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The CURE trial: Using clopidogrel in acute coronary syndromes without ST-segment elevation

ABSTRACT

In a large, randomized, placebo-controlled trial in centers that use a conservative approach to acute coronary syndromes, the antiplatelet drug clopidogrel (Plavix) decreased the rate of the combined end point of cardiovascular death, nonfatal myocardial infarction, or stroke by 20% in patients presenting with acute coronary syndromes without ST-segment elevation. The benefit was at the cost of an increase in bleeding, however. This strategy may need to be tailored in centers that use a more aggressive treatment strategy of early angiography and revascularization.

IN HOSPITALS that use a conservative treatment strategy for acute coronary syndromes, clopidogrel (Plavix) should be added to the standard medical regimen for acute coronary syndromes without ST-segment elevation, according to the findings of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.¹ The drug was approved by the US Food and Drug Administration for this indication on February 28, 2002.

However, the benefit of clopidogrel comes with the risk of increased bleeding. Additionally, the results of the trial may be less applicable to many hospitals in the

United States that use an aggressive treatment strategy of early angiography, percutaneous intervention, and glycoprotein (GP) IIb/IIIa inhibition.

We review and interpret the findings of this important trial.

PLATELETS IN ACUTE CORONARY SYNDROMES

The platelet is central to the pathogenesis of acute coronary syndromes. Platelets become activated and start to adhere to one another when a vulnerable endothelial plaque ruptures, exposing the lipid-rich core and subendothelial collagen. Platelet aggregation is completed by the formation of fibrinogen crossbridges between GP IIb/IIIa receptors on adjacent platelets.²

The management of acute coronary syndromes usually involves blocking platelet activation at one or more pathways.

Aspirin inhibits platelet activation through the thromboxane A₂ pathway, but does not affect activation through the adenosine diphosphate or thrombin pathways. This may be especially important in the subpopulation of patients whose platelets are resistant to the effects of aspirin.^{3,4}

GP IIb/IIIa receptor inhibitors can block platelet aggregation when given intravenously either on presentation or during percutaneous coronary interventions, but there is currently no role for long-term therapy with these agents because the oral GP IIb/IIIa inhibitors have been shown to worsen outcomes.⁵

Heparin, an anticoagulant, is beneficial

An important advance, but at the cost of excess bleeding

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TABLE 1

Medical therapy in the CURE population

	AT RANDOMIZATION	IN-HOSPITAL
Aspirin	66.5%	99.1%
Unfractionated heparin	37.9%	46.0%
Low-molecular-weight heparin	32.2%	54.0%
Intravenous glycoprotein IIb/IIIa inhibitors	0.1%	3.2%
Angiotensin-converting enzyme inhibitors	36.0%	48.9%
Beta-blockers	57.5%	77.5%
Calcium channel blockers	27.8%	35.0%
Lipid-lowering agents	24.9%	45.6%
Intravenous nitrates	44.4%	52.9%

ADAPTED FROM THE CURE STUDY INVESTIGATORS. THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS (CURE) TRIAL PROGRAMME; RATIONALE, DESIGN AND BASELINE CHARACTERISTICS INCLUDING A META-ANALYSIS OF THE EFFECTS OF THIENOPYRIDINES IN VASCULAR DISEASE. EUR HEART J 2000; 21:2033–2041.

Clopidogrel and aspirin block platelets by different mechanisms

in the acute management of acute coronary syndromes, but long-term therapy is difficult and lacks durable benefit.⁶

Clopidogrel inhibits platelet activation through the adenosine diphosphate pathway. Because it blocks platelet activation via a different route than aspirin does, combination therapy with aspirin may offer benefits over either drug alone. Clopidogrel has been shown to be superior to aspirin in the secondary prevention of vascular events,⁷ especially in patients at high risk for adverse sequelae.^{8,9} The combination of clopidogrel plus aspirin is effective in preventing coronary stent thrombosis.^{10–12} Since clopidogrel is given orally, long-term use is feasible. Long-term therapy is also safe and well tolerated.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial investigators sought to determine if the benefits seen with clopidogrel in secondary prevention and in preventing stent thrombosis would be seen in the short-term and long-term treatment of patients presenting with acute coronary syndromes.

STUDY DESIGN

The CURE study compared the effects of clopidogrel and placebo in a randomized, double-blind fashion in patients with unstable

angina or myocardial infarction without ST-segment elevation.¹³

Inclusion criteria. Hospitalized patients with acute coronary syndromes and either electrocardiographic evidence of ischemia or abnormal serum cardiac markers were recruited for enrollment. The investigators enrolled patients only from centers favoring a conservative approach to managing acute coronary syndromes (ie, centers with a low rate of angiography and revascularization).

Exclusion criteria included contraindications to antithrombotic or antiplatelet therapy, use of oral anticoagulants, severe heart failure, any recent percutaneous coronary intervention, and recent GP IIb/IIIa inhibitor use.

Treatment. Patients were randomized to receive either a loading dose of clopidogrel 300 mg followed by 75 mg daily for the duration of follow-up (6,259 patients) or a matching placebo (6,303 patients). All patients received aspirin 75 mg to 325 mg daily at the discretion of the treating physician. Other conventional medical therapy was also left to the discretion of the treating physician (TABLE 1).

Follow-up was every 3 months, up to 1 year for patients enrolled early in the study. The average duration of treatment was 9 months.

Outcomes measured. The first primary outcome measure was a composite of cardio-

TABLE 2

The CURE trial: Clopidogrel is beneficial, but increases the risk of bleeding

OUTCOME	CLOPIDOGREL (N = 6,259)	PLACEBO (N = 6,303)	RELATIVE RISK	P VALUE
Primary outcome (any of the following)	9.3%	11.4%	0.80	< .001
Cardiovascular death	5.1%	5.5%	0.93	
Nonfatal myocardial infarction	5.2%	6.7%	0.77*	
Stroke	1.2%	1.4%	0.86	
Major bleeding	3.7%	2.7%	1.38	.001
Life-threatening	2.2%	1.8%	1.21	
Minor bleeding	5.1%	2.4%	2.12	< .001
All bleeding	8.5%	5.0%	1.69	< .001

*95% CI 0.67–0.89

ADAPTED FROM THE CURE STUDY INVESTIGATORS. EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION. N ENGL J MED 2001; 345:494–502. WITH PERMISSION.

vascular death, myocardial infarction, and stroke. The second primary end point measure was the primary outcome measure plus refractory ischemia. Bleeding complications were tracked as a measure of safety.

PCI-CURE substudy

The percutaneous coronary intervention substudy of CURE (PCI-CURE)¹⁴ investigated the benefits of giving clopidogrel before percutaneous coronary intervention and long-term afterward. A total of 2,658 patients underwent percutaneous coronary interventions at the discretion of the treating physician.

RESULTS

Clopidogrel treatment led to a 20% relative risk reduction in the primary composite outcome (TABLE 2).¹ This risk reduction was largely driven by a 23% relative risk reduction in myocardial infarctions. There were also non-significant trends toward a lower mortality rate and fewer strokes in the clopidogrel group. Benefit was seen in all subgroups reported. The benefit of clopidogrel was seen early, within a few hours of randomization, and persisted for the duration of follow-up (FIGURE 1).

On the other hand, major and minor bleeding was significantly more common in the clopidogrel group than in the placebo

group (TABLE 2). Although the risk of life-threatening bleeding was not significantly increased, more patients in the clopidogrel group required blood transfusions. The sites of excess major bleeding were gastrointestinal and at arterial puncture sites.

In the clopidogrel group, patients who underwent coronary artery bypass grafting (CABG) experienced rates of bleeding similar to those in the placebo group if clopidogrel was withheld for at least 5 days preoperatively. There was, however, a worrisome trend toward higher rates of postoperative bleeding in patients who received clopidogrel within 5 days of CABG (9.6% vs 6.3% in the placebo group; relative risk 1.53; $P = .06$).

The rates of thrombocytopenia and neutropenia were similar in the two groups.

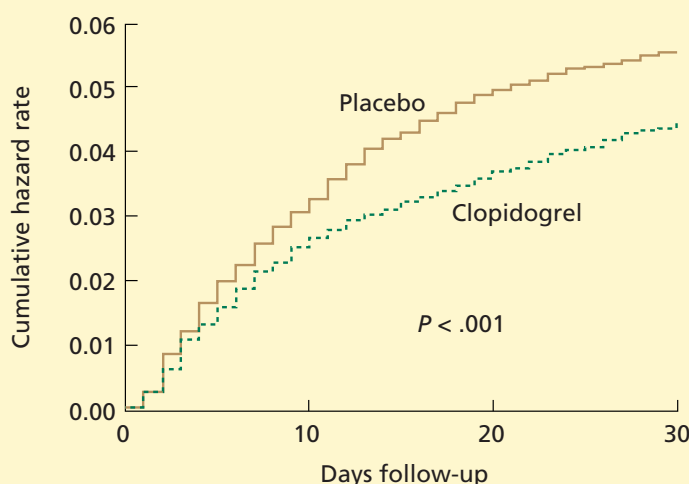
Results of the PCI-CURE substudy

Among patients who underwent percutaneous coronary intervention after enrollment in the study, 59 (4.5%) in the clopidogrel group had the primary end point of cardiovascular death, myocardial infarction, or urgent target-vessel revascularization within 30 days, compared with 86 (6.4%) in the placebo group (relative risk 0.70, $P = .03$).

These patients underwent percutaneous coronary intervention a median of 10 days after enrollment. About 25% of patients in

The strategy was more conservative than at many American hospitals

Clopidogrel is beneficial early



... and in the long term

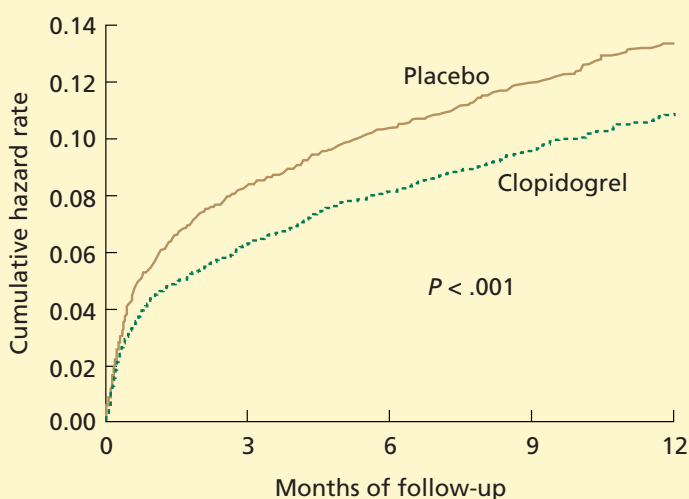


FIGURE 1. Cumulative hazard rates for cardiovascular death, myocardial infarction, and stroke in patients presenting with acute coronary syndromes without ST-segment elevation in the CURE trial. The results demonstrate the early (top) and sustained (bottom) benefit of clopidogrel.

ADAPTED FROM THE CURE STUDY INVESTIGATORS. EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION. N ENGL J MED 2001; 345:494-502. WITH PERMISSION.

both groups received open-label adenosine diphosphate antagonist therapy before the percutaneous coronary intervention. Stented patients received open-label adenosine diphosphate antagonist therapy for 2 to 4

weeks following percutaneous coronary intervention.

Bleeding was not significantly increased in the clopidogrel group. Fewer patients received a GP IIb/IIIa inhibitor in the clopidogrel group than in the placebo group (20.9% vs 26.6%, relative risk 0.70, $P = .001$). The benefit of clopidogrel persisted through the end of the study.

Thus, in patients presenting with acute coronary syndromes, pretreatment with clopidogrel prior to percutaneous coronary intervention followed by long-term therapy is superior to standard treatment.

■ INTERPRETATION: WHEN TO USE OR WITHHOLD CLOPIDOGREL

The CURE study demonstrated long-term clopidogrel therapy to be superior to placebo in high-risk patients presenting with acute coronary syndromes without ST-segment elevation. This is an impressive result, since the benefit is in addition to that of aspirin.

The benefit of a reduction in the rate of myocardial infarction is at the cost of an increase in bleeding, however.

The findings support the routine use of long-term clopidogrel in the management of acute coronary syndromes everywhere as well as the use of clopidogrel on presentation at centers pursuing a conservative approach with medical therapy.

To reduce the morbidity and mortality of bleeding complications, it would be advisable to avoid other medications, such as non-steroidal anti-inflammatory drugs, that may also increase bleeding risk.

The PCI-CURE substudy demonstrates benefit with pretreatment with clopidogrel prior to percutaneous coronary intervention. This study, together with the results of other studies,^{15,16} offers justification for pretreatment with clopidogrel before percutaneous coronary intervention, as opposed to beginning clopidogrel therapy only after the intervention is completed.

Limitations of the study

Certain points may limit the direct application of these findings in many American hospitals.

The approach was conservative, and hospitals that favor routine early angiography and revascularization were excluded. Likewise, the use of GP IIb/IIIa inhibitors was discouraged. In contrast, many American hospitals favor a more aggressive strategy, with higher rates of angiography, percutaneous coronary intervention, and GP IIb/IIIa inhibitor use. The benefit of clopidogrel may be different when incorporated into an aggressive strategy.

Patients enrolled were at high risk, with electrocardiographic evidence of ischemia or elevated cardiac markers. This high-risk population represents a minority of patients being evaluated for chest pain, and the results should not be extrapolated to all patients presenting with chest pain syndromes.

Bleeding was increased in the clopidogrel group, raising additional concerns about the use of clopidogrel as part of an aggressive management strategy. At hospitals with aggressive strategies, many patients with acute coronary syndromes receive an intravenous GP IIb/IIIa inhibitor "up front." What would happen to the bleeding rate if they also received clopidogrel? The up-front use of clopidogrel with GP IIb/IIIa inhibitors cannot be recommended, based on the findings of the CURE study, but this topic should be investigated. The decision of which class of drug to use should be based on practice patterns, cost, and reversibility. Small-molecule GP IIb/IIIa inhibitors are favored at aggressive centers because these agents have short half-lives, allowing for surgical revascularization without long delays.

Clopidogrel might necessitate delaying CABG. Patients in the CURE trial started taking the study medication before their coronary anatomy was delineated. The study medication was withheld for a mean of 5 days for patients who were referred for surgical revascularization. There was no significant increase in bleeding for patients in whom the drug was withheld for at least 5 days; however, there was an expected trend toward higher rates of

bleeding for patients receiving clopidogrel within 5 days of cardiac surgery.

Many cardiac surgeons at The Cleveland Clinic insist that clopidogrel be withheld for at least 5 days prior to cardiac surgery, owing to concerns about increased bleeding. A strategy incorporating clopidogrel in the early management of acute coronary syndromes would likely prolong the length of hospitalization in patients requiring CABG.

Cost. Other than bleeding risk, the major issue of more widespread use of clopidogrel is cost. However, given the reduction in the rate of myocardial infarction seen in CURE, clopidogrel is likely to be approximately as cost-effective as ACE inhibitors and statins.

Duration of treatment. The average duration of therapy in the study was 9 months. Benefit persisted at 12 months of follow-up, and the Kaplan-Meier curves continued to diverge. It is possible that prolonged therapy beyond the study average of 9 months may offer additional benefit.

CONCLUSIONS

The findings of the CURE study are an important advance in the global treatment of acute coronary syndromes. The benefit of clopidogrel is clear, but the excess bleeding seen and conservative management strategy used by the investigators may limit the use of clopidogrel in the management of acute coronary syndromes prior to coronary angiography at many American centers.

High-risk patients presenting with acute coronary syndromes should receive clopidogrel on admission at conservative centers and, if appropriate, after coronary angiography in aggressive centers. The benefit with pretreatment before percutaneous coronary intervention is clinically relevant and consistent with previous studies.^{15,16} The value of long-term clopidogrel use is substantial, making this drug a valuable addition to the effective medications for secondary prevention in high-risk patients.

REFERENCES

1. **CURE Study Investigators.** Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345:494-502.
2. **Bhatt DL, Topol EJ.** Antiplatelet and anticoagulant therapy in the secondary prevention of ischemic heart disease. *Med Clin North Am* 2000; 84(1):163-179.
3. **Weiss EJ, Bray PF, Tayback M, et al.** A polymorphism of a platelet glycoprotein receptor as an inherited risk factor for coronary thrombosis. *N Engl J Med* 1996; 334:1090-1094.

Clopidogrel likely is as cost-effective as ACE inhibitors and statins



4. **Gum PA, Kottke-Marchant K, Poggio ED, et al.** Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol* 2001; 88:230–235.
5. **Chew DP, Bhatt DL, Sapp S, et al.** Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a meta-analysis of phase III multicenter randomized trials. *Circulation* 2001; 103:201–206.
6. **FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators.** Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study [published erratum appears in *Lancet* 1999; 354:1478]. *Lancet* 1999; 354:701–707.
7. **CAPRIE Steering Committee.** A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348:1329–1339.
8. **Bhatt DL, Hirsch AT, Ringleb PA, et al.** Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. *Am Heart J* 2000; 140:67–73.
9. **Bhatt DL, Chew DP, Hirsch AT, et al.** Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001; 103:363–368.
10. **Muller C, Buttner HJ, Petersen J, et al.** A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000; 101:590–593.
11. **Taniuchi M, Kurz HI, Lasala JM.** Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001; 104:539–543.
12. **Bertrand ME, Rupprecht HJ, Urban P, et al.** Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; 102:624–629.
13. **Mehta SR, Yusuf S, for CURE Study Investigators.** The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J* 2000; 21:2033–2041.
14. **Mehta SR, Yusuf S, Peters RJ, et al.** Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358:527–533.
15. **Steinhubl SR, Ellis SG, Wolski K, et al.** Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events: data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPIS-TENT) Trial. *Circulation* 2001; 103:1403–1409.
16. **Chew DP, Bhatt DL, Robbins MA, et al.** Effect of clopidogrel added to aspirin before percutaneous coronary intervention on the risk associated with C-reactive protein. *Am J Cardiol* 2001; 88:672–674.

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