (13) Y Guo; Shenyang 245 hospital (12) J Ma; Jinzhou Taihe district hospital (11) S Ding; Fuxin central hospital (10) F Ma; Tieling county first hospital (10) Y Wang; Shenyang 242 hospital (10) D Wang; Kazuo first people's hospital (9) L Zhang; Xifeng first hospital (9) Y Yang; Dawa first people's hospital (8) Y Zhang.
Ningxia—Pingluo county hospital (189) X Sun; Ningxia municipality second people's hospital (145) J Zhang, Y Zhao; Ningxia people's hospital (77) L Ge; Ningxia medical college affiliated hospital (73) X Liu; Shizuishan second people's hospital (71) Z Xie; Ningxia Shitanjing hospital (45) F Yu.
Qinghai—Qinghai medical college affiliated hospital (97) Y Liu; Qinghai provincial people's hospital (24) B Zhou; Qinghai red cross hospital (16) B Xu; Xining first people's hospital (12) X Zhao.
Shandong—Weifang people's hospital (600) Y Zhang; Jining first people's hospital (345) X Sun; Pingdu people's hospital (329) P Yu, B Han, L Liu; Dezhou people's hospital (327) R Mou, K Li, Y Wei, X Ren, P Wang; Ling county hospital (217) M Wang; Qingdao medical college affiliated hospital (200) C Zhou; Cangshan county hospital (194) H Wang, Y Guan; Qingdao municipal hospital (173) F Zhang, X Guo; Zibo mining bureau general hospital (169) J Li; Yanzhou people's hospital (156) T Wang, Z Guan; Weihai Navy 404 hospital (147) S Deng; Yucheng people's hospital (137) W Wan; Yuncheng county hospital (128) Y Liang, Y Li; Shouguang people's hospital (119) W Chai; Chengwu county hospital (114) H Liu, D He; Zhucheng people's hospital (107) P Zhao; Liaocheng people's hospital (102) Y Li, Y Liu; Pingyin people's hospital (96) X Jia; Taishan medical university affiliated hospital (92) T Wu; Jiaxiang county hospital (86) Q Qu; PLA 91 hospital (86) Z Wang; Binzhou city people's hospital (84) J Cui, Y Lu; Taian first people's hospital (80) Y Wang; Dongying people's hospital (78) H Su; Dongping people's hospital (77) D Zhang; Linyi county hospital (72) J Liu; Zhifu hospital (71) W Du; Guangrao people's hospital (69) R Nie; Qihe county hospital (67) Y Zhang; Shanghe people's hospital (65) Y Pang; Liangshan county hospital (63) R Wang; Juye county hospital (63) X Fu; Qingzhou people's hospital (61) Z Pan; Hanting People's hospital (61) S Pan; Yangxin people's hospital (58) J Lao; Jimo people's hospital (56) Z Xiu; Zaozhuang mining corporation hospital (56) Y Zhao; Jining second people's hospital (56) Z Tan; Heze

municipal hospital (55) G Li; Linyi people's hospital (54) Z Hou; Boxing county hospital (51) T Yan; Weifang Yidou central hospital (47) J Ma; Wucheng people's hospital (46) J Li; Liaocheng second people's hospital (45) Y Liu; Kenli county hospital (44) Y Wei; Laiwu steel corporation hospital (44) C Lu; Yutai county hospital (44) J Wang; Dongming people's hospital (43) S Luo; Jinan first people's hospital (41) C Han; Cao county hospital (41) Z Shao; Jinan third municipal people's hospital (41) L Dan; Muping county hospital (41) M Sun; Qingdao eighth people's hospital (40) Z Kean; Jiaonan people's hospital (40) X Zhao; Yantai Taocun central hospital (40) D Lin; Fei county hospital (40) D Xu; Longkou people's hospital (39) C Wang; Zoucheng people's hospital (38) S Zhang; Jining medical college affiliated hospital (37) Q Li; Huantai people's hospital (37) H Zhang; Qufu people's hospital (36) R Du; Linqu people's hospital (35) X Li; Zouping people's hospital (33) G Zhao; Hekou hospital (33) B Zhao; Zhangqiu people's hospital (32) X Li; Yinan people's hospital (32) C Huang; Shengli petroleum bureau hospital (31) M Zhang; Binzhou medical college affiliated hospital (30) Y Zhang; Pingdu traditional Chinese medical hospital (30) R Zhu; Rushan people's hospital (30) S Xiang; Fushan district hospital (29) K Yang; Leling people's hospital (28) Y Li; Fangzi district hospital (28) J Yu; Zibo Shengjie hospital (27) J Ren; Gaomi people's hospital (27) F Yan; Yantai Yantaishan hospital (26) C Guo; Weifang Weichai hospital (25) S Liu; Jining Zhongqu people's hospital (24) X Geng; Juancheng county hospital (24) W Zhang; Qingdao medical college second hospital (24) Z Yin; Rizhao traditional Chinese medicine hospital (24) W Li; Jiyang county hospital (24) Y Li; Changle people's hospital (24) R Qin; Yantai Municipal Laiyang Central hospital (23) A Liu; Chan county central hospital (23) C Gao; Pingdu third people's hospital (23) G Jiang; Rongcheng people's hospital (22) S Deng; Shandong millitary police general hospital (21) H Wei; Qingdao third people's hospital (20) B Zhang; Haiyang people's hospital (19) J Chen; Zhoucun people's hospital (19) G Li; Wenshang people's hospital (18) Z Guo; Qingdao fifth people's hospital (18) X Zhang; Jinxiang county hospital (18) P Shao; Guangrao county Chinese traditional medicine hospital (17) C Gu; Rongcheng second people's hospital (16) Y Qi; Yishui central hospital (16) W Gao; Jinan PLA General hospital (16) N You; Zibo central hospital (16) X Zhang; Qingdao port hospital (16) X Shi; Taian City central hospital (15) W Sun; Zaozhuang municipal hospital (15) Y Liu; PLA 89 hospital (14) J Gao; Yan mining corporation general hospital (13) Y Sui; Laiwu second people's hospital (13) Y Xie; Xintai second people's hospital (13) F Yu; Tancheng county first people's hospital (12) Q Xu; Shen county hospital (11) T Bai; Xintai people's hospital (10) C Chen; Qingdao Shibei district hospital (10) Z Lu; Heze second people's hospital (9) F Yang; Linqing people's hospital (9) D Feng; Changyi people's hospital (9) X Zhang; Shandong provincial transport hospital (9) W Wang; Laizhou third people's hospital (9) X Jia; Yuncheng county third hospital (8) Z Sun; Zhucheng municipal hospital (8) L Li; Qufu traditional Chinese medicine hospital (8) Z Demin; Linshu county hospital (8) J Lao; Wendeng first people's hospital (8) Z Zhang; Anqiu people's hospital (8) M Wang.

Shanghai—Shanghai first people's hospital (40) A Zhang; Pudong public hospital (29) J Qiu; Ruijin corporation Minhang central hospital (20) D Zhang; Songjiang district central hospital (14) Z Jin; Putuo district hospital (14) D Zhang; Yangpu central hospital (14) E Hua; Zhoupu hospital (13) X Zhang; Jiading district central hospital (9) A Bi.

Shanxi—Yangquan first people's hospital (315) X Wang, F Wang; Pingyao county hospital (195) C Guo, Z Li; Yuanqu county hospital (135) W Xing; Linyi people's hospital (98) Y Jin; Xiangfen county hospital (91) J Qin; Yangquan mining corporation general hospital (91) M Zhao; Wanrong county hospital (90) Z Li; Fenyang hospital (72) R Guo; Yuncheng central hospital (71) H Lei; Gaoping people's hospital (70) K Jin; Kelan county hospital (66) R Li; Taiyuan railway central hospital (61) S Du; Yuanping first hospital (60) M Cheng; Jiaocheng county hospital (56) G Yan; Taiyuan steel corporation general hospital (56) J Tang; Shanxi cardiology institute (52) Z Fang; Wenshui county hospital (52) J Li; Pinglu county hospital (51) Q Meng; Shuozhou district hospital (50) W Liu; Liulin county hospital (41) L Xiao; Jinzhong second people's hospital (40) Y Liang; Shanxi mining bureau general hospital (35) Q Zhang; Jincheng people's hospital (34) F Zhang; Yu county hospital (34) X Cui; Jishan county hospital (32) T Xu; Yicheng county hospital (32) J Zhang; Datong third people's hospital (31) H Ma; Jinzhong first people's hospital (31) Y Yan; Luliang district hospital (27) L Xue; Ruicheng people's hospital (25) J Dan; PLA 264 hospital (25) Y Wang; Huozhou people's hospital (24) J Guan; Lucheng people's hospital (24) Y Zhou; Changzhi county hospital (23) J Jing; Yuci people's hospital (23) S Cheng; Linfen first people's hospital (22) E Li; Hequ people's hospital (19) M Zhou; Tunliu county hospital (19) Y Dong; Taiyuan central hospital (19) X Chen; Shouyang people's hospital (14) B Zhang; Ningwu county hospital (13) J An; Linfen medical school affiliated hospital (13) J Zhang; Datong county hospital (11) Y Di; Qingxu people's hospital (8) X Han; Shanxi medical university first affiliated hospital (8) Z Liu.

Shaanxi—Fengxiang county hospital (105) Z Xie; Sanyuan county hospital (80) C Ru; Shaanxi provincial people's hospital (77) X Chen; Xian Jungong hospital (71) D Liu; Tongguan county hospital (64) B Song; Xian fourth military medical university Xijing hospital (63) W Qiong; Xianyang second people's hospital (62) A Wang; PLA 323 hospital (57) H Li; Huanglong county hospital (55) Q Cao; Weinan central hospital (48) D Li; Xian Jiaotong university first hospital (44) A Ma; Dali county hospital (39) G Wang; Xian fourth hospital (34) F Xie; Xian Beifang hospital (34) W Zhu; Chengcheng county hospital (32) J Zhang; Shangluo central hospital (24) X Yang; Baishui county hospital (22) H Wang; Hanzhong people's hospital (21) Q Wang; Qianyang county hospital (21) G Zhao; Lantian county hospital (19) X Yan; Heyang county hospital (18) H Xiao; Ankang central hospital (15) J Zhang; Baoji railway hospital (15) Q Li; Mian county hospital (14) Z Zhang; Shaanxi railway central hospital (13) R Cheng; Long county hospital (12) J Li; Shenmu county hospital (11) Z Li; Tongchuan mining bureau central hospital (11) S Wang; Luonan county hospital (10) Z Ding; Baoji people's hospital (9) L Li; Qishan county hospital (9) Z Li; Xian railway bureau first hospital (8) G Ren; Yulin district first hospital (8) S Ye; Fugu county hospital (8) W Jia; Yulin district second hospital (8) X Xu.

Sichuan—Chengdu second people's hospital (46) Q Li; Chengdu first people's hospital (32) Y Yan; Zhongjiang county hospital (31) S Li; Langzhong people's hospital (31) S Pu; Panzhihua central hospital (28) J Tian; Deyang people's hospital (25) S Wen; Pi county hospital (24) T Liu; Huaxi medical college first hospital (21) X Chen; Neijiang second people's hospital (21) J Liao; Shuangliu county first people's hospital (20) D Su; Chengdu third people's hospital (20) W Wang; Sichuan provincial people's hospital (19) X Zhou; Jianyang people's hospital (19) Z Gong; Nanbu county hospital (16) Y He; Dazhou central hospital (15) M Li; Gong county hospital (15) J Yang; Yibin first people's hospital (14) C Li; Pingchang county hospital (14) D Zhang; Puge county hospital (13) J Yang; Bazhong people's hospital (13) Z Wang; Leshan Redcross hospital (12) X Su; Guangyuan 410 hospital (12) Y He; Leshan people's hospital (10) H Liu; Pujiang people's hospital (9) J Yang; Chengdu seventh people's hospital (9) C Ceng; Santai county hospital (8) G Liu; Chengdu railway bureau central hospital (8) Y Lu; Panzhihua steel and iron corporation hospital (8) S Zhou.

Tianjin—Tianjin third hospital (297) G Zheng, Z Liu; Tianjin fifth hospital (114) W Zheng, J Zheng; Tianjin Hexi hospital (106) Z Qu, H Man; Tianjin medical university second hospital (76) T Huang; Tianjin fourth hospital (71) C Song; Tianjin second hospital (64) G Ma; Tianjin Chinese medicine college second hospital (54) W Du; Tianjin chest hospital (52) C Liang; Tianjin Ninghe county hospital (48) D Yu; Tianjin People's hospital (44) Q Li; Tianjin medical university general hospital (40) Z Wan; PLA 254 hospital (36) K Pu; Tianjin Tianhe hospital (34) Z Zhang; Tianjin third central hospital (21) S Zhou; Tianjin Huanhu hospital (21) C Zhang; Tianjin Nankai hospital (20) R Yuan.

Xinjiang—Shihezi people's hospital (84) G He; Urumqi railway bureau central hospital (36) Y Wang; Urumqi airforce hospital (26) Z Yuan; Urumqi friendship hospital (22) X Xia; Xinjiang medical university first hospital (10) X Hong.

Yunnan—Dali first people's hospital (49) Z Liu; Yunnan provincial third hospital (40) H Li; Baoshan second people's hospital (22) G Lu; Luxi county hospital (15) T Da; Shilin county hospital (15) J Yin; Yunnan provincial red cross hospital (8) X Huang.

Zhejiang—Shaoxing second hospital (27) F Qin; Lanxi people's hospital (19) X He; Zhoushan people's hospital (15) J Yu; Cangnan county second people's hospital (14) M Chen.

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References

1 Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases, part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001; **104:** 2746–53.

2 ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **2:** 349–60.

3 Herbert JM, Frechel D, Vallee E, Kieffer G, Gouy D, Berger Y. Clopidogrel, a novel antiplatelet and antithrombotic agent. *Cardiovasc Drug Rev* 1993; **11:** 180–98.

4 Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999; **100:** 1667–72.

5 CAPRIE steering committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; **348:** 1329–39.

6 Gregorini L, Marco J. Ticlopidine and aspirin interactions. *Heart* 1997; **77:** 11–12.

7 Mishkel GJ, Aguirre FV, Ligon RW, Rocha-Singh KJ, Lucore CL. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *JACC* 1999; **34:** 1884–90.

8 Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288:** 2411–20.

9 CURE investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *NEJM* 2001; **345:** 494–502.

10 Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352:** 1179–89.

11 CCS-2 collaborative group. Rationale, design and organisation of the second Chinese cardiac study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. *J Cardiovasc Risk* 2000; **7:** 435–41.

12 COMMIT collaborative group. Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1622–32.

13 Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995; **345:** 686–87.

14 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1976; **34:** 585–612.

15 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.

16 Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10-year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 1998; **316:** 1337–43.

17 Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: Rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2004; **148:** 263–68.

18 Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: a meta-analysis. *JACC* 1992; **19:** 671–77.

19 Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation* 2000; **101:** 2823–28.

20 Angiolillo DJ, Fernández-Ortiz A, Bernardo E, et al. High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability. *Eur Heart J* 2004; **25:** 1903–10.

21 Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003; **107:** 966–72.

EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*

ABSTRACT

Background Despite current treatments, patients who have acute coronary syndromes without ST-segment elevation have high rates of major vascular events. We evaluated the efficacy and safety of the antiplatelet agent clopidogrel when given with aspirin in such patients.

Methods We randomly assigned 12,562 patients who had presented within 24 hours after the onset of symptoms to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) (6259 patients) or placebo (6303 patients) in addition to aspirin for 3 to 12 months.

Results The first primary outcome — a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke — occurred in 9.3 percent of the patients in the clopidogrel group and 11.4 percent of the patients in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95 percent confidence interval, 0.72 to 0.90; $P<0.001$). The second primary outcome — the first primary outcome or refractory ischemia — occurred in 16.5 percent of the patients in the clopidogrel group and 18.8 percent of the patients in the placebo group (relative risk, 0.86, $P<0.001$). The percentages of patients with in-hospital refractory or severe ischemia, heart failure, and revascularization procedures were also significantly lower with clopidogrel. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7 percent vs. 2.7 percent; relative risk, 1.38; $P=0.001$), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 percent vs. 1.8 percent, $P=0.13$) or hemorrhagic strokes.

Conclusions The antiplatelet agent clopidogrel has beneficial effects in patients with acute coronary syndromes without ST-segment elevation. However, the risk of major bleeding is increased among patients treated with clopidogrel. (N Engl J Med 2001;345: 494-502.)

THROMBOSIS caused by a ruptured or eroded atherosclerotic plaque is the usual underlying mechanism of acute coronary syndromes.[1] Aspirin and heparin reduce the risk of death from cardiovascular causes, new myocardial infarction, and recurrent ischemia,[2,3] but there is still a substantial risk of such events in both the short term and the long term. Intravenous glycoprotein IIb/IIIa receptor blockers have been shown to reduce the incidence of early events, mainly among patients who are treated according to an invasive strategy,[4,5] but long-term oral therapy with glycoprotein IIb/IIIa receptor blockers is not beneficial and may even increase mortality.[6] Similarly, continuing treatment with low-molecular-weight heparin beyond one week has not been shown to be effective.[7] Although the long-term use of oral anticoagulants may be useful, no convincing evidence of their benefit is yet available.[8] Therefore, there is a need to reduce further the risk of ischemic events in a broad spectrum of patients both when they first present with acute coronary syndromes and in the long term.

The thienopyridine derivatives, ticlopidine and clopidogrel, are antiplatelet agents that inhibit the platelet aggregation induced by adenosine diphosphate, thereby reducing ischemic events.[9] Combining one of these drugs with aspirin, which blocks the thromboxane-mediated pathway, may have an additive effect. In patients who are undergoing percutaneous transluminal coronary angioplasty (PTCA) with stenting, short-term aspirin treatment plus a thienopyridine derivative results in a substantially lower rate of myocardial infarction than does either aspirin alone or warfarin.[10] However, the role of long-term combined therapy with aspirin and an antiplatelet agent in a broader group of patients at high risk for cardiovascular events is unknown. We therefore designed the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial to compare the efficacy and safety of the early and long-term use of clopidogrel plus aspirin with those of aspirin alone in patients with acute coronary syndromes and no ST-segment elevation.

METHODS

Study Design

We undertook a randomized, double-blind, placebo-controlled trial comparing clopidogrel with placebo in patients who presented with acute coronary syndromes without ST-segment elevation. The design and rationale of the study have been reported previously.[9]

Study Patients

Patients were eligible for the study if they had been hospitalized within 24 hours after the onset of symptoms and did not have ST-segment elevation. Initially, patients older than 60 years

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of age with no new electrocardiographic changes but with a history of coronary artery disease were included. However, after a review of the overall rates of events among the first 3000 patients, the steering committee recommended that we enroll only patients who had either electrocardiographic changes or an elevation in the serum level of cardiac enzymes or markers at entry. We excluded patients with contraindications to antithrombotic or antiplatelet therapy, those who were at high risk for bleeding or severe heart failure, those who were taking oral anticoagulants, and those who had undergone coronary revascularization in the previous three months or had received intravenous glycoprotein IIb/IIIa receptor inhibitors in the previous three days.

After we had obtained written informed consent, patients were randomly assigned to either the clopidogrel group or the placebo group by a central, 24-hour, computerized randomization service. Permuted-block randomization, stratified according to clinical center, was used. A loading dose of clopidogrel (300 mg orally) or matching placebo was administered immediately, followed by clopidogrel (75 mg per day) or matching placebo for 3 to 12 months (mean duration of treatment, 9 months). Aspirin (recommended dose, 75 to 325 mg daily) was started or continued simultaneously with the study drug. Follow-up assessments occurred at discharge, at one and three months, and then every three months until the end of the study.

Study Organization

Patients were recruited between December 1998 and September 2000 at 482 centers in 28 countries. The ethics review board at each institution approved the study. The study was organized and coordinated and all the data were managed and analyzed by the Canadian Cardiovascular Collaboration Project Office, McMaster University, Hamilton, Ontario. A steering committee consisting of national coordinators oversaw the study. The data were periodically reviewed by an independent data and safety monitoring board.

Outcomes

The first primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, and the second primary outcome was the composite of the first primary outcome or refractory ischemia. The secondary outcomes were severe ischemia, heart failure, and the need for revascularization. The safety-related outcomes were bleeding complications, which were categorized as life-threatening, major (requiring the transfusion of 2 or more units of blood), or minor. All primary outcomes and life-threatening and major bleeding complications were adjudicated by persons who were unaware of the patients' treatment-group assignments.

Definitions

Death from cardiovascular causes was defined as any death for which there was no clearly documented nonvascular cause. Myocardial infarction was defined by the presence of at least two of the following: ischemic chest pain; the elevation of the serum levels of cardiac markers or enzymes (troponin, creatine kinase, creatine kinase MB isoenzyme, or other cardiac enzymes) to at least twice the upper limit of the normal reference range or three times the upper limit of normal within 48 hours after percutaneous coronary intervention (or to a level 20 percent higher than the previous value if the level had already been elevated because of an early myocardial infarction); and electrocardiographic changes compatible with infarction.[9] Stroke was defined as a new focal neurologic deficit of vascular origin lasting more than 24 hours. Stroke was further classified as the result of intracranial hemorrhage, ischemia (if a computed tomographic or magnetic resonance imaging scan was available), or uncertain cause.

Refractory ischemia in the hospital was defined as recurrent chest pain lasting more than five minutes with new ischemic electrocardiographic changes while the patient was receiving optimal medical therapy (two antianginal agents, one of which was intravenous nitrate unless such therapy was contraindicated) and leading to additional interventions (such as thrombolytic therapy, cardiac catheterization, the insertion of an intraaortic balloon pump, coronary revascularization, or transfer to a referral hospital for an invasive procedure) by midnight of the next calendar day. Refractory ischemia after discharge was defined by rehospitalization lasting at least 24 hours for unstable angina, with ischemic electrocardiographic changes. Severe ischemia (in the hospital) was defined as ischemia that was similar to in-hospital refractory ischemia but for which no urgent intervention was performed. Recurrent angina (in the hospital) was defined similarly, but electrocardiographic changes were not required.

Major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood. Major bleeding was classified as life-threatening if the bleeding episode was fatal or led to a reduction in the hemoglobin level of at least 5 g per deciliter or to substantial hypotension requiring the use of intravenous inotropic agents, if it necessitated a surgical intervention, if it was a symptomatic intracranial hemorrhage, or if it necessitated the transfusion of 4 or more units of blood. Minor bleeding episodes included other hemorrhages that led to the interruption of the study medication.

Statistical Analysis

The study was initially designed to include 9000 patients, with an expected rate of events in the placebo group of 12 to 14 percent. However, because the rate of events appeared to be lower than had originally been expected, the size of the study was increased. Assuming a rate of 10 percent in the placebo group for the first primary outcome and a two-sided alpha level of 0.045, a study with 12,500 patients would have 90 percent power to detect a 16.9 percent reduction in risk. For the second primary outcome, assuming a 14 percent rate of events in the placebo group and a two-sided alpha level of 0.01, the study had 90 percent power to detect a reduction of 16.4 percent in risk. Partitioning the alpha maintains an overall level of 0.05, after adjustment for the overlap between the two sets of outcomes. All analyses were based on the intention-to-treat principle and used either the log-rank statistic or the chi-square test. Subgroup analyses were conducted with the use of tests for interactions in the Cox regression model.

The data and safety monitoring board monitored the incidence of the primary outcome to determine the benefit of clopidogrel, using a modified Haybittle–Peto boundary of 4 SD in the first half of the study and 3 SD in the second half of the study. The boundary had to be exceeded at two or more consecutive time points, at least three months apart, for the board to consider terminating the study early. There were two formal interim assessments performed at the times when approximately one third and two thirds of the expected events had occurred. Despite the fact that the preset boundary indicating efficacy had been crossed by the time of the second interim analysis, the board recommended that the trial continue until its planned end, in order to define more clearly whether the risks of major bleeding episodes could offset the benefits of therapy.

All unrefuted events that occurred up to the end of the scheduled follow-up period on December 6, 2000, are included in the analyses. Vital status was ascertained for 12,549 of the 12,562 patients who underwent randomization (99.9 percent), with 6 patients in the clopidogrel group and 7 in the placebo group lost to follow-up.

RESULTS

The base-line characteristics of the patients are shown in Table 1.

Primary Outcomes

The first primary outcome — death from cardiovascular causes, nonfatal myocardial infarction, or stroke — occurred in 582 of the 6259 patients in the clo-

pidogrel group (9.3 percent) as compared with 719 of the 6303 patients in the placebo group (11.4 percent); relative risk, 0.80; 95 percent confidence interval, 0.72 to 0.90; P<0.001) (Fig. 1 and 2 and Table 2). The rate of the second primary outcome — death from cardiovascular causes, nonfatal myocardial infarction, stroke, or refractory ischemia — was also higher in the placebo group (1187 patients [18.8 percent]) than in the clopidogrel group (1035 patients [16.5 percent]; relative risk, 0.86; 95 percent confidence interval, 0.79 to 0.94; P<0.001). The rate of each component of these composite outcomes also tended to be lower in the clopidogrel group. However, the clearest difference was observed in the rates of myocardial infarction (Table 2). With respect to refractory ischemia, the difference was observed primarily in first events that occurred during the initial hospitalization (85 in the clopidogrel group as compared with 126 in the placebo group; relative risk, 0.68; 95 percent confidence interval, 0.52 to 0.90; P=0.007), with little difference in the rate of rehospitalization for unstable angina.

Table 1. Base-Line Demographic Characteristics, Medical History, Electrocardiographic Changes, and Drug Therapy.*

Characteristic	Clopidogrel Group (N=6259)	Placebo Group (N=6303)
Age — yr	64.2±11.3	64.2±11.3
Female sex — no. (%)	2420 (38.7)	2416 (38.3)
Time from onset of pain to randomization — hr	14.2±7.2	14.1±7.1
Heart rate — beats/min	73.2±14.8	73.0±14.6
Systolic blood pressure — mm Hg	134.4±22.5	134.1±22.0
Diagnosis at study entry — no. (%)		
Unstable angina	4690 (74.9)	4724 (74.9)
Suspected myocardial infarction	1569 (25.1)	1579 (25.1)
Associated myocardial infarction — no. (%)†	1624 (25.9)	1659 (26.3)
Medical history — no. (%)		
Myocardial infarction	2029 (32.4)	2015 (32.0)
CABG or PTCA	1107 (17.7)	1139 (18.1)
Stroke	274 (4.4)	232 (3.7)
Heart failure	462 (7.4)	492 (7.8)
Hypertension	3750 (59.9)	3642 (57.8)
Diabetes	1405 (22.4)	1435 (22.8)
Current or former smoker	3790 (60.6)	3841 (60.9)
Electrocardiographic abnormality — no. (%)‡		
Any	5863 (93.7)	5921 (93.9)
ST segment		
Depression ≥1 mm	2642 (42.2)	2646 (42.0)
Elevation ≤1 mm	203 (3.2)	199 (3.2)
Transient elevation >2 mm	38 (0.6)	37 (0.6)
T-wave inversion		
Major (≥2 mm)	1589 (25.4)	1635 (25.9)
Other (<2 mm)	721 (11.5)	713 (11.3)
Other	670 (10.7)	690 (10.9)
Medications at time of randomization — no. (%)		
Aspirin	4168 (66.6)	4134 (65.6)
Heparin or LMW heparin	4522 (72.3)	4605 (73.1)
ACE inhibitor	2347 (37.5)	2309 (36.6)
Beta-blocker	3678 (58.8)	3690 (58.5)
Calcium-channel blocker	1784 (28.5)	1771 (28.1)
Lipid-lowering agent	1599 (25.6)	1586 (25.2)
Intravenous nitrate	2836 (45.3)	2906 (46.1)

*Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, LMW low molecular weight, and ACE angiotensin-converting enzyme.

†An associated myocardial infarction was defined as a myocardial infarction associated with the episode of pain that occurred before randomization.

‡Data on the particular type of abnormality were missing for one patient in the placebo group.

Other In-Hospital Outcomes

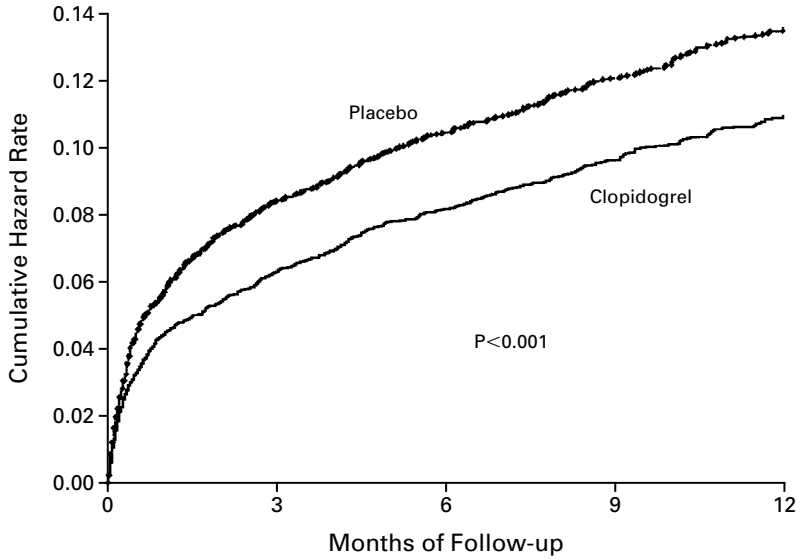
Significantly fewer patients in the clopidogrel group than in the placebo group had severe ischemia (176 patients [2.8 percent] vs. 237 patients [3.8 percent]; relative risk, 0.74; 95 percent confidence interval, 0.61 to 0.90; P=0.003) or recurrent angina (1307 [20.9 percent] vs. 1442 [22.9 percent]; relative risk, 0.91; 95 percent confidence interval, 0.85 to 0.98; P=0.01) (Fig. 3). Slightly fewer patients in the clopidogrel group underwent coronary revascularization during the study (36.0 percent vs. 36.9 percent), but the difference was accounted for entirely by a difference in the rate of revascularization during the initial period of hospitalization (20.8 percent in the clopidogrel group vs. 22.7 percent in the placebo group, P=0.03). Radiologic evidence of heart failure was found in fewer patients in the clopidogrel group (229 [3.7 percent], vs. 280 [4.4 percent] in the placebo group; relative risk, 0.82; 95 percent confidence interval, 0.69 to 0.98; P=0.03).

Temporal Trends

The rate of the first primary outcome was lower in the clopidogrel group both within the first 30 days after randomization (relative risk, 0.79; 95 percent confidence interval, 0.67 to 0.92) and between 30 days and the end of the study (relative risk, 0.82; 95 percent confidence interval, 0.70 to 0.95) (Fig. 1 and 2). Further analysis indicated that the benefit of clopidogrel was apparent within a few hours after randomization, with the rate of death from cardiovascular causes, nonfatal myocardial infarction, stroke, or refractory or severe ischemia significantly lower in the clopidogrel group by 24 hours after randomization (1.4 percent in the clopidogrel group vs. 2.1 percent in the placebo group; relative risk, 0.66; 95 percent confidence interval, 0.51 to 0.86).

Subgroup Analyses

The consistency of the results in a number of key subgroups is documented in Figure 4. The benefits were also consistent among subgroups receiving different doses of aspirin and among those receiving or not receiving lipid-lowering drugs, beta-blockers, heparin, or angiotensin-converting–enzyme inhibitors at



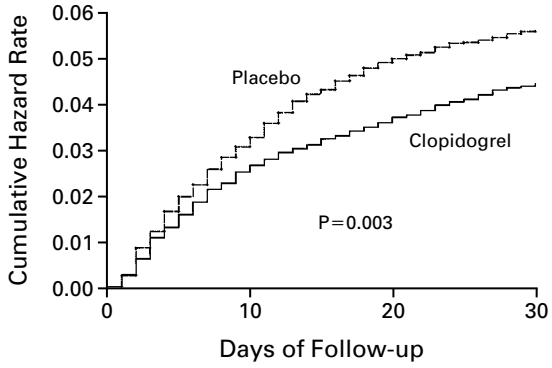
No. at Risk					
Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

Figure 1. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study.
The results demonstrate the sustained effect of clopidogrel.

the time of randomization. There was a tendency toward a greater benefit among patients who had previously undergone revascularization (relative risk of the first primary outcome, 0.56; 95 percent confidence interval, 0.43 to 0.72) than among those who had not (relative risk, 0.88; 95 percent confidence interval, 0.78 to 0.99; P for interaction = 0.002). However, these results should be interpreted cautiously, given the large numbers of subgroup analyses that were performed. Furthermore, consistent benefits were observed irrespective of whether patients underwent revascularization procedures after randomization.

Safety

Major bleeding was significantly more common in the clopidogrel group (3.7 percent in the clopidogrel group as compared with 2.7 percent in the placebo group; relative risk, 1.38; 95 percent confidence interval, 1.13 to 1.67; P=0.001) (Table 3). There were 135 patients with life-threatening bleeding episodes in the clopidogrel group (2.2 percent) as compared with 112 in the placebo group (1.8 percent; relative risk, 1.21; 95 percent confidence interval, 0.95 to 1.56). There was no excess rate of fatal bleeding, bleeding requiring surgical intervention, or hemorrhagic stroke. The excess major bleeding episodes were gastrointestinal hemorrhages and bleeding at the sites of



No. at Risk				
Placebo	6303	6108	5998	5957
Clopidogrel	6259	6103	6035	5984

Figure 2. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the First 30 Days after Randomization.
The results demonstrate the early effect of clopidogrel.

TABLE 2. INCIDENCE OF THE MAIN STUDY OUTCOMES.*

OUTCOME	CLOPIDOGREL GROUP (N=6259)	PLACEBO GROUP (N=6303)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
First primary outcome: nonfatal myocardial infarction, stroke, or death from cardiovascular causes	582 (9.3)	719 (11.4)	0.80 (0.72–0.90)	<0.001
Second primary outcome: first primary outcome or refractory ischemia	1035 (16.5)	1187 (18.8)	0.86 (0.79–0.94)	<0.001
Death from cardiovascular causes	318 (5.1)	345 (5.5)	0.93 (0.79–1.08)	
Myocardial infarction†	324 (5.2)	419 (6.7)	0.77 (0.67–0.89)	
Q-wave	116 (1.9)	193 (3.1)	0.60 (0.48–0.76)	
Non–Q-wave	216 (3.5)	242 (3.8)	0.89 (0.74–1.07)	
Stroke	75 (1.2)	87 (1.4)	0.86 (0.63–1.18)	
Refractory ischemia‡	544 (8.7)	587 (9.3)	0.93 (0.82–1.04)	
During initial hospitalization	85 (1.4)	126 (2.0)	0.68 (0.52–0.90)	
After discharge	459 (7.6)	461 (7.6)	0.99 (0.87–1.13)	
Death from noncardiovascular causes	41 (0.7)	45 (0.7)	0.91 (0.60–1.39)	

*The number of patients who died from cardiovascular causes or had a nonfatal myocardial infarction was 539 (8.6 percent) in the clopidogrel group and 660 (10.5 percent) in the placebo group (P<0.001; relative risk, 0.81; 95 percent confidence interval, 0.72 to 0.91). The corresponding numbers at 30 days were 241 (3.9 percent) and 305 (4.8 percent) (relative risk, 0.79; 95 percent confidence interval, 0.67 to 0.94; P=0.007). CI denotes confidence interval.

†Some patients had both a Q-wave and a non–Q-wave myocardial infarction.

‡Only the first ischemic event was counted for each patient.

arterial punctures. The number of patients who required the transfusion of 2 or more units of blood was higher in the clopidogrel group (177 [2.8 percent]) than in the placebo group (137 [2.2 percent], P=0.02). The rate of major bleeding episodes was higher early (within 30 days after randomization: 2.0 percent vs. 1.5 percent; relative risk, 1.31; 95 percent confidence interval, 1.01 to 1.70) and also late (more than 30 days after randomization: 1.7 percent vs. 1.1 percent; relative risk, 1.48; 95 percent confidence interval, 1.10 to 1.99). Overall, there was no significant excess of major bleeding episodes after coronary-artery bypass grafting (CABG) (1.3 percent vs. 1.1 percent; relative risk, 1.26; 95 percent confidence interval, 0.93 to 1.71). However, in most patients scheduled for CABG surgery, the study medication was discontinued before the procedure (median time before the procedure, five days). In the 910 patients in whom the study medication was discontinued more than five days before the procedure (five days being the duration of the effect of clopidogrel), there was no apparent excess of major bleeding within seven days after surgery (4.4 percent of the patients in the clopidogrel group vs. 5.3 percent of those in the placebo group). In the 912 patients who stopped taking the medications within five days before CABG surgery, the rate of major bleeding was 9.6 percent in the clopidogrel group and 6.3 percent in the placebo group (relative risk, 1.53; P=0.06). Overall, the risk of minor bleeding was significantly higher in the clopidogrel group than in the placebo group (322 [5.1 percent] vs. 153 [2.4 percent]; P<0.001). The numbers of patients with thrombocytopenia (28 in the placebo group and 26 in the clopidogrel group) or neutropenia (5 and 8, respectively) were similar.

Adherence to Study Medication and Aspirin

A total of 46.2 percent of the patients in the clopidogrel group discontinued the study medication temporarily (for more than five days), as compared with 45.4 percent in the placebo group. The most common reason for the temporary discontinuation of the study medication was the need for revascularization or another surgical procedure; 84 percent of the patients with such a need discontinued the medication before the procedure. A total of 21.1 percent of the patients in the clopidogrel group discontinued the study medication permanently, as compared with 18.8 percent in the placebo group. A total of 99 percent of the patients in both groups were taking aspirin while they were in the hospital, 96 percent were taking it at three months, and 94 percent at the final visit. The use of all other medications (other than thrombolytic therapy and glycoprotein IIb/IIIa receptor inhibitors) was similar in the clopidogrel group and the placebo group.

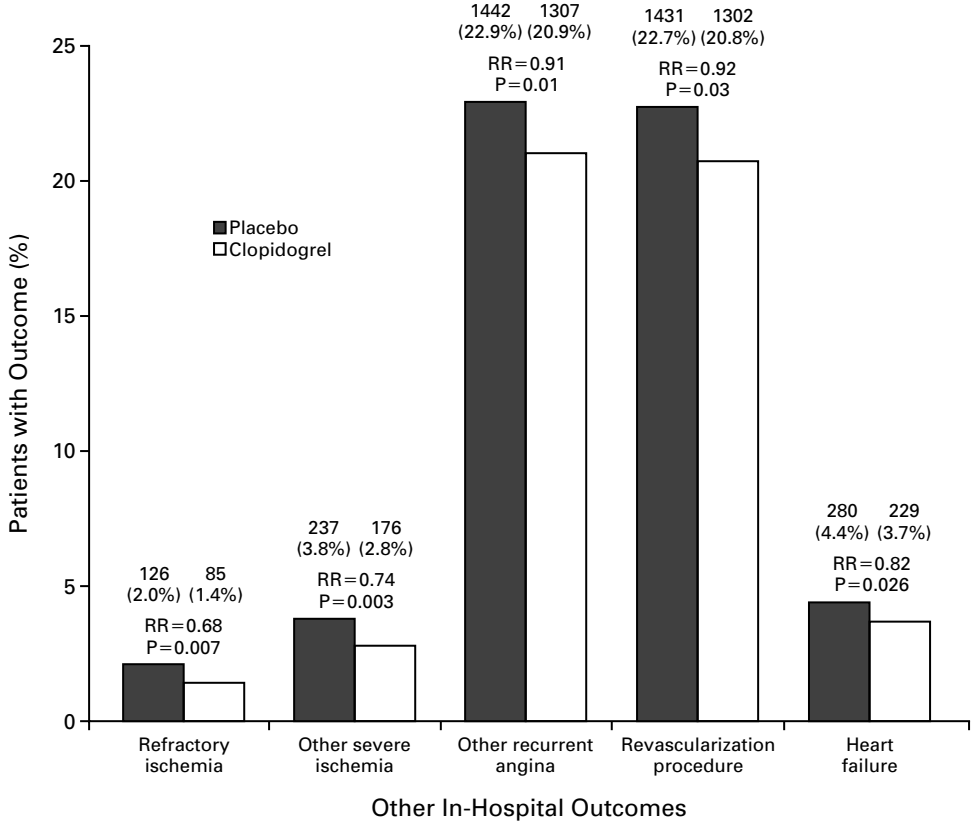


Figure 3. Proportions of Patients Who Had Events Other Than Those Included in the First Primary Outcome while They Were in the Hospital.

The numbers and percentages of patients in each group with the specified outcome are given above the bars. RR denotes relative risk.

Thrombolytic Therapy and Glycoprotein IIb/IIIa Receptor Inhibitors

A total of 71 patients in the clopidogrel group (1.1 percent) and 126 patients in the placebo group (2.0 percent) received thrombolytic therapy (relative risk, 0.57; 95 percent confidence interval, 0.43 to 0.76; $P<0.001$); 369 patients in the clopidogrel group (5.9 percent) and 454 in the placebo group (7.2 percent) received a glycoprotein IIb/IIIa receptor inhibitor (relative risk, 0.82; 95 percent confidence interval, 0.72 to 0.93; $P=0.003$).

DISCUSSION

Our study demonstrates the benefit of adding clopidogrel to the regimen of treatment for patients with acute coronary syndromes without ST-segment elevation who are receiving aspirin and other medications. Treatment with clopidogrel reduced the risk of myocardial infarction and recurrent ischemia, with a trend toward lower rates of stroke and death from cardiovascular causes. Fewer patients in the clopidogrel group received a thrombolytic agent or an intravenous glycoprotein IIb/IIIa receptor inhibitor. The benefits we observed were in addition to those of aspirin, which was recommended for all patients, indicating that blocking the adenosine diphosphate–receptor pathway with clopidogrel leads to further benefit.

Our study primarily included centers in which there was no routine policy of early use of invasive procedures, since such a policy would have led to a high rate of immediate discontinuation of the study medication and the use of an open-label thienopyridine derivative. Once a patient had been randomly assigned to a treatment group, there were no restrictions on the use of any therapy or intervention. In particular, if the clinician believed that angiography and revascularization were needed or that a thienopyridine derivative was indicated, the study medication could be stopped or open-label clopidogrel or ticlopidine could be used. In fact, 5491 patients (43.7 percent) underwent angiography, 2072 patients (16.5 percent) underwent CABG, and 2658 patients (21.2 percent) underwent PTCA. In 85.8 percent of the patients who underwent PTCA and 84.9 percent of those who underwent

Characteristic	No. of Patients	Percentage of Patients with Event	
		Placebo	Clopidogrel
Overall	12562	11.4	9.3
Associated MI	3283	13.7	11.3
No associated MI	9279	10.6	8.6
Male sex	7726	11.9	9.1
Female sex	4836	10.7	9.5
≤65 yr old	6354	7.6	5.4
>65 yr old	6208	15.3	13.3
ST-segment deviation	6275	14.3	11.5
No ST-segment deviation	6287	8.6	7.0
Enzymes elevated at entry	3176	13.0	10.7
Enzymes not elevated at entry	9386	10.9	8.8
Diabetes	2840	16.7	14.2
No diabetes	9722	9.9	7.9
Low risk	4187	6.7	5.1
Intermediate risk	4185	9.4	6.5
High risk	4184	18.0	16.3
History of revascularization	2246	14.4	8.4
No history of revascularization	10316	10.7	9.5
Revascularization after randomization	4577	13.9	11.5
No revascularization after randomization	7985	10.0	8.1

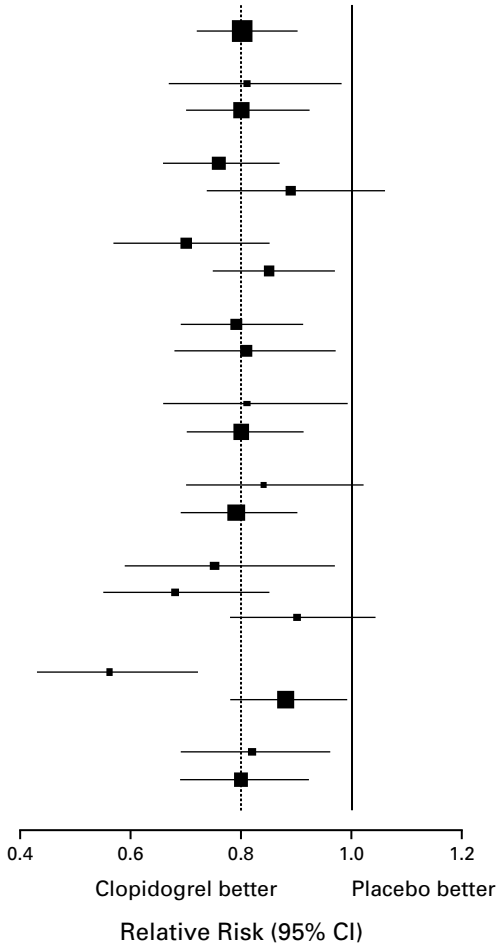


Figure 4. The Rates and Relative Risks of the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) in Various Subgroups.

The data show the consistency of the benefit of clopidogrel. The dotted line represents the average treatment effect. The size of each box is proportional to the number of patients in the individual analysis. An associated myocardial infarction (MI) was defined as a myocardial infarction associated with the episode of pain that occurred before randomization. Because of missing data, six patients could not be classified in a risk category. CI denotes confidence interval.

CABG, the use of the study medication was temporarily interrupted for more than five days, and the vast majority of the patients who underwent PTCA received a thienopyridine-type antiplatelet agent for about two to four weeks. In the patients who underwent CABG, the study medication was restarted after a median of 11 days. Although these interruptions of therapy with the study medication would tend to result in an underestimate of the difference between the clopidogrel group and the placebo group, they also permit us to make useful estimates of the benefits and risks of clopidogrel when it is used routinely and over the long term, as compared with a strategy of more selective and short-term use among those undergoing implantation of a coronary stent.

Clopidogrel prevented a range of ischemic coronary events — among them, myocardial infarction and severe and refractory ischemia. Clopidogrel was associated with a trend toward fewer ischemic strokes, and there was no increase in the rate of hemorrhagic stroke that would offset these benefits. There was a significant reduction in the incidence of heart failure with clopidogrel that was of about the same magnitude as the reduction in the incidence of ischemic events, suggesting that the reduction of ischemia can prevent heart failure. The benefits of clopidogrel were observed in

TABLE 3. BLEEDING COMPLICATIONS.*

VARIABLE	CLOPIDOGREL GROUP (N=6259)	PLACEBO GROUP (N=6303)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
Major bleeding	231 (3.7)	169 (2.7)	1.38 (1.13–1.67)	0.001
Necessitating transfusion of ≥2 units of blood	177 (2.8)	137 (2.2)	1.30 (1.04–1.62)	0.02
Life-threatening	135 (2.2)	112 (1.8)	1.21 (0.95–1.56)	0.13
Fatal	11 (0.2)	15 (0.2)		
Causing 5 g/dl drop in hemoglobin level	58 (0.9)	57 (0.9)		
Requiring surgical intervention	45 (0.7)	43 (0.7)		
Causing hemorrhagic stroke	7 (0.1)	5 (0.1)		
Requiring inotropic agents	34 (0.5)	34 (0.5)		
Necessitating transfusion of ≥4 units of blood	74 (1.2)	60 (1.0)		
Non–life-threatening	96 (1.5)	57 (0.9)	1.70 (1.22–2.35)	0.002
Site of major bleeding				
Gastrointestinal	83 (1.3)	47 (0.7)		
Retroperitoneal	8 (0.1)	5 (0.1)		
Urinary (hematuria)	4 (0.1)	5 (0.1)		
Arterial puncture site	36 (0.6)	22 (0.3)		
Surgical site	56 (0.9)	53 (0.8)		
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75–2.56)	<0.001
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48–1.94)	<0.001

*The number of patients with bleeding that met the criteria for major bleeding established by the Thrombolysis in Myocardial Infarction trial[11] was 68 in the clopidogrel group and 73 in the placebo group (relative risk, 0.94; 95 percent confidence interval, 0.68 to 1.30; P=0.70). The number with bleeding that met the criteria for life-threatening or severe bleeding established by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial[12] was 78 in the clopidogrel group and 70 in the placebo group (relative risk, 1.12; 95 percent confidence interval, 0.81 to 1.55; P=0.48). Some patients had more than one bleeding episode. CI denotes confidence interval.

a range of patients, including both patients who were undergoing revascularization procedures and those who were not. The benefits were also observed in those at low, medium, and high risk of cardiovascular events and those who were receiving various proven therapies such as aspirin, lipid-lowering drugs, angiotensin-converting–enzyme inhibitors, and beta-blockers.[13-16] The benefits of clopidogrel were apparent as early as the first 24 hours after randomization, indicating that the oral loading dose was rapidly effective. Thereafter, the differences between the two groups were maintained until the end of the study.

Clopidogrel increased the risk of minor and major bleeding episodes. For every 1000 patients treated with clopidogrel, 6 will require a transfusion. However, there was no excess in bleeding that caused strokes, required surgical intervention or inotropic agents, or caused permanent disability. Furthermore, the excess risk of bleeding we observed is similar to that observed with aspirin alone, as compared with a control, in previous studies and lower than that observed in most trials of the short-term intravenous use or the prolonged oral use of glycoprotein IIb/IIIa receptor inhibitors.[4,16,17] The risk of bleeding may have been partly mitigated by the temporary discontinuation of the study medication before surgery. Treatment with clopidogrel was not associated with an excess rate of any other type of adverse event that necessitated the discontinuation of the study drug; this finding indicates that the combination of clopidogrel and aspirin is as well tolerated as aspirin alone.

In summary, clopidogrel significantly reduces the risk of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, as well as a range of related ischemic events. The use of the drug, in addition to aspirin, is associated with an increased risk of bleeding.

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Drs. Yusuf, Mehta, Tognoni, and Fox have received honorariums for educational activities or have served as consultants to Bristol-Myers Squibb and Sanofi-Synthelabo.

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APPENDIX

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REFERENCES

1. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. N Engl J Med 2000;342:101-14.

2. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106. [Erratum, BMJ 1994;308:1540.]

3. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996;347:561-8.

4. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non–Q-wave acute myocardial infarction. N Engl J Med 1998;338:1488-97.

5. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularization: the GUSTO IV-ACS randomized trial. Lancet 2001;357:1915-24.

6. Chew DP, Bhatt D, Sapp S, Topol EJ. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a meta-analysis of phase III multicenter randomized trials. Circulation 2001;103:201-6.

7. FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999;354:701-7. [Erratum, Lancet 1999;354:1478.]

8. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. J Am Coll Cardiol 2001;37:475-84.

9. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.

10. CURE Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme: rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J 2000;21:2033-41.

11. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial — phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1-11.

12. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436-43.

13. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53. [Erratum, N Engl J Med 2000;342:748.]

14. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA 1988;260:2259-63.

15. Tonkin AM, Colquhoun D, Emberson J, et al. Effects of pravastatin in 3260 patients with unstable angina: results from the LIPID study. Lancet 2000;356:1871-5.

16. Anti-thrombotic Trialists Collaboration. Prevention of death, myocardial infarction and stroke by antiplatelet therapy: collaborative meta-analysis of 266 trials involving 200,000 patients at high risk of occlusive vascular disease. BMJ (in press).

17. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Lancet 2000;355:337-45.

CORRECTION

Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation

Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation . On page 502, 20 lines from the bottom of the left-hand column, ``B. Pontillo´´ should have been listed as ``D. Pontillo.´´

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CORRECTION

Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation

Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation . On page 494, at the end of the Results section of the abstract, the percentages of patients with episodes of life-threatening bleeding should have been ``*2.2* percent vs. 1.8 percent,´´ not ``*2.1* percent vs. 1.8 percent,´´ as printed. In the Manuscript Writing Committee listed at the bottom of the right-hand column, ``Keith K. Fox´´ should have read ``Keith A.A. Fox.´´ On page 498, on line 13 of the left-hand column, the rates of bleeding after coronary-artery bypass grafting should have read, ``*8.3* percent vs. *6.6* percent,´´ not ``*1.3* percent vs. *1.1* percent,´´ as printed.

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