Articles

Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study

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Summary

Background Despite the use of aspirin, there is still a risk of ischaemic events after percutaneous coronary intervention (PCI). We aimed to find out whether, in addition to aspirin, pretreatment with clopidogrel followed by long-term therapy after PCI is superior to a strategy of no pretreatment and short-term therapy for only 4 weeks after PCI.

Methods 2658 patients with non-ST-elevation acute coronary syndrome undergoing PCI in the CURE study had been randomly assigned double-blind treatment with clopidogrel (n=1313) or placebo (n=1345). Patients were pretreated with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, most patients (>80%) in both groups received open-label thienopyridine for about 4 weeks, after which study drug was restarted for a mean of 8 months. The primary endpoint was a composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI. The main analysis was by intention to treat.

Findings There were no drop-outs. 59 (4·5%) patients in the clopidogrel group had the primary endpoint, compared with 86 (6·4%) in the placebo group (relative risk 0·70 [95% CI 0·50–0·97], p=0·03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, myocardial infarction, or any revascularisation (p=0·03), and of cardiovascular death or myocardial infarction (p=0·047). Overall (including events before and after PCI) there was a 31% reduction cardiovascular death or myocardial infarction (p=0·002). There was less use of glycoprotein IIb/IIIa inhibitor in the clopidogrel group (p=0·001). At follow-up, there was no significant difference in major bleeding between the groups (p=0·64).

Interpretation In patients with acute coronary syndrome receiving aspirin, a strategy of clopidogrel pretreatment followed by long-term therapy is beneficial in reducing major cardiovascular events, compared with placebo.

Introduction

Antiplatelet therapy is an important adjunctive treatment that reduces ischaemic complications in patients undergoing percutaneous coronary intervention (PCI).[1–5] Ischaemic events after PCI are mainly the result of a platelet-dependent process that results in thrombosis at the site of mechanical plaque disruption and distal embolisation of platelet thrombi into the coronary microcirculation.[6–9] Although treatment with aspirin before PCI (pretreatment) reduces cardiac events, a substantial risk still remains. Therefore, there is a need to develop more effective antiplatelet strategies that can be given before PCI, with the goal of reducing events after the procedure.

In addition to pretreatment, long-term oral administration of antiplatelet therapy after PCI might also be beneficial because atherothrombosis is a generalised vascular disease that affects not only the target coronary lesion, but also other vascular territories. Despite the beneficial effects of long-term treatment with aspirin after PCI, there remains a significant risk of major cardiovascular events.[10–13] Although the intravenous glycoprotein IIb/IIIa inhibitors improve clinical outcomes when given for a short time,[5,14] longer term oral administration of these agents has not been effective, and might even be harmful.[12,15] Whether other, more effective long-term antiplatelet regimens can add to the beneficial effects of aspirin after PCI is currently unknown.

Clopidogrel is an oral antiplatelet agent of the thienopyridine class, which selectively and irreversibly inhibits the platelet ADP receptor. When clopidogrel is given with aspirin, the antiplatelet effect is synergistic.[16–18] This observation has been confirmed clinically in patients receiving intracoronary stents, in whom ticlopidine plus aspirin given after PCI for about 4 weeks was superior to aspirin alone or aspirin plus oral anticoagulation.[19]

The PCI CURE study was designed to test the hypothesis that, in addition to aspirin, treatment with clopidogrel before PCI is superior to placebo in preventing major ischaemic events afterwards. The second objective of

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the study was to determine whether long-term treatment with clopidogrel for up to 1 year after PCI would result in additional clinically relevant benefit.

Methods

Patients

PCI-CURE was a prospectively designed study of patients undergoing PCI who were randomised to double-blind therapy with clopidogrel or placebo in the Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE) trial.[19]

The inclusion and exclusion criteria for the CURE trial have been described previously.[19] Briefly, patients were eligible for inclusion if they had had symptoms indicative of acute coronary syndrome within the past 24 h and if they did not have ST-segment elevation of greater than 1 mm on their electrocardiogram. Other electro-cardiographic evidence of new ischaemia or concentrations of cardiac enzymes (including troponin) at least twice the upper limit of normal was required. Patients were excluded if they had contraindications to antithrombotic or antiplatelet therapy, if they were at high risk of bleeding, if they had New York Heart Association Class IV heart failure, if they required long-term oral anticoagulants, if they had undergone PCI or coronary-artery bypass grafting in the previous 3 months, or if they had received a glycoprotein IIb/IIIa inhibitor fewer than 3 days before randomisation. Informed consent and local ethics approval was obtained for all patients enrolled into the CURE trial.

Procedures

Patients were randomly assigned clopidogrel or placebo by a central, 24-h, computerised randomisation service located at the Canadian Cardiovascular Collaboration Project Office, McMaster University, Hamilton, Canada. A loading dose of clopidogrel 300 mg orally or matching placebo was given immediately on a double-blind basis. Aspirin (recommended dose 75–325 mg) was started or continued simultaneously with clopidogrel or placebo. PCI was done after randomisation at the discretion of the local investigator, and clopidogrel or placebo was continued up until this point.

After PCI, stented patients received an open-label thienopyridine (either clopidogrel or ticlopidine) in combination with aspirin for 2–4 weeks, after which administration of the randomly assigned study medication resumed until the end of the scheduled follow-up (3–12 months after randomisation). Although use of glycoprotein IIb/IIIa inhibitors was discouraged in the trial unless patients developed refractory ischaemia, their use was allowed during PCI.

The primary outcome of the study was the composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI. Cardiovascular death or myocardial infarction from the time of PCI to the scheduled end of the trial was also assessed to determine the effects of continuing clopidogrel long-term after PCI.

All deaths were regarded as cardiovascular (including deaths that were sudden, of unknown cause, or secondary to complications of a cardiac procedure) unless there was documented evidence of a clear non-cardiovascular cause. Myocardial infarction was defined as the presence of at least two of the three following criteria: ischaemic symptoms; cardiac enzyme concentration at least three times the upper limit of normal if within 48 h of PCI, and two times the upper limit of normal thereafter; or new electrocardiographic changes compatible with myocardial infarction. We did not routinely screen for periprocedural
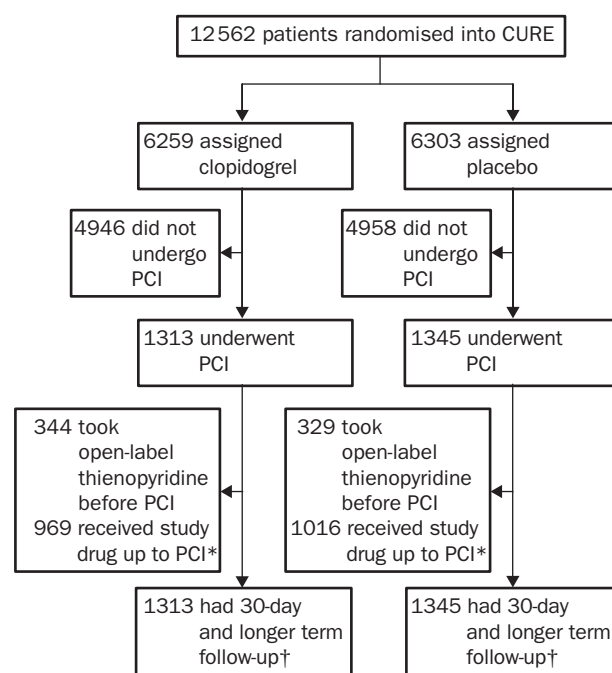

Figure 1: **Study profile**
*Per-protocol analysis. †Intention-to-treat analysis.

increases in cardiac enzyme concentrations; myocardial infarction was reported when it was clinically apparent. Urgent target-vessel revascularisation within 30 days of PCI was defined as either a second PCI or any coronary-artery bypass graft procedure done on a non-elective basis in the target vessel because of recurrent myocardial ischaemia. Major bleeding was defined as bleeding that was significantly disabling, intraocular, or requiring at least 2 units of blood. Major bleeding was subclassified as life threatening if it was fatal, if it led to a decrease in haemoglobin concentration of 50 g/L, if it caused significant hypotension requiring intravenous inotropes or surgical intervention, if it resulted in symptomatic intracranial haemorrhage, or if it necessitated transfusion of 4 or more units of blood. Minor bleeding was defined as other bleeding that led to interruption of study medication. Death, myocardial infarction, refractory ischaemia, and major and life-threatening bleeding were adjudicated by a

	Placebo (n=1345)	Clopidogrel (n=1313)
Patients' characteristics		
Mean (SD) age (years)	61·4 (10·9)	61·6 (11·2)
Women	405 (30·1%)	399 (30·3%)
Diabetes	255 (19·0%)	249 (19·0%)
Previous myocardial infarction	349 (26·0%)	359 (27·3%)
Previous PCI	185 (13·8%)	176 (13·4%)
Previous CABG	175 (13·0%)	157 (12·0%)
Smokers	396 (29·5%)	406 (30·9%)
ST depression	571 (42·4%)	567 (43·2%)
ST elevation	59 (4·4%)	65 (5·1%)
Stent use	1092 (81·3%)	1080 (82·4%)
Median (IQR) days after randomisation on which PCI done		
All PCI	10 (5–25)	10 (5–30)
PCI during initial hospital stay	6 (4–10)	6 (3–10)
PCI after initial hospital stay	49 (24–106)	49 (23–89)
Open-label thienopyridine use		
Before PCI	329 (24·7%)	344 (26·4%)
Overall	1131 (84·1%)	1089 (82·9%)

PCI=percutaneous coronary intervention. CABG=coronary-artery bypass graft.

Table 1: **Baseline characteristics, day of PCI, and use of open-label thienopyridine**

	Placebo (n=1345)	Clopidogrel (n=1313)	Relative risk (95% CI)	p
Events before PCI				
Myocardial infarction or refractory ischaemia	206 (15·3%)	159 (12·1%)	0·76 (0·62–0·93)	0·008
Myocardial infarction	68 (5·1%)	47 (3·6%)	0·68 (0·47–0·99)	0·04
Events from PCI to 30 days				
CV death, myocardial infarction, urgent revascularisation	86 (6·4%)	59 (4·5%)	0·70 (0·50–0·97)	0·03
CV death, myocardial infarction	59 (4·4%)	38 (2·9%)	0·66 (0·44–0·99)	0·04
CV death	13 (1·0%)	14 (1·1%)	1·10 (0·52–2·35)	
Myocardial infarction	51 (3·8%)	28 (2·1%)	0·56 (0·35–0·89)	
Q-wave myocardial infarction	32 (2·4%)	11 (0·8%)	0·35 (0·18–0·70)	
Urgent revascularisation	38 (2·8%)	25 (1·9%)	0·67 (0·41–1·11)	
Events from PCI to end of follow-up				
CV death, myocardial infarction	108 (8·0%)	79 (6·0%)	0·75 (0·56–1·00)	0·047
CV death, myocardial infarction, any revascularisation	292 (21·7%)	240 (18·3%)	0·83 (0·70–0·99)	0·03
CV death	31 (2·3%)	32 (2·4%)	1·07 (0·65–1·75)	
Myocardial infarction	85 (6·4%)	59 (4·5%)	0·71 (0·51–0·99)	
Q-wave myocardial infarction	47 (3·5%)	20 (1·5%)	0·43 (0·26–0·73)	
Any revascularisation	230 (17·1%)	186 (14·2%)	0·82 (0·68–1·00)	
Overall results: events before and after PCI				
CV death, myocardial infarction	169 (12·6%)	116 (8·8%)	0·69 (0·54–0·87)	0·002

PCI=percutaneous coronary intervention; CV=cardiovascular.

Table 2: **Major outcome events**

committee, the members of which were unaware of treatment allocation.

Statistical analysis
An intention-to-treat analysis was used as the primary analysis. Each patient's first PCI was counted as the index procedure. Results of a predefined per protocol analysis, in which patients who received open-label thienopyridine before PCI were excluded, was also done. All analyses of primary, secondary, and other outcomes were compared between the clopidogrel and placebo groups by use of the log-rank statistic. Time-to-event curves for the primary and other outcomes were generated with the Kaplan-Meier estimator.

To keep PCI selection bias to a minimum, we developed a propensity-score model using logistic regression to identify baseline factors (including treatment allocation) that were predictive of having a PCI in a randomly selected sample of half the patients from the CURE database; the model was then validated in the remaining half.[20–22] The validated propensity score was included in a Cox's regression model that compared the effect of clopidogrel and placebo in patients undergoing PCI. This approach allowed us to determine the effect of treatment allocation on clinical outcomes in patients undergoing PCI, after adjustment for selection bias, while still preserving the integrity of the randomised treatment allocation.

Results
Overall, 2658 of the 12 562 patients in the CURE trial underwent PCI. 1313 were assigned clopidogrel and 1345 placebo. No patients were lost to follow-up (figure 1). 1730 PCIs were done during the initial hospital stay, and 928 after discharge. During the initial hospital stay, the median number of days before PCI was 6 days in both groups and 10 days overall. The average duration of follow-up after PCI was 8 months, also in both groups.

Baseline characteristics among patients assigned placebo and clopidogrel were well balanced (table 1). Most patients in each group received an intracoronary stent. Unfractionated heparin was used during the procedure in 2313 (87%) of patients, and low-molecular-weight heparin in about 309 (12%). Target vessels for PCI were well balanced between the placebo and clopidogrel groups (left main 24 [1·8%] vs 23 [1·8%], proximal 351 [26·1%] vs

374 [28·5%] or mid/distal 300 [22·3%] vs 308 [23·5%], left anterior descending, circumflex 393 [29·3%] vs 380 [29·0%], right coronary 440 [32·8%] vs 419 [31·9%], and saphenous vein graft 32 [2·4%] vs 43 [3·3%]).

About a quarter of patients in each group received open-label thienopyridines before PCI (table 1), and more than 80% received them afterwards for a median of 30 days (IQR 19–33). The most common reason for open-label thienopyridine use after PCI was stent implantation (or expected stent implantation if started before PCI).

Before PCI, significantly fewer patients on clopidogrel than on placebo had a myocardial infarction or the composite of myocardial infarction or refractory ischaemia (table 2). Significantly fewer patients in the clopidogrel group than the placebo group had a primary outcome of cardiovascular death, myocardial infarction, or urgent revascularisation by 30 days after PCI (table 2, figure 2). The composite of cardiovascular death or myocardial infarction was also lower in the clopidogrel group. All deaths within the first 30 days were cardiovascular deaths and were similar between the groups (13 vs 14). Individually, patients on clopidogrel had significantly fewer myocardial infarctions and Q-wave myocardial infarctions than patients on placebo (table 2).

The per protocol analysis, which excluded patients who received open-label thienopyridine before PCI, showed that
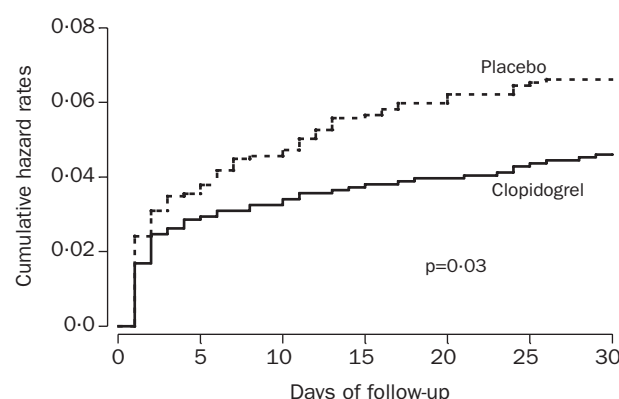

Figure 2: **Kaplan-Meier cumulative hazard rates for primary outcome of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation at 30 days after PCI**

Number of days after PCI	Placebo (n=1345)	Clopidogrel (n=1313)	Absolute risk	Relative risk (95% CI)
≤2	41 (3·0%)	32 (2·4%)	–0·6%	0·80 (0·50–1·27)
≤7	59 (4·4%)	40 (3·0%)	–1·4%	0·69 (0·46–1·03)
≤14	73 (5·4%)	48 (3·7%)	–1·7%	0·67 (0·47–0·96)
≤30	86 (6·4%)	59 (4·5%)	–1·9%	0·70 (0·50–0·97)

Table 3: **Primary outcome (cardiovascular death, myocardial infarction, urgent revascularisation) events prevented at various times within 30 days of PCI (intention-to-treat analysis)**

the number of patients with the primary endpoint of cardiovascular death, myocardial infarction, or urgent revascularisation was significantly lower in the clopidogrel group than in the placebo group (73 [7·2%] *vs* 41 [4·2%], relative risk 0·58 [95% CI 0·40–0·85], p=0·005]). This trend remained significant in those who received an
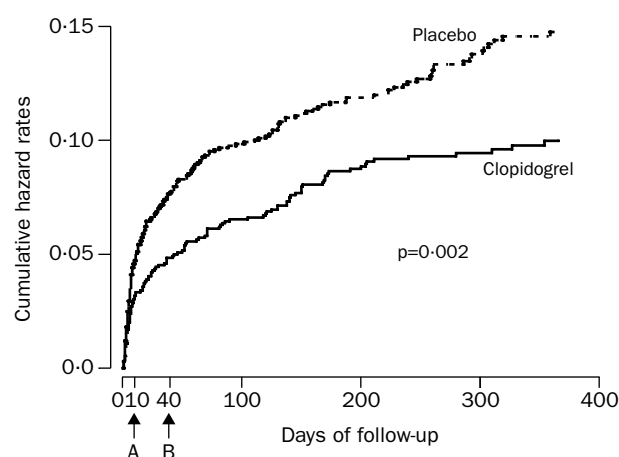

Figure 3: **Kaplan-Meier cumulative hazard rates for cardiovascular death or myocardial infarction from randomisation to end of follow-up**
A=median time from randomisation to percutaneous coronary intervention. B=30 days after median time of PCI.

intracoronary stent (49 [6·1%] *vs* 27 [3·5%], 0·56 [0·35–0·90], p=0·016).

The lower rate of cardiovascular death, myocardial infarction, or urgent revascularisation in the clopidogrel group was seen as early as 2 days after PCI, with continuing benefit until 30 days (table 3). Most patients received open-label thienopyridine after PCI (>80% in both groups), indicating that this early postprocedural benefit was mainly due to the effects of clopidogrel pretreatment.

From the time of PCI to the end of follow-up (mean 8 months after PCI), there were significantly fewer cardiovascular deaths or myocardial infarctions with clopidogrel than placebo (table 2). The number of cardiovascular deaths was similar between the groups at follow-up (31 *vs* 32); however, there were significantly fewer myocardial infarctions in the clopidogrel group than the placebo group (table 2). The difference in the number of myocardial infarctions between the groups was mainly due to a difference in Q-wave myocardial infarctions. There were also fewer patients with the composite of cardiovascular death, myocardial infarction, or any revascularisation in the clopidogrel group (table 2).

Between 30 days and the end of follow-up, the rate of cardiovascular death or myocardial infarction was consistently lower in the clopidogrel group than in the placebo group (52 [3·9%] *vs* 40 [3·1%], 0·79 [0·53–1·20]), as was the rate of cardiovascular death, myocardial infarction, or rehospitalisation (381 [28·9%] *vs* 324 [25·3%], 0·86 [0·74–1·00]).

Overall, when events before and after PCI were considered, there was a highly significant difference in

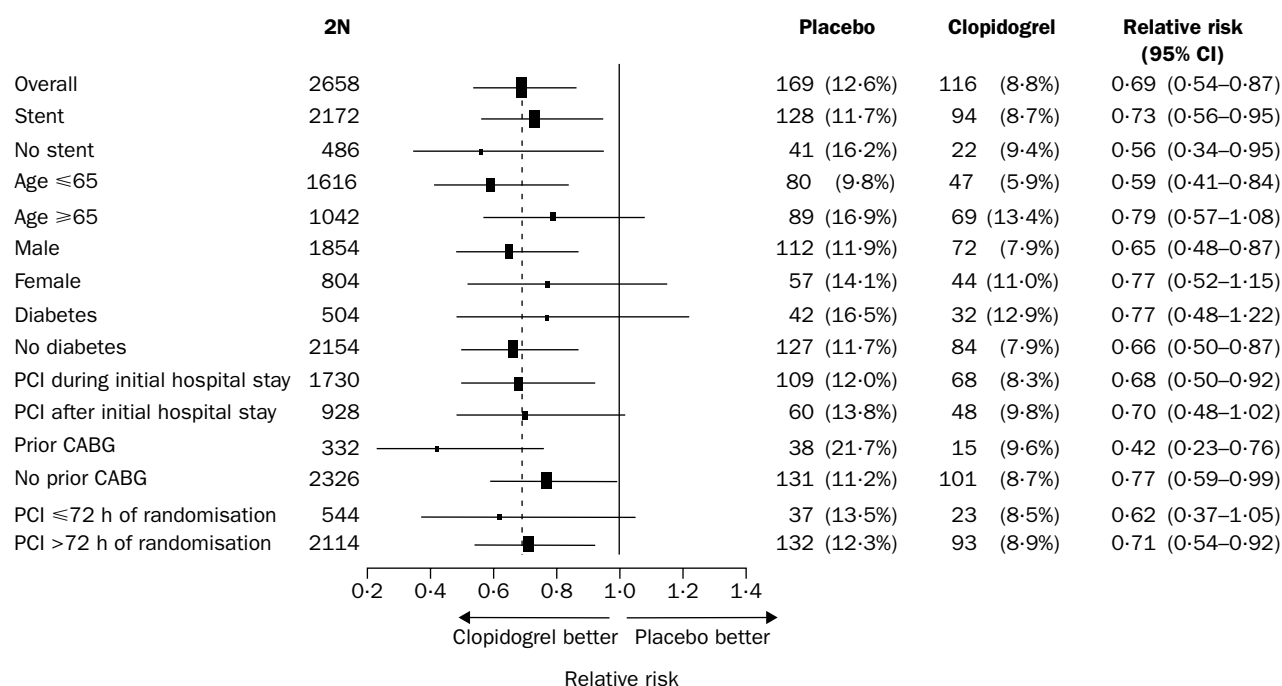|	2N		Placebo	Clopidogrel	Relative risk (95% CI)
Overall	2658		169 (12·6%)	116 (8·8%)	0·69 (0·54–0·87)
Stent	2172		128 (11·7%)	94 (8·7%)	0·73 (0·56–0·95)
No stent	486		41 (16·2%)	22 (9·4%)	0·56 (0·34–0·95)
Age ≤65	1616		80 (9·8%)	47 (5·9%)	0·59 (0·41–0·84)
Age ≥65	1042		89 (16·9%)	69 (13·4%)	0·79 (0·57–1·08)
Male	1854		112 (11·9%)	72 (7·9%)	0·65 (0·48–0·87)
Female	804		57 (14·1%)	44 (11·0%)	0·77 (0·52–1·15)
Diabetes	504		42 (16·5%)	32 (12·9%)	0·77 (0·48–1·22)
No diabetes	2154		127 (11·7%)	84 (7·9%)	0·66 (0·50–0·87)
PCI during initial hospital stay	1730		109 (12·0%)	68 (8·3%)	0·68 (0·50–0·92)
PCI after initial hospital stay	928		60 (13·8%)	48 (9·8%)	0·70 (0·48–1·02)
Prior CABG	332		38 (21·7%)	15 (9·6%)	0·42 (0·23–0·76)
No prior CABG	2326		131 (11·2%)	101 (8·7%)	0·77 (0·59–0·99)
PCI ≤72 h of randomisation	544		37 (13·5%)	23 (8·5%)	0·62 (0·37–1·05)
PCI >72 h of randomisation	2114		132 (12·3%)	93 (8·9%)	0·71 (0·54–0·92)

Figure 4: **Cardiovascular death or myocardial infarction from randomisation to study end in key subgroups**
PCI=percutaneous coronary intervention. CABG=coronary-artery bypass graft.

Outcome	Adjusted relative risk* (95% CI)	p
PCI to 30 days		
CV death, myocardial infarction, urgent revascularisation	0·65 (0·46–0·92)	0·01
CV death, myocardial infarction	0·60 (0·39–0·92)	0·02
PCI to end of follow-up		
CV death, myocardial infarction	0·72 (0·53–0·96)	0·03

*Clopidogrel vs placebo. CV=cardiovascular.

Table 4: **Main outcomes adjusted for covariates that influence likelihood of undergoing PCI (propensity score)**

cardiovascular death or myocardial infarction between the two groups (table 2, figure 3). This difference was seen in almost every subgroup examined (figure 4).

Significantly fewer patients assigned clopidogrel received intravenous glycoprotein IIb/IIIa inhibitors during PCI than those assigned placebo (357 [26·6%] vs 274 [20·9%], 0·79 [0·69–0·90], p=0·001). Abciximab was the most commonly used glycoprotein IIb/IIIa inhibitor; it was used less frequently in the clopidogrel group than in the placebo group (281 [21·6%] vs 223 [17·4%]). The need for a second revascularisation was also lower in the clopidogrel group than the placebo group (230 [17·1%] vs 186 [14·2%], 0·82 [0·68–1·00], p=0·049), mainly because of a reduced need for a repeat PCI (174 [12·9%] vs 141 [10·7%], 0·83 [0·66–1·03]).

Table 4 shows the results of the adjusted analysis, which includes the propensity score for PCI. The propensity score was highly predictive of the likelihood of having a PCI (p<0·0001). After adjustment, the benefits of clopidogrel over placebo were still evident and significant for all major outcomes at 30 days and at the end of long-term follow-up.

There was very little difference in major bleeding between the groups at 30 days and at the end of follow-up (table 5). Life-threatening bleeding at 30 days and at the end of follow-up was also similar between the groups. In patients who received a glycoprotein IIb/IIIa receptor antagonist, there was no difference in the occurrence of major bleeding between the placebo and clopidogrel groups (8 [2·2%] vs 6 [2·2%], 0·98 [0·34–2·78], p=0·97) or in life-threatening bleeding (4 [1·1%] vs 3 [1·1%], 0·98 [0·22–4·33], p=0·98) at 30 days. There was more minor bleeding in the clopidogrel group than the placebo group at the end of follow-up (table 5).

Discussion

Our study has shown that, in patients with acute coronary syndrome without ST-segment elevation undergoing PCI, clopidogrel reduces the risk of cardiovascular death or myocardial infarction by about a third, compared with placebo. This benefit was consistently seen in the period before PCI, in the 4 weeks after PCI (during which >80% of patients in both groups received open-label thienopyridine), and in the months thereafter when double-blind study medication was continued long-term. There was a non-significant excess in major, but not life threatening, bleeding with clopidogrel compared with placebo.

Aspirin is standard therapy in patients undergoing PCI, and was the first oral antiplatelet agent shown to reduce ischaemic events after PCI.[1–4] We have now shown that when clopidogrel is combined with aspirin and given before PCI, there are significant and clinically relevant further reductions in important cardiac events. The early benefits of clopidogrel pretreatment were due mainly to a reduction in the thrombus-mediated events of myocardial infarction and urgent target-vessel revascularisation. There was a clear reduction in myocardial infarction, with the impact on Q-wave myocardial infarction being most pronounced. Investigators did not routinely screen for symptomless increases in periprocedural cardiac enzyme concentrations, and so some smaller, non-Q-wave myocardial infarctions might not have been documented. However, since the study was randomised and double-blind, this approach should still lead to an unbiased estimate of the effect of clopidogrel.

There was a non-significant reduction in the primary endpoint as early as 48 h after PCI, with incremental benefit at 7 and 14 days. Most patients in both the clopidogrel and placebo groups had intracoronary stent implantation and therefore received open-label thienopyridine, which was almost identical between the two groups for about 4 weeks after PCI. The benefit at 30 days after PCI is therefore probably due to pretreatment with clopidogrel for several days before PCI. This benefit is probably an underestimate of the true treatment effect, because about 25% of patients in both groups also received open-label thienopyridine before the procedure, thus potentially diluting the therapeutic benefits of clopidogrel pretreatment. Indeed, the per-protocol analysis, in which the patients who received open-label drug before PCI were excluded, suggests a 42% reduction in the primary outcome. This finding supports our hypothesis that an effective antiplatelet regimen started before PCI will reduce clinical events for a relatively long period after the procedure.[23] Meanwhile, the observation that clopidogrel also significantly reduced events before PCI by 32%, with further and incremental reduction after PCI, supports prolonged use of dual antiplatelet therapy in patients with non-ST-elevation acute coronary syndrome in whom an invasive strategy is planned. Our data suggest that clopidogrel is likely to be useful not only in centres with invasive facilities, but also in those that do not have ready access to cardiac catheterisation facilities, because it allows time to stabilise the patient medically, before the procedure is done or before transfer for invasive therapy. Consistent benefit was found with clopidogrel pretreatment, irrespective of

	Placebo (n=1345)	Clopidogrel (n=1313)	Relative risk (95% CI)	p
From PCI to 30 days				
Major	19 (1·4%)	21 (1·6%)	1·13 (0·61–2·10)	0·69
Life-threatening	10 (0·7%)	9 (0·7%)	0·92 (0·38–2·26)	0·86
Non-life-threatening	9 (0·7%)	12 (0·9%)	1·37 (0·58–3·23)	0·48
Minor	10 (0·7%)	13 (1·0%)	1·33 (0·59–3·03)	0·49
Blood transfusion of 2 or more units	15 (1·1%)	14 (1·1%)	0·96 (0·46–1·97)	0·90
From PCI to follow-up				
Major	33 (2·5%)	36 (2·7%)	1·12 (0·70–1·78)	0·64
Life-threatening	18 (1·3%)	16 (1·2%)	0·91 (0·47–1·78)	0·78
Non-life-threatening	15 (1·1%)	20 (1·5%)	1·37 (0·70–2·66)	0·36
Minor	28 (2·1%)	46 (3·5%)	1·68 (1·06–2·68)	0·03
Blood transfusion of 2 or more units	27 (2·0%)	28 (2·1%)	1·06 (0·63–1·79)	0·82

Table 5: **Bleeding after PCI**

whether PCI was done more urgently during the initial hospital stay (including those undergoing PCI within the first 72 h of admission) or more electively after the initial hospital stay, suggesting that a relatively short duration of pretreatment before PCI leads to its full benefits.

The significant reduction in death or myocardial infarction at 8 months follow-up in patients receiving clopidogrel strongly supports the long-term use of dual antiplatelet therapy after PCI. Although PCI of the culprit lesion in patients with acute coronary syndrome might improve symptoms and prognosis compared with a conservative strategy,[24,25] it is not expected to prevent rupture and thrombosis of athersclerotic plaques (both flow-limiting and non-flow-limiting) elsewhere in the vascular system. This assumption is further supported by registries and clinical trial databases showing that, even after apparently successful PCI, there remains a significant risk in ischaemic events over the long term.[11–13,24,25] This reason might be why long-term aspirin administration after PCI is beneficial.[26] In a clinical trial of coumarin started before PCI and continued for 1 year, there was also a reduction in early and long-term ischaemic events.[27] There is also evidence that complete neointimal and endothelial coverage of the stent may take 3–6 months, suggesting that longer term dual antiplatelet therapy might be also be beneficial in preventing late stent occlusion in some patients.[28,29]

There was a reduction in the use of intravenous glycoprotein IIb/IIIa antagonist during PCI in the clopidogrel group, which is confirmatory evidence that the combination of clopidogrel and aspirin pretreatment can prevent procedural events deemed serious enough by operators to warrant the use of these agents. Our study was not designed to address the value of clopidogrel pretreatment in patients receiving up-front intravenous glycoprotein IIb/IIIa antagonists in the setting of PCI. However, in a post hoc, non-randomised analysis from a large clinical trial that compared the effects of tirofiban with those of abciximab in patients undergoing PCI, patients who were pretreated with clopidogrel fared significantly better than those not pretreated, irrespective of glycoprotein IIb/IIIa inhibitor used, suggesting that the two methods of platelet inhibition might be complementary.[30] There was no increase in major or life-threatening bleeding with clopidogrel compared with placebo in patients receiving an intravenous glycoprotein IIb/IIIa inhibitor in our study, suggesting that these two antiplatelet regimens are relatively safe when used together in the setting of PCI. This inference reinforces the benefits of a strategy of clopidogrel and aspirin pretreatment, followed by long-term therapy, irrespective of whether glycoprotein IIb/IIIa inhibitors are used.

Although the overall CURE study was randomised, double-blind, and prospectively designed, the treatments themselves might have influenced the proportion and types of patients ultimately undergoing PCI. To assess whether the results in patients undergoing PCI were likely to be affected by any potential selection biases, we did an analysis adjusted for the propensity of patients to undergo PCI. The results of this analysis confirmed those of the main study, and suggested that our findings were not due to any differential biases in patient selection for PCI between the two randomised groups.

We have shown that pretreatment with clopidogrel in addition to aspirin in patients with acute coronary syndrome undergoing PCI is beneficial in reducing major ischaemic events up to 30 days after PCI. Longer-term administration of clopidogrel therapy for a mean period of 8 months after PCI was associated with a reduction in cardiovascular death or myocardial infarction at the end of follow-up. These results imply that in patients with non-ST-elevation acute coronary syndrome in whom an invasive strategy with PCI is planned, clopidogrel started on admission before the procedure and continued long term afterwards is beneficial in reducing both early and late major ischaemic cardiovascular events.

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Clinical picture: Para-ileostomy pyoderma gangrenosum

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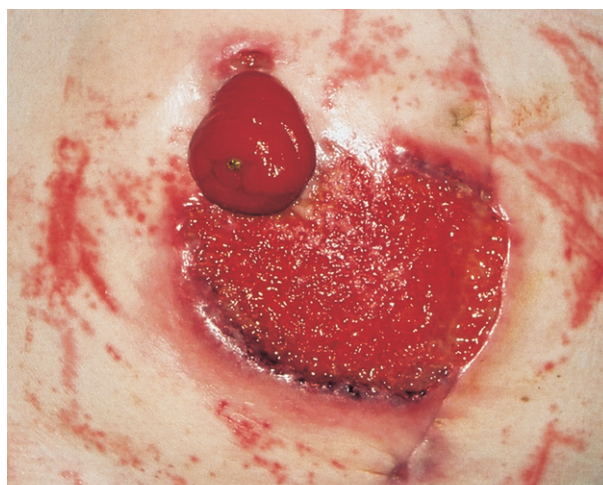
A 60-year-old schizophrenic woman with an acute exacerbation of ulcerative colitis underwent urgent total colectomy with end ileostomy formation. Ten days later she developed para-ileostomy cutaneous ulceration initially thought to be a contact dermatitis to the stomal appliance sealant although these are generally hypoallergenic. The ulceration progressed and was diagnosed as pyoderma gangrenosum. The lesion resolved with resumption of high dose oral and topical steroids.

Pyoderma gangrenosum is an unusual skin manifestation of ulcerative colitis, especially when it occurs around a newly formed stoma. It rarely presents so early, with the majority of cases seen months or years after surgery. Fortunately, most resolve with medical therapy.

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