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Scientific Update™

Long-term therapy with clopidogrel in addition to aspirin in the management of patients with acute coronary syndromes undergoing percutaneous coronary intervention: The PCI CURE Study.

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Ischemic complications after percutaneous coronary intervention (PCI) for patients with acute coronary syndromes (ACSs) remain frequent despite improvements in angioplasty techniques and adjunctive treatment. These events can occur early after the procedure, from local thrombosis or distal embolization, or later, due to new plaque rupture. Platelet aggregation plays a pivotal role in the thrombotic process in both angioplasty-provoked and spontaneous arterial wall injury. Treatment with antiplatelet agents such as ASA, clopidogrel, and GP IIb/IIIa inhibitors has been shown to improve outcomes from both types of injury. Following PCI and stent deployment, the combination of ASA and a thienopyridine such as clopidogrel for 4 weeks markedly reduces the incidence of acute thrombotic occlusion of the stented artery. Whether this combination is beneficial in patients with recent non-ST segment elevation ACS who undergo PCI when treatment is given before the procedure and for a longer period after PCI, was the question addressed by the PCI-CURE study.

The CURE trial[1]

The CURE trial examined the benefits of the combination of ASA and clopidogrel compared to ASA alone, when administered early in the management of non-ST segment elevation ACSs. An earlier *Cardiology Scientific Update* reported the results of the CURE trial in more detail.

Patients with chest pain in the past 24 hours, and either ischemic ECG abnormalities or elevated biomarkers, were included in the CURE trial (Figure 1). After receiving a loading dose of clopidogrel 300 mg or matching placebo, the patients were given clopidogrel 75 mg daily or placebo for an average 9-month treatment period. The combination of clopidogrel and ASA, in comparison with treatment using ASA alone, reduced the primary end-point of cardiovascular death, myocardial infarction (MI) and stroke by 20%. In addition, refractory ischemia was reduced within hours of treatment, and there was less need for urgent revascularization during the initial hospitalization. Although the CURE trial was performed at sites without a policy of routine early PCI, more than 20% of patients underwent revascularization during the index admission, and 36% during the 9-month period of the trial. In patients undergoing revascularization, 2658 (21%) had a PCI. It is this cohort of patients — with ACS enrolled in the CURE trial and undergoing PCI — that formed the study group for PCI-CURE.

PCI CURE study[2]

The PCI CURE Study aimed to examine whether pretreatment with clopidogrel, in addition to standard treatment (including ASA), for patients with recent non-ST segment elevation ACS who undergo PCI, prevents ischemic events within the 30 days following the intervention. The second goal of PCI CURE was to show whether there is benefit from a longer period (up to 1 year) of combination treatment beyond the customary 1-month treatment with clopidogrel after stent implantation.

The patients managed with PCI had baseline characteristics similar to those described in the overall CURE study: average age, 61 years; 70% male; 19% diabetic; and 26% had a previous MI. Over 25% of the patients had prior revascularization with either PCI or CABG, and in just under half, an ECG ST shift was noted at presentation. Although 26% of the overall CURE study patients had evidence of an associated acute MI (AMI), it is not

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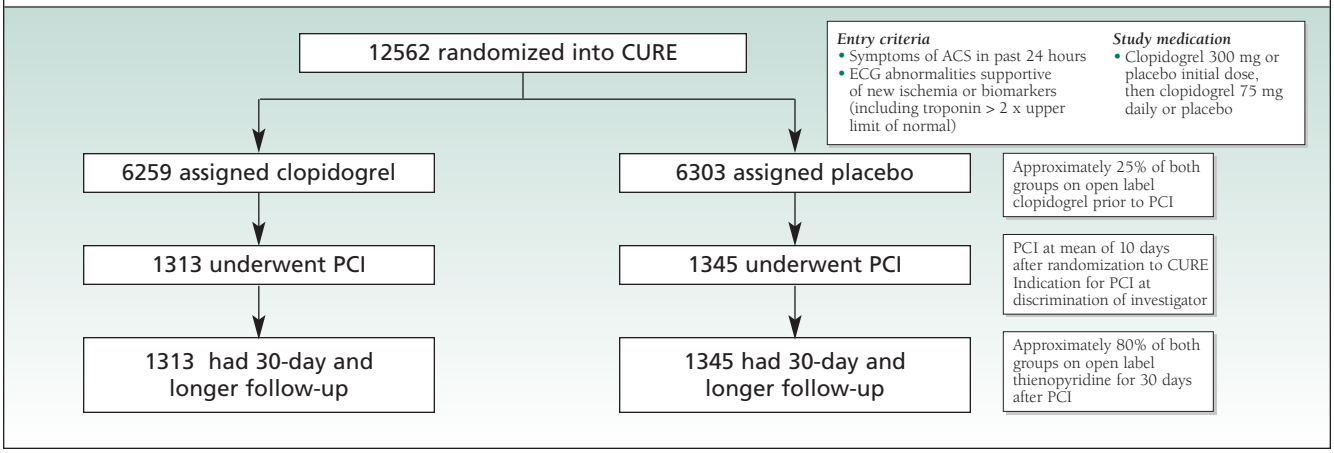
Figure 1: Study design of PCI-CURE



clear whether the PCI-CURE population had the same AMI rate at the time of presentation.

PCI was performed during the initial hospitalization in almost two-thirds of the patients following a median period of 6 days from entry into the trial, and in the remainder after the hospital stay, at a median of 49 days. Target vessels were equally distributed in the native coronary circulation, but only 3% of patients had PCI to saphenous vein grafts. Stents were used in over 80% of patients; however, GP IIb/IIIa inhibitors were given to less than 25% at the time of the procedure. Over 80% of patients received open label clopidogrel or ticlopidine for a median of 30 days, usually following stent deployment. However, 25% received an open label thienopyridine prior to the procedure for an unspecified period.

Results of PCI-CURE

Patients randomized to receive clopidogrel who underwent PCI, had less ischemic events both before and after the procedure. MI or refractory ischemia was reduced by 24% before PCI (placebo 15.3%, clopidogrel 12.1%, RR 0.76, 95% CI, 0.62-0.93). By 30 days following the PCI, there was a further 30% reduction of the composite of cardiovascular mortality, acute MI, and the need for urgent revascularization (placebo 6.4%, clopidogrel 4.5%, RR 0.70, 95% CI, 0.50-0.97; Figure 2). Most of this early benefit was from a 44% reduction of MI, especially Q-wave infarction (placebo 2.4%, clopidogrel 0.8%, RR 0.35, 95% CI, 0.18-0.70). As most patients received an open label thienopyridine after the procedure, it is likely that the benefit observed at 30 days was due to pre-PCI treatment with clopidogrel. This conclusion is supported by analysis of the per-protocol patients (the patients who received an open label thienopyridine prior to PCI are removed from the analysis), when an even greater 42% reduction of CV death, AMI, recurrent ischemia was observed 30 days after PCI (placebo 7.2%, clopidogrel 4.2%, RR 0.58, 95% CI, 0.40-0.85).

The patients randomized to clopidogrel had lasting benefit during the mean 8-month follow-up period. Clopidogrel or placebo was restarted after the average 28-day open label treatment with a thienopyridine following PCI. During this long-term follow-up, randomization to clopidogrel was associated

Figure 2: Risk of cardiovascular death, acute myocardial infarction, and need for urgent revascularization during the first 30 days from time of PCI, in the patients pretreated with either placebo or clopidogrel.

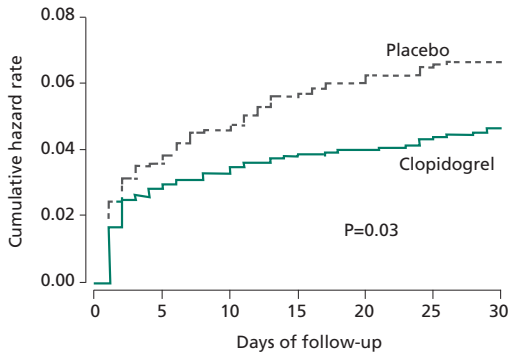


Figure 3: Cumulative event rates (cardiovascular death or acute myocardial infarction) from randomization to the end of follow-up

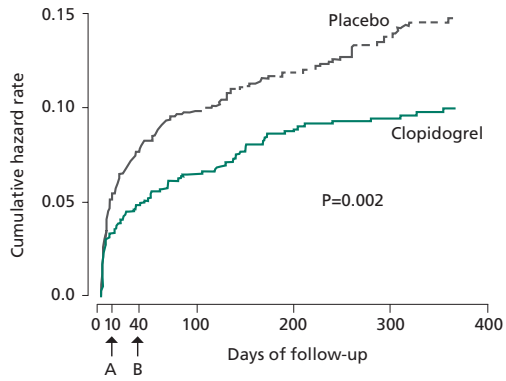
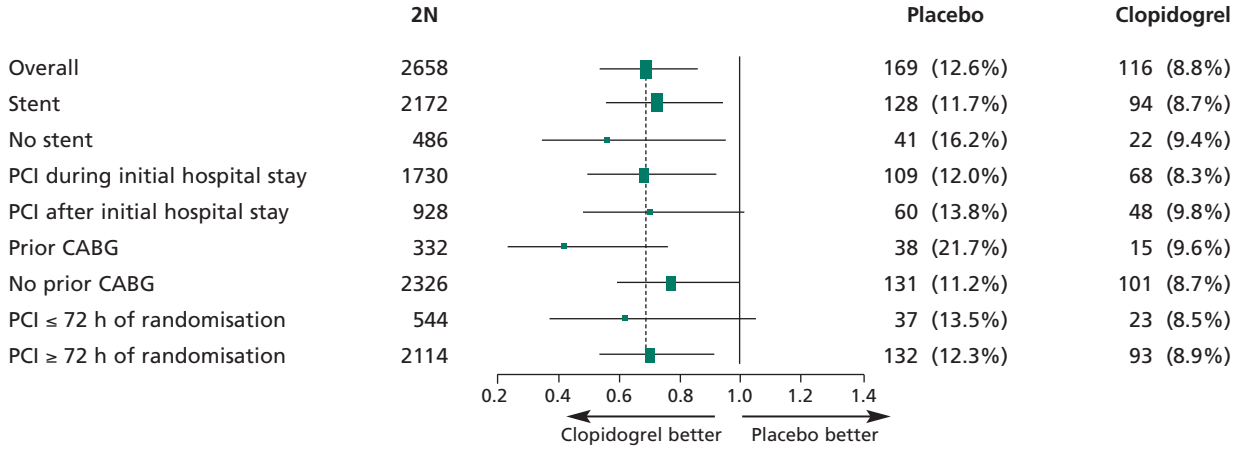


Figure 4: Risk of cardiovascular death or myocardial infarction from randomization to study end in sub-groups



with a 25% reduction of cardiovascular death or MI (placebo 8.0%, clopidogrel 6.0%, RR 0.75, 95% CI, 0.56-1.00; Figure 3). Again, the benefit was primarily due to a reduction of Q-wave AMI. The need for further revascularization by either PCI or CABG was also reduced in the clopidogrel group (placebo 17.1%, clopidogrel 14.2%, RR 0.82, 95% CI, 0.68-1.00). The benefits of clopidogrel are seen to begin early after PCI and continue long after the average 30-day open label treatment period post-PCI. Similar benefits were observed in a wide range of subgroups such as age > or < 65 years, male or female sex, diabetes or no diabetes, and a history of coronary bypass grafting. Procedural parameters such as stent utilization, or the timing of PCI (in the first 72 hours or during the initial hospitalization), had no influence on the benefits of clopidogrel (Figure 4). As in the main CURE study, patients with prior coronary bypass surgery appeared to have an especially large benefit from clopidogrel.

Major bleeding (life-threatening, or non-life threatening) was not increased during either the first 30 days or the 8-month follow-up period after PCI. Also bleeding did not increase in the 20% who received a peri-procedural GP IIb/IIIa inhibitor.

Interpretation and applicability of PCI-CURE

The PCI-CURE study is an observational study of a sub-population entered into the CURE trial. The CURE trial by design, promoted an early non-interventional strategy to avoid excessive early PCI and open-label usage of clopidogrel. For patients with non ST-segment elevation ACS and CURE entry criteria, as defined above, clopidogrel begun within 24 hours of the onset of symptoms resulted in an important reduction of a wide spectrum of adverse outcomes. Events were reduced both early and up to the average 9-month duration of follow-up, irrespective of whether revascularization by either PCI or CABG was undertaken. For the sub-group of patients undergoing PCI at the discretion of the investigator, pre-PCI treatment with clopidogrel was associated with early benefit, despite open label treatment following the PCI. Those patients maintained on treatment with clopidogrel and ASA for an additional 7 months, had continued benefit compared to treatment with ASA alone. Treatment with clopidogrel within 24 hours of symptom onset reduced the early risk of MI and refractory ischemia, both before and after PCI, presumably by stabilizing the culprit plaque. The later benefits of clopidogrel observed from 30-days post-PCI to the end of the 8-month follow-up period are most likely due to prevention of atherothrombosis at other coronary sites, (in patients at high risk of recurrent ACS) rather than the prevention of either late in-stent thrombosis or restenosis. Consequently, it is unclear if the results of PCI-CURE can be extrapolated to patients outside the context of a recent ACS.

There are questions concerning the applicability of the PCI-CURE observations to an aggressive invasive strategy of ACS management. However, the vast majority of patients with non-ST segment elevation ACS in Canada are neither started on a GP IIb/IIIa inhibitor, nor taken to the catheterization laboratory within 48-72 hours, as is the case in some areas of the USA and Europe today. The benefits of up-front usage of GP IIb/IIIa inhibitors appear to be confined to the highest risk non-ST segment elevation ACS patient,[3-5] whereas clopidogrel reduced events in a wider spectrum of risk in both the total population of the CURE trial and in the PCI-CURE sub-study. Furthermore, the TACTICS-TIMI 18 trial[6] showed that the use of a GP IIb/IIIa inhibitor preceding an early interventional strategy was also most effective in the higher risk patient. Thus, early clopidogrel treatment is more applicable in a wider range of intermediate- and high-risk patients and will provide both early and late benefit should they undergo PCI.

Patients undergoing PCI and pre-treated with clopidogrel in the PCI-CURE sub-study may not have had the same risk for adverse outcomes as those receiving placebo. Although the baseline characteristics of the two groups at the time of randomization

to clopidogrel or placebo who eventually underwent PCI appear similar, pre-treatment with clopidogrel may have selected an overall lower risk group of patients undergoing PCI. Patients with either recurrent ischemia or undergoing revascularisation were less frequent in the clopidogrel-treated group of the CURE population. Yet, there were equal numbers of patients pre-treated with either clopidogrel or placebo who underwent PCI, a proportion of whom likely had PCI because of recurrent ischemia. The balance of patients probably had PCI driven by findings at the time of the clinical presentation, such as ECG ST segment depression; such patients would have been at lower risk than the group with recurrent ischemia. Thus the clopidogrel-treated group may have been at an overall lower risk, with a lower proportion of high risk recurrent ischemia patients. An additional indicator of higher risk in the placebo group is the greater use of IIb/IIIa inhibitor at the time of PCI, perhaps due to a greater thrombus load and tendency for early vessel closure. However, despite less use of GP IIb/IIIa inhibition – a therapy of proven benefit – the apparent advantage of clopidogrel was still achieved.

Many questions will remain unanswered until trials are performed to address the issues. Can clopidogrel be used together with GP IIb/IIIa inhibition with enhanced benefit and without excessive bleeding in the immediate emergency room management of high risk patients? Although the combination of clopidogrel, ASA, heparin, and a GP IIb/IIIa inhibitor is used safely for short periods in patients undergoing PCI, the safety of this potent anti-thrombotic combination administered for 72-96 hours prior to PCI is largely unknown. Perhaps the up-front usage of a GP IIb/IIIa inhibitor such as eptifibatide or tirofiban should be directed to the highest risk patients with > 2mm ST segment depression and a decisive troponin elevation. In these patients, clopidogrel could be withheld until either several hours before cardiac catheterization or until the coronary anatomy is defined. Would greater usage of a GP IIb/IIIa inhibitor at the time of PCI have increased the benefit in the clopidogrel-treated group or reduced the difference between the clopidogrel and placebo treated patients? Observations from the TARGET study[7] suggest that the benefits of pre-treatment with clopidogrel and the peri-procedural use of a GP IIb/IIIa inhibitor are synergistic and result in better outcomes. However, there is no evidence to suggest that pre-treatment with clopidogrel could replace the benefits obtained from peri-PCI GP IIb/IIIa inhibition.

What is the optimal duration of clopidogrel treatment following coronary artery PCI with stenting? The PCI-CURE study showed long-term benefits from clopidogrel started prior to PCI in patients with ACS that continued for a mean period of 8 months after intervention. How much of this benefit is due to pre-PCI treatment with clopidogrel, and how much from longer term treatment after PCI, is unknown. However, the CURE study showed continued benefit during the mean 9-month follow-up, whether or not the patient underwent revascularization. It is likely that patients with ACS will receive pre-PCI clopidogrel, followed by clopidogrel for one month, to prevent early in-stent thrombosis. The decision to continue with clopidogrel for a further 7-8 months will then depend on how well the patient fits into the CURE trial entry criteria and the risk of bleeding during long-term treatment.

Conclusions

The CURE study has shown that treatment with clopidogrel (300 mg loading dose followed by 75 mg daily) started within 24 hours onset of symptoms of a non-ST-segment elevation ACS reduces early MI and refractory myocardial ischemia. Continued treatment for up to 9 months is associated with an important reduction in adverse events in a wide range of subgroups and risk strata.

For patients undergoing PCI and pretreated with clopidogrel for an average of 10 days, there are less events prior to PCI, and a reduction of both clinically apparent MI and the need for repeat revascularization over the 30 days following the procedure, despite the widespread use of either clopidogrel or ticlopidine during this early period.

Clopidogrel continued for a an average period of 8 months following PCI in this population was associated with less MI or need for repeat revascularization for recurrent ACS.

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