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

*COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group**

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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*Collaborators and participating hospitals listed at end of paper

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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

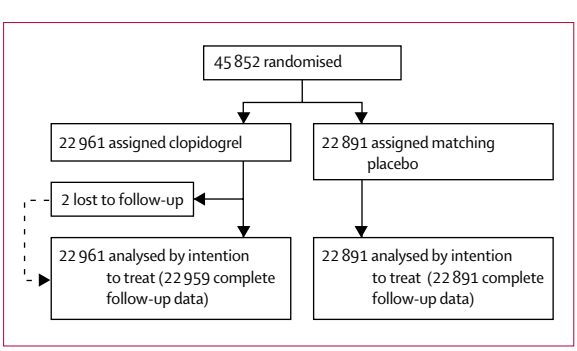


Figure 1: **Trial profile**

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

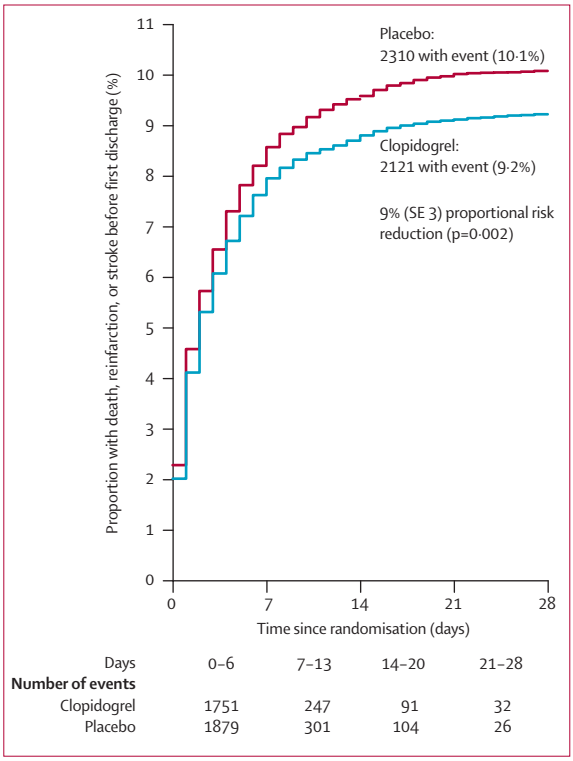
Both of the co-primary outcomes were significantly reduced during the scheduled treatment period by allocation to clopidogrel. For the primary composite outcome of death, reinfarction, or stroke, 2121 (9·2%) patients had at least one such event among the 22 961 clopidogrel-allocated patients compared 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

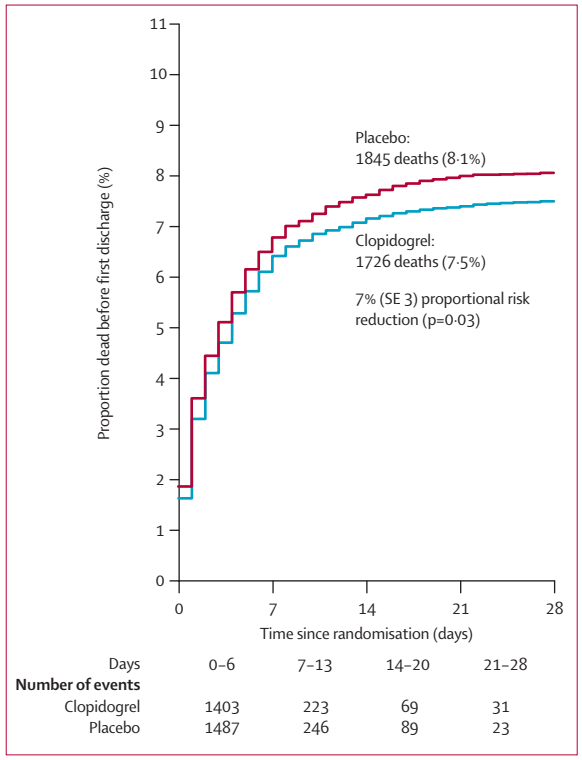
Data are number (%) unless otherwise indicated. *652 patients (301 clopidogrel *vs* 351 placebo) had more than one cause reported (including 530 patients with two, 111 with three, and 11 with four), all of which are tabulated as possible causes (ie, some deaths included in more than one row). †Nine patients (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

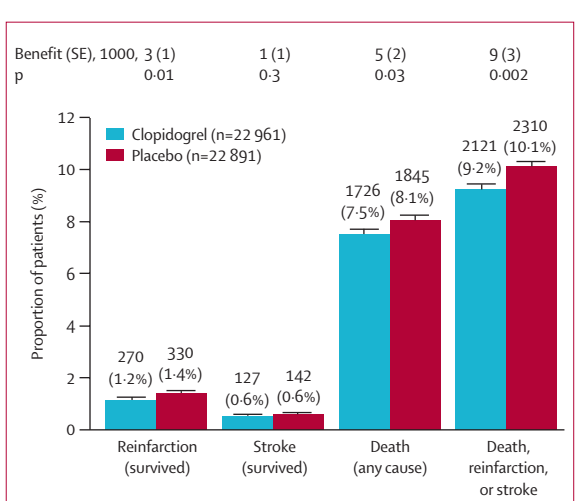


Figure 4: **Absolute effects of clopidogrel on death, reinfarction, or stroke**

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

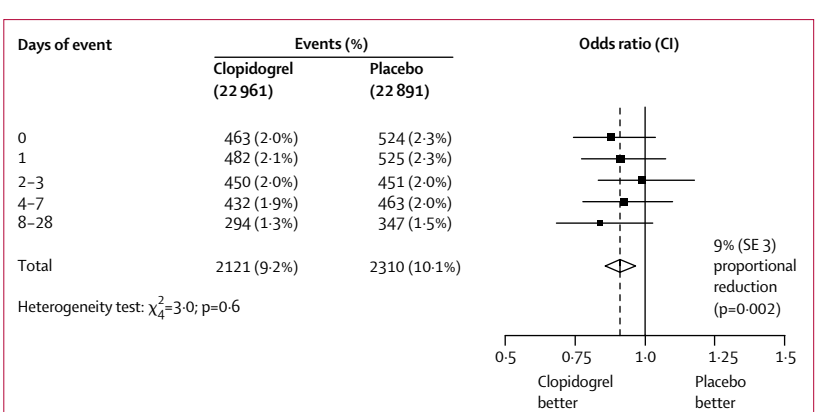
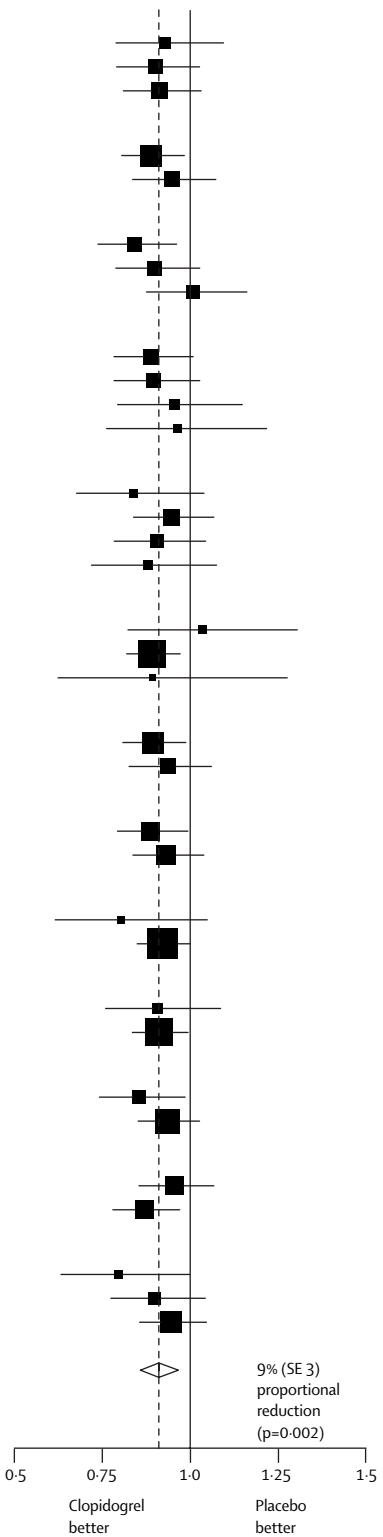


Figure 5: **Effects of clopidogrel allocation on death, reinfarction, or stroke by day of event**
Odds ratio in each period (black square with area proportional to number of events) and 99% CI (horizontal line). Broken vertical line indicates overall result, and diamond indicates its 95% CI.

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 (%)		Odds ratio (CI)	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%)	9% (SE 3) proportional reduction (p=0·002)	
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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Guizhou—The affiliated hospital of Guiyang medical College (101) P Li, Y Fang; Guizhou provincial people's hospital (85) X Wang; Liupanshui hospital (29) J Lin; Guiyang first people's hospital (21) H Mao; Xingyi people's hospital (20) S Zhou.
Hainan—Haikou people's hospital (62) M Chen; Danzhou first people's hospital (44) Y Zhou; Qiongshan people's hospital (34) S Hu; Hainan medical college affiliated hospital (29) M Yun; Hainan provincial second workers' hospital (24) Y Xu; Wenchang people's hospital (8) L Huang.
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 hospital (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.

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