Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

Cardiology

UNIVERSITY OF TORONTO

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Clopidogrel Use in Myocardial Infarction Results of the CLARITY-TIMI 28 and COMMIT/CCS-2 Trials

Originally presented by: Marc S. Sabatine, M.D., and Zhenming Chen, M.D.

A Report on a Presentation at the Late-breaking Clinical Trials Session of the American College of Cardiology Annual Scientific Session 2005

Orlando, Florida March 6-9, 2005

Reported and discussed by:
WARREN J. CANTOR, MD, FRCPC

Platelet activation and aggregation play a pivotal role in the initiation and propogation of coronary thrombosis underlying the pathogenesis of acute coronary syndromes (ACS), including acute myocardial infarction (AMI). Antiplatelet therapy with aspirin has been shown to be effective in reducing morbidity and mortality associated with ACS and AMI.[1-4] Clopidogrel, a thienopyridine that inhibits ADP-mediated platelet activation, is a more potent antiplatelet agent than aspirin. In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, the combination of aspirin and clopidogrel was more effective than aspirin alone in preventing the composite of cardiovascular (CV) death, myocardial (re-) infarction, and stroke in patients with non-ST elevation ACS and either electrocardiographic changes or elevated cardiac marker levels.[5] The combination of clopidogrel and aspirin is used routinely after coronary stenting procedures.[6,7] However, the safety and efficacy of clopidogrel for the initial management of AMI, particularly ST-elevation MI (STEMI) treated with thrombolysis, has not been previously studied. This issue of *Cardiology Scientific Update* presents the results of 2 trials examining the addition of clopidogrel to fibrinolytic regimens (including aspirin) in the treatment of AMI and the reduction of associated morbidity and mortality.

The CLARITY-TIMI 28 trial

The Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction (CLARITY TIMI) 28 trial was a double-blind, randomized, placebo-controlled trial designed to test the hypotheses that the addition of clopidogrel to fibrinolytic regimens (including aspirin) improves patency of the infarct-related artery (IRA) and reduces ischemic complications.[8,9] A total of 3,491 patients with STEMI being treated with thrombolysis were randomized to receive clopidogrel (300 mg bolus followed by 75 mg daily) or placebo. All patients were to undergo coronary angiography within 2-8 days of enrolment. The primary endpoint of the trial was IRA occlusion, defined as TIMI grade 0 or 1 flow on coronary angiography, or the occurrence of death or reinfarction by the time of angiography. Patients who underwent percutaneous coronary intervention (PCI) received open-label clopidogrel. All patients were followed to 30 days.

Exclusion criteria included age >75 years, planned treatment with clopidogrel or glycoprotein (GP) IIb/IIIa inhibitors before angiography, cardiogenic shock, intention to perform coronary angiography within 48 hours in the absence of a new clinical indication, or use of an initial heparin bolus in excess of guideline recommendations (American College of Cardiology/American Heart Association STEMI guidelines for the management of STEMI).[10] The study was sponsored by Sanofi-Aventis and Bristol-Myers Squibb, but was performed independently by the TIMI Research Group and the Nottingham Clinical Research Data Coordinating Centre. Patients were enroled from 319 centres in 23 countries.

Results of CLARITY-TIMI 28 were recently presented and published.[9] There were no significant differences in baseline characteristics between treatment groups. The mean age was 57 years and 80% of the patients were male. The infarct location was anterior in 40% of patients. Fibrin-specific fibrinolytic agents were used in 69% of patients. Unfractionated heparin was used

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: CLARITY – Primary and angiographic outcomes (median 3.5 days)

Outcome	Clopidogrel	Placebo	Odds Ratio	P value
Primary endpoint (%)	15.0	21.7	0.64	<0.001
TIMI Flow Grade 0/1	11.7	18.4	0.59	<0.001
MI	2.5	3.6	0.70	0.08
Death	2.6	2.2	1.17	0.49
Angiographic (%)				
TIMI Flow Grade 3	67.8	60.8	1.36	<0.001
TIMI Myocardial Perfusion 3	55.8	51.2	1.21	0.008
Thrombus	43.0	50.8	0.73	<0.001

in 46% and low molecular weight heparin was used in 30% of patients. Over 80% received beta-blockers and statins, while >70% received angiotensin-converting enzyme (ACE) inhibitors or angiotension receptor blockers (ARBs). The mean time from symptom onset to fibrinolysis was 2.7 hours and the mean time from fibrinolysis to study drug administration was 10 minutes. Coronary angiography was performed in 94% of patients at a median of 84 hours (3.5 days) after enrolment. Coronary revascularization was performed in 63% of patients (PCI in 57 % and coronary artery bypass surgery [CABG] in 6%).

The primary endpoint of IRA occlusion occurred in 15.0% of the clopidogrel group and in 21.7% of the placebo group [36% odds reduction, p<0.001, number needed to treat (NNT) 16] (Table 1). This benefit was consistent among all pre-specified subgroups, including stratification by age, gender, infarct location, fibrinolytic type, and heparin type (Figure 1). Angiographically, clopidogrel was also associated with significantly higher rates of normal (TIMI-3) myocardial perfusion grade and significantly lower rates of visible thrombus. Patients in the clopidogrel group had significantly lower rates of early angio-

Figure 1: CLARITY – Subgroups Primary Endpoints

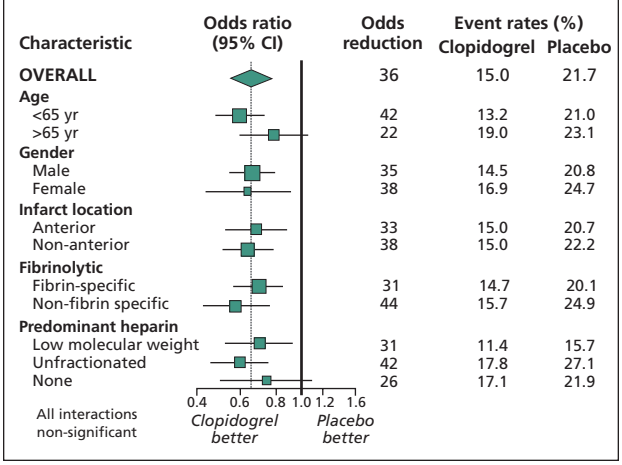
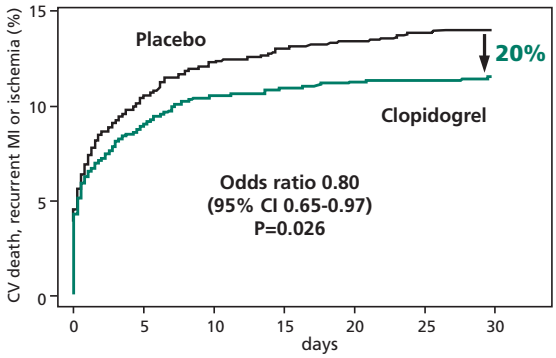


Figure 2: CLARITY – CV death, recurrent MI, or recurrent ischemia leading to urgent revascularization



MI = myocardial infarction

graphy within 48 hours, and urgent revascularization during the index hospitalization. There was a trend towards lower use of GP IIb/IIIa inhibitors during PCI in the clopidogrel group. Clopidogrel was also associated with a significant 20% reduction in the incidence of cardiovascular death, MI, or recurrent ischemia requiring urgent revascularization (11.6% vs. 14.1%, p=0.026, NNT=36) (Figure 2). There was a trend towards less stroke with clopidogrel (0.9% vs. 1.7%, p > 0.05). There were no significant differences in the rates of major bleeding, minor bleeding. or intracranial hemorrhage (Table 2). Even among the patients who underwent CABG within 5 days of study drug administration, there were no statistically significant differences in the rates of TIMI major bleeding (9.1% vs. 7.9%, p=1.00).

The COMMIT/CCS-2 study

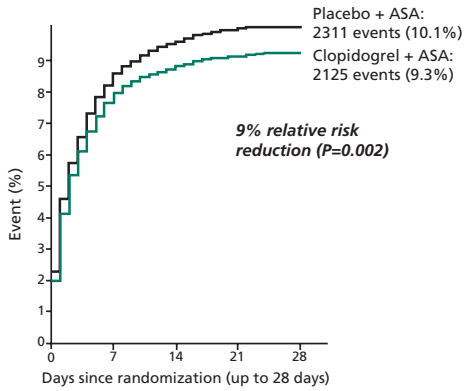
The ClOpidogrel and Metoprolol in Myocardial Infarction Trial /Second Chinese Cardiac Study (COMMIT/CCS-2) study was a 2-by-2 factorial design, randomized, placebo-controlled trial that evaluated the use of clopidogrel and metoprolol for

Table 2: CLARITY – Bleeding

Outcome	Clopidogrel (%)	Placebo (%)	P value
Through angiography			
TIMI major (Hgb ↓ >5 g/dL or ICH)	1.3	1.1	NS
TIMI minor (Hgb ↓ 3-5 g/dL)	1.0	0.5	NS
Intracranial hemorrhage	0.5	0.7	NS
Through 30 days			
TIMI major	1.9	1.7	NS
In those undergoing CABG	7.5	7.2	NS
CABG w/in 5 days of study med	9.1	7.9	NS
TIMI minor	1.6	0.9	NS

ICH = intracranial hemorrhage; Hgb = hemoglobin

Figure 3: COMMIT – Effects of clopidogrel on death, re-MI or stroke



AMI.[11] A total of 45,852 patients with AMI were enrolled at 1,250 centres in China. All patients had ST segment changes (depression or elevation) or left bundle branch block (LBBB) who had presented within 24 hours of symptom onset. Patients were excluded if they were to undergo primary PCI or if they were at high-risk of bleeding. Patients were randomized to receive clopidogrel 75 mg daily (no loading dose) vs. placebo, in addition to aspirin 162 mg daily. The two primary outcomes were death and the composite of death, reinfarction, and stroke at 4 weeks or prior to hospital discharge. The mean treatment and follow-up duration was 16 days.

The preliminary results of COMMIT/CCS-2 were recently presented. The baseline characteristics were similar between groups: 26% of patients were ≥ 70-years-old and ST-elevation or LBBB was present in 93% of cases. Thrombolysis was used in 50% (68% of patients with STEMI within 12 hours of symptom onset). Heparin or other anticoagulants were used in 75% of patients.

- The primary endpoint of death, reinfarction, or stroke occurred in 9.3% of the clopidogrel group and 10.1% of the placebo group (9% relative risk reduction, p=0.002) (Figure 3).

Figure 4: COMMIT – Effects of clopidogrel on in-hospital deaths

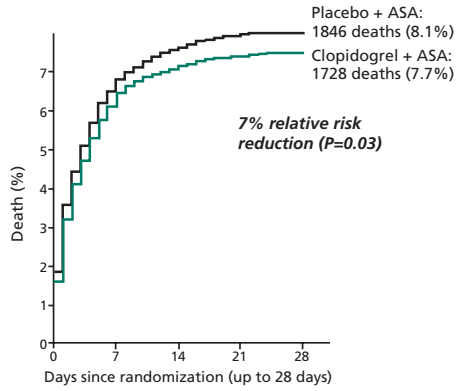


Table 3: COMMIT – Major bleed in hospital

	Clopidogrel (n = 22,958)	Placebo (n = 22,891)
Cerebral		
Fatal	39	40
Non-fatal	16	15
Non-cerebral		
Fatal	36	37
Non-fatal	46	36
Any major bleed	134 (0.58%)	124 (0.54%)

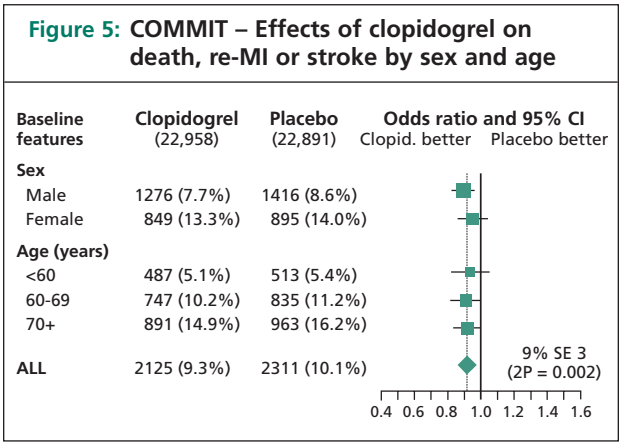
- In-hospital deaths occurred in 7.7% of the clopidogrel group and 8.1% of the placebo group (7% relative risk reduction, p = 0.03) (Figure 4).
- Reinfarction (fatal and non-fatal) was significantly reduced with clopidogrel (2.1% vs. 2.4%, p = 0.02).
- There was a non-significant trend towards less stroke with clopidogrel (0.9% vs. 1.1%, p > 0.1).
- Major bleeding was infrequent in both treatment groups (0.58% for clopidogrel, 0.54% for placebo, p > 0.05).
- There were no significant differences in cerebral or non-cerebral bleeds (Table 3).

The benefit of clopidogrel on the primary endpoint was consistent across all subgroups, stratified by age, gender, use of thrombolysis, and timing of enrolment after symptom onset (Figure 5). Patients aged ≥70 years had the highest absolute event rates and the highest absolute risk reduction with clopidogrel. When the primary endpoint event rates were broken down into days after enrolment, a benefit from clopidogrel was evident, even on the first day (2.0% vs. 2.3%), despite the fact that no loading dose was used (Figure 6).

Summary

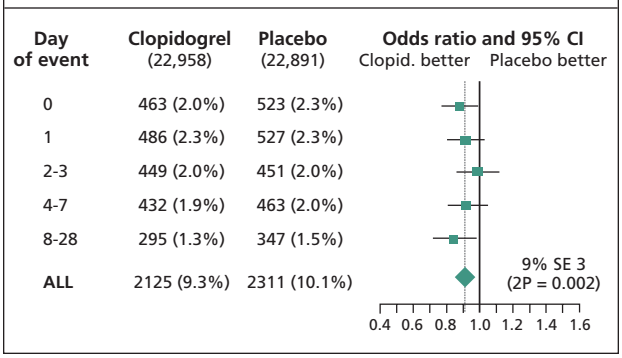
The CLARITY TIMI-28 and COMMIT/CCS-2 trials provide consistent data demonstrating the efficacy of clopidogrel for acute MI. The addition of clopidogrel to aspirin, anticoagulants,

Figure 5: COMMIT – Effects of clopidogrel on death, re-MI or stroke by sex and age



re-MI = recurrent myocardial infarction

Figure 6: COMMIT – Effects of Clopidogrel on death, Re-MI or stroke by day of event



re-MI = recurrent myocardial infarction

and fibrinolytic therapy improved patency of the IRA at 2-8 days and significantly reduced the incidence of death and reinfarction, with a trend towards less stroke. Importantly, neither trial demonstrated any excess in major bleeding complications, despite the fact that all patients in CLARITY TIMI-28 and most in COMMIT/CCS-2 received fibrinolytic therapy and other potent antithrombotic therapies. Even among the patients undergoing CABG during the initial hospitalization or within 5 days of receiving the study drug, no differences in major bleeding were observed. This may reflect increased surgical experience and improved strategies for minimizing bleeding in patients undergoing CABG who have received clopidogrel.

The COMMIT/CCS-2 results complement the CLARITY TIMI-28 trial results, demonstrating that improvement in IRA patency translates into a significant improvement in clinical outcomes, including mortality. Furthermore, the COMMIT/CCS-2 trial demonstrates that the early benefit of clopidogrel also applies to patients with STEMI or LBBB not receiving thrombolysis and those >70 years old. Despite the lack of a loading dose for clopidogrel in the COMMIT/CCS-2 study, an early benefit was apparent in the first 24 hours. The CLARITY TIMI-28 trial confirmed that a 300 mg loading dose was safe, but excluded patients >75 years old. A reasonable strategy suggested by commentator Dr. Chris Cannon is to use the 300 mg loading dose in patients ≤ 75 years old, but avoid it in patients >75 years old until safety data for the loading dose in elderly patients with AMI are available.

The optimum duration of treatment with clopidogrel following AMI cannot be established from these 2 trials. However, based on the CURE, PCI-CURE, and the Clopidogrel for the Reduction of Events During Observation (CREDO) results, it would be reasonable to continue clopidogrel for 1 year, particularly in patients undergoing PCI.[5-7] Longer treatment durations may be required for patients who are unable to take aspirin, those who experience recurrent events while on aspirin, or those who remain at high risk for atherothrombotic events, including late stent thrombosis.

The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE), CURE, and CREDO trials demonstrate the benefit of clopidogrel for non-ST elevation ACS, following PCI, and for secondary prevention.[5,7,12] The results of the CLARITY TIMI-28 and COMMIT/CCS-2 trials further extend the indications for clopidogrel to include initial treatment for patients with AMI. The ongoing CHARISMA trial will determine whether the combination of clopidogrel and aspirin is superior to aspirin alone in primary prevention for high-risk patients.[13]

References

1. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *J Am Coll Cardiol* 1988;12:3A-13A.
2. Wallentin LC. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. Research Group on Instability in Coronary Artery Disease in Southeast Sweden. *J Am Coll Cardiol* 1991;18: 1587-93.
3. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
4. Lewis HD, Jr., Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1983; 309:396-403.
5. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial 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.
6. 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;358:527-33.
7. Steinhubl SR, Berger PB, Mann JT, III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20.
8. Sabatine MS, McCabe CH, Gibson CM, et al. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial. *Am Heart J* 2005;149:227.
9. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. Published at www.nejm.org, March 9, 2005.
10. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 2004; 44(3):E1-E211.
11. Second Chinese Cardiac Study (CCS-2) Collaborative Group. Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. *J Cardiovasc Risk* 2000;7:435-41.
12. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348:1329-39.
13. Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: Rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2004;148:263-68.