

# Scientific Update™

## Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events: The CURE trial

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Despite substantial improvements in the outcomes of patients presenting with non-ST segment elevation acute coronary syndromes (myocardial infarction [MI] and unstable angina), mortality and (re-)infarction rates over the 6-month period after discharge from hospital remain high. Although most of these events occur within the initial 30 days, further life-threatening MI and unstable angina recur in the following months (Figure 1). Most recurrent myocardial ischemic events result from thrombotic re-occlusion of the culprit coronary artery. Following atherosclerotic plaque rupture, thrombus formation transiently occludes the artery resulting in myocardial ischemia and the clinical presentation of an acute coronary syndrome. Persistence of thrombus after the acute event provides a nidus for further thrombosis and re-occlusion of the vessel. Treatment strategies in the early management of patients with non-ST segment elevation coronary syndromes aim to prevent recurrent thrombosis and reduce both short- and long-term events. Antiplatelet agents (aspirin and glycoprotein [GP] IIb/IIIa inhibitors), and anti-thrombotic agents (unfractionated heparin and low molecular weight heparin) reduce death and MI in the short-term. Until recently, ASA was the only proven short- and long-term medical strategy preventing early and later recurrent ischemic events. Low molecular weight heparin administered for prolonged periods is not beneficial, and oral GP IIb/IIIa inhibitors appear to be harmful. Results of the CURE study were initially presented at the annual meeting of the American College of Cardiology in March 2001 and have now been published; they indicate

that clopidogrel prevents both early and late complications after an acute coronary event.

### CURE

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events trial had a randomized, placebo-controlled, double-blinded design.<sup>2</sup> The study compared the outcomes of patients with non-ST segment elevation acute coronary syndromes treated with either clopidogrel 75 mg daily or placebo, in addition to aspirin, for 3 months to 1 year. The trial was performed in 28 countries where 12,562 patients were enrolled. The Canadian sites enrolled 1762 patients. The CURE trial was coordinated by McMaster University with Dr. Salim Yusuf as the principal investigator.

Patients entered into the trial had symptoms compatible with ischemic cardiac pain, yet no persistent electrocardiographic ST segment elevation. To be included in the trial, the pain onset was within the past 24 hours and there was either an electrocardiogram compatible with new ischemia or elevated biomarkers of myocardial necrosis (CK, CK-MB or troponin) to twice the upper limit of the normal range. Patients were excluded if they had a high risk of bleeding, severe congestive heart failure, a long-term need for oral anticoagulation, or had a percutaneous coronary intervention within the preceding 3 months.

On entry into the trial, patients were given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg daily or matching placebos for a minimum of 3 months and a maximum 1 year. The two co-primary endpoints were a) cardiovascular death, MI, or stroke, and b) cardiovascular death, MI, stroke, or refractory ischemia. The patients were evaluated at 1 month, and then at 3, 6, 9 and 12 months.

### Division of Cardiology

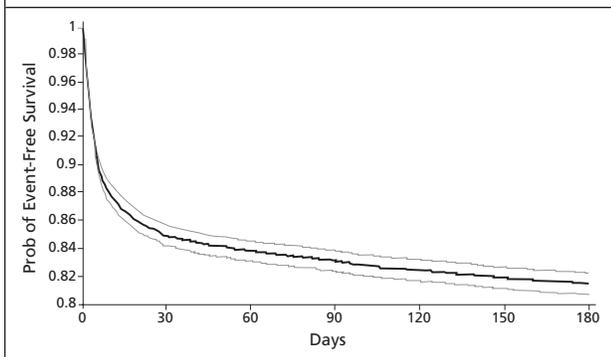
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**Figure 1: Probability of event-free survival ( $\pm 95\%$  C.I.; death/MI in non-ST segment elevation acute coronary syndrome.)**



The patient demographics were typical for an acute coronary disease population. The average age was 64.2 years, and 61.5% were male. One-third of the patients had a prior MI and approximately 20% had either coronary bypass surgery or percutaneous coronary revascularization. Almost 60% were hypertensive and 22.5% were diabetic. The time between the onset of pain and randomization was  $14.1 \pm 7.1$  hours and the mean duration of study treatment was 9 months.

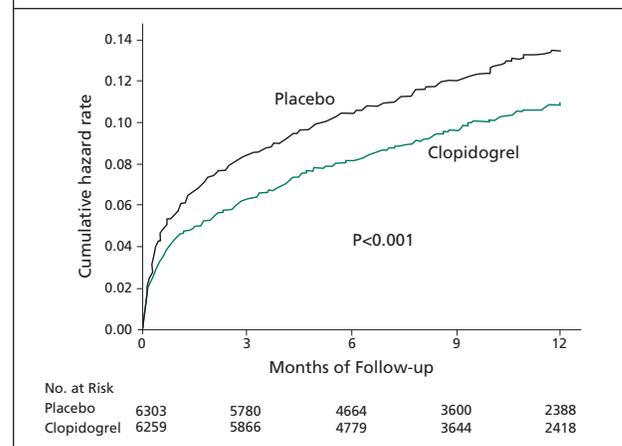
A final diagnosis of non-ST segment elevation MI was made in 25%. Over 90% of patients had abnormal electrocardiograms, with ST depression present in 41.9%, and major T-wave inversion in 25.6%. Almost all patients received heparin, and 56% received low molecular weight heparin. Beta-adrenergic blockers were used in 78%, ACE inhibitors in 50%, and lipid-lowering treatment in 25%.

### Results of CURE<sup>3</sup>

Treatment with clopidogrel, in addition to standard therapy (which included ASA), resulted in a 20% reduction of the combined primary endpoint of cardiovascular death, MI, and stroke over the period of observation (from 11.4% to 9.3%, RRR 0.80, 95% CI, 0.72-0.90,  $P < 0.001$ ). Similar relative reductions were observed over both the first 30 days and during the remaining follow-up period (Figure 2).

All components of the primary endpoint showed a strong trend to lower event rates: MI was reduced 23% (placebo 6.7%, clopidogrel 5.2%, RR 0.77 (0.68-0.89)  $P < 0.001$ ), CV death 8% (RR 0.92 (0.79-1.07), and stroke 15% (RR 0.85 (0.63-1.16)) Refractory myocardial ischemia (as defined by severe ischemic chest pain occurring during the initial hospitalization with ECG ST segment changes, while the patient was on maximal medical treatment) was reduced by 24% (placebo 5.0%, clopidogrel 3.8%, RR 0.76 (0.64-0.89)). In addition, refractory ischemia with a need for urgent revascularization within 24 hours of the ischemic event was reduced 33% in the clopidogrel-treated group. After discharge from hospital, clopidogrel had no added impact on rehospitalization for unstable angina with associated ECG changes over that

**Figure 2: Cumulative incidence of primary endpoint of cardiovascular death, myocardial infarction and stroke in the CURE trial over the 1-year period of observation.**



achieved by standard treatment (clopidogrel 7.66%, placebo 7.67%). The benefits of clopidogrel were observed as early as 2 hours after the loading dose (RR 0.67,  $P = 0.002$ ). After 24 hours of treatment, there was a 33% reduction of the combined endpoint death, MI, stroke, or refractory ischemia. Furthermore, the need for urgent cardiac catheterization or urgent transfer for catheterization, and revascularization by percutaneous coronary revascularization or bypass surgery during the initial hospitalization were reduced 20% in the clopidogrel-treated patients.

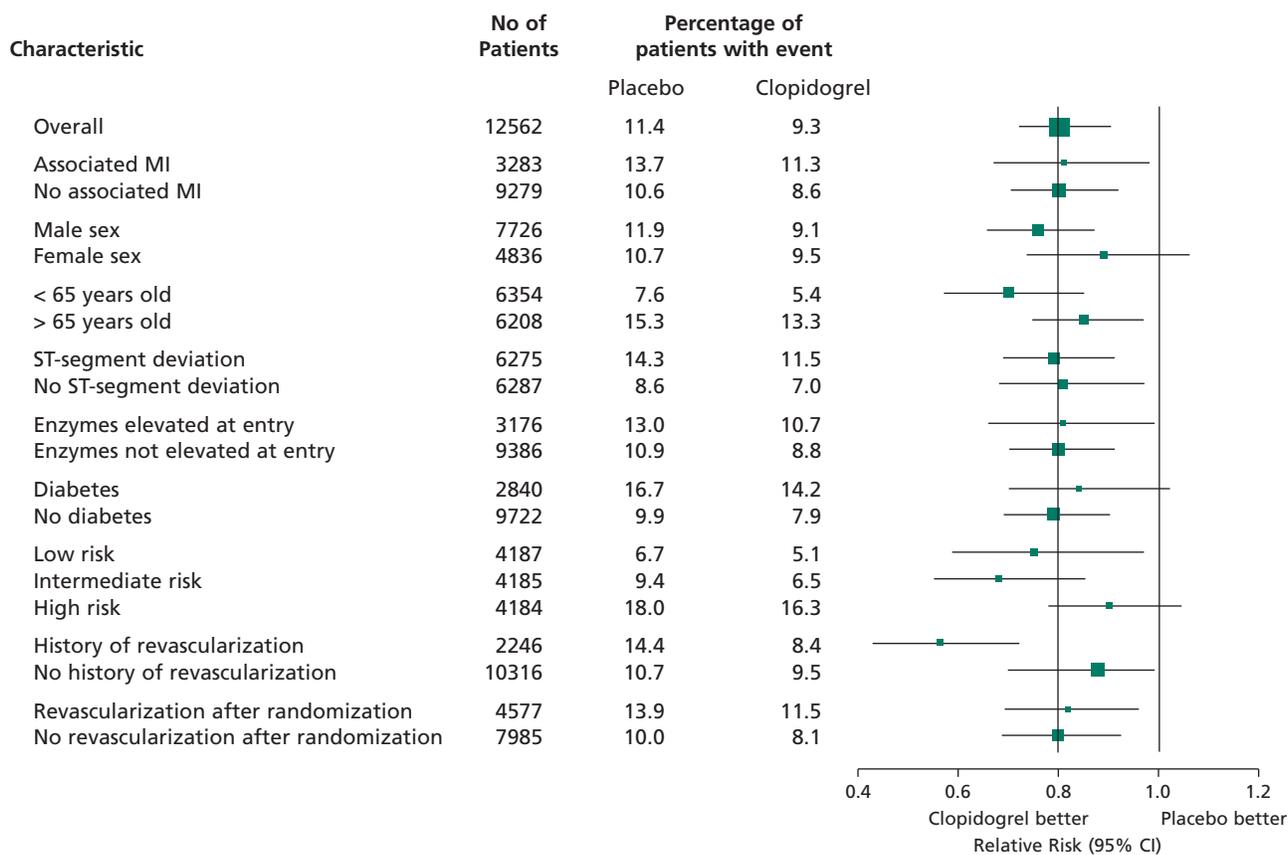
### Benefits across risk subgroups

Improved outcomes were observed in a wide range of pre-specified subgroups (Figure 3). Patients with ST segment depression and with biomarker elevation (CK, CK-MB, and troponin) had similar 20% reductions of the combined endpoint of cardiovascular death/MI and stroke as patients without these higher risk features. This finding is in contrast to findings in the low molecular weight heparin<sup>4,5</sup> and the GP IIb/IIIa inhibitors trials,<sup>6,7</sup> where biomarker elevation (especially troponin) was associated with a large therapeutic benefit from the anti-thrombotic/anti-platelet agent, and little or no benefit in the patients who were biomarker negative.

There was a large benefit from clopidogrel in the 2246 patients who had prior revascularization, with a 45% reduction of events during the average 9-month follow-up period. (placebo 14.6%, clopidogrel 8.4%, RR 0.55 (0.43-0.72)). In the remaining patients who had no prior revascularization, the reduction of events was considerably less (placebo 10.8%, clopidogrel 9.5%, RR 0.87 (0.77-0.98)), yet the benefit still achieved statistical significance. Patients who underwent revascularization after entry into the study had the same 20% reduction of events as those who had no revascularization.

Thus, clopidogrel appears to benefit patients with acute non-ST segment elevation acute coronary syndromes whether

**Figure 3: Benefits across risk subgroups**



they are at high risk (as suggested by ST-segment depression or elevated biomarkers) or at lower risk of early adverse outcomes.

### Bleeding due to clopidogrel

An absolute 1.0% increase in major bleeding was seen in the patients treated with clopidogrel compared to the standard treatment group. Major bleeding (disabling, symptomatic, intraocular, or requiring a transfusion > 2U) occurred in 3.7% of subjects on clopidogrel, and in 2.7% of patients receiving placebo. In contrast, life-threatening bleeding (intracranial, with hypotension requiring inotropes or emergency surgery, transfusion > 4U, or a fall in hemoglobin > 5G/dl) was not increased by clopidogrel. Minor bleeding, mainly from epistaxis, occurred in 15.3% of the clopidogrel-treated patients, in contrast to 8.6% in the placebo group. Patients undergoing coronary artery bypass surgery randomized to receive clopidogrel had no overall increase in major bleeding. However, the study protocol recommended discontinuation of treatment at least 5 days before surgery. When treatment was discontinued more than 5 days prior to the operation, there was no increase in major bleeding in the 7 days after surgery (n=910, clopidogrel 4.4%, placebo 5.5% ns). In the 912 patients in whom treatment was discon-

tinued less than 5 days prior to surgery, there was a strong trend towards increased major bleeding in the clopidogrel treated group (clopidogrel 9.6%, placebo 6.3%, RR 1.53, P=0.06)

### Duration of treatment

Although the greatest benefit from clopidogrel occurs within the first 2-3 months after the index event, the survival curves continue to diverge throughout the 1-year observation period. The same relative risk reduction was observed during the first 30 days and after 30 days. However, further analysis of the benefits and bleeding risk during the last 6- and 9-month treatment periods will be necessary before the optimal duration of treatment can be determined. It is likely that higher risk patients such as those with diabetes<sup>8</sup> and previous coronary artery bypass surgery<sup>9</sup> will derive benefit from more prolonged treatment with clopidogrel. Whether long-term treatment with the combination of clopidogrel and aspirin would be beneficial beyond that of clopidogrel alone remains to be determined.

### Who should receive clopidogrel?

Patients with symptoms compatible with an acute coronary syndrome which began within the preceding 24 hours, who

have either ECG ST depression >1 mm (yet no ECG ST elevation) or increased levels of circulating biomarkers of myocardial necrosis, should be considered for treatment with the combination of clopidogrel and aspirin. With a very early benefit, clopidogrel should be administered as soon as a diagnosis is made to obtain maximal benefit from the medication. As the risk of serious bleeding is increased significantly by the combination of clopidogrel and aspirin, patients at higher risk of bleeding complications (such as prior hemorrhagic stroke, recent GI bleeding, patients receiving oral anticoagulants [eg, warfarin] and long-term treatment with non-steroidal anti-inflammatory agents) should not receive the combination.

The increased bleeding risk from clopidogrel and aspirin could impact the outcome of coronary artery bypass surgery. In the CURE trial it was recommended that patients discontinue clopidogrel for at least 5 days before surgery to minimize peri-operative hemorrhage. Such a wait is possible in the stabilized patient, yet in up to 20% of patients with high-risk features, an urgent coronary bypass operation is required. In the patient with high risk features (such as a history of frequent episodes of pain, a crescendo anginal pattern preceding rest pain, ST depression  $\geq 2$  mm with or without pain, extensive T-wave inversion >2 mm, especially with a clear elevation of troponin or CK MB, heart failure or hypotension associated with the ischemic episodes), it is preferable to use a short-acting intravenous GP IIb/IIIa inhibitor such as eptifibatid or tirofiban, and refer the patient for urgent coronary angiography. Clopidogrel can be administered as a 300 mg loading dose in these patients when coronary angiography identifies anatomy amenable to percutaneous intervention.

### Outstanding issues

Further analysis of the CURE data will be required to answer many of the important questions that this landmark trial has generated. What duration of combination treatment optimizes the benefits of clopidogrel, yet minimizes the risk of serious bleeding? As many patients with high-risk acute coronary syndromes are currently treated with an intravenous GP IIb/IIIa inhibitor, should clopidogrel now be added, or could clopidogrel replace a GP IIb/IIIa inhibitor? In certain high-risk subgroups of patients with acute non-ST segment elevation ACS, GP IIb/IIIa inhibitors may confer benefits greater than those observed in the CURE trial.<sup>7</sup> Although clopidogrel is routinely combined with GP IIb/IIIa inhibitors in the interventional laboratory, the combination is rarely used for more than 24 hours. The safety or benefits of a longer period of combined GP IIb/IIIa inhibition, heparin, ASA, and clopidogrel for up to 96 hours is unknown.

### Conclusions

The CURE trial<sup>3</sup> has unequivocally demonstrated the important benefits achieved by adding clopidogrel to standard therapy (including ASA) in patients with definite non-ST segment elevation acute coronary syndromes who have either ECG abnormalities or biomarkers positive for MI. Cardiovascular death, (re-) myocardial infarction and stroke were reduced by 20%, refractory ischemia during the initial hospitalization by 20-25%, early revascularization and heart failure in hospital by 20%, for an absolute 1.0% increase in major bleeding, which were all managed by transfusion. For every 1000 patients treated with clopidogrel and aspirin, this result translates into a benefit of 28 major events prevented in 23 patients at the cost of 6 patients requiring a transfusion.

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