

The role of clopidogrel in the emergency department

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Introduction

Despite major advances in the management of acute coronary syndromes (ACS), 1 in 3 Canadians die from cardiovascular disease.^{1,2} In 1998, the total economic burden of cardiovascular illness in Canada was \$159 434.5 million dollars — \$83 953.9 million in direct costs and \$75 479.6 million in indirect costs.² During the past 20 years, several pharmacologic adjuncts have been investigated with hopes of ameliorating the consequences of ACS. Notably, clopidogrel has become a common component of ACS therapeutic regimens since its introduction in 1998. Both new medications and those already accepted as standard treatment deserve critical evaluation to ensure they are safe and effective.

The purpose of this evidence-based review was to systematically examine the best-published literature regarding the current role of clopidogrel in the management of ACS. We performed a comprehensive Medline (1966 to August 2004) and EMBASE (1980 to present) search for human, randomized controlled trials using the search terms “clopidogrel,” “thienopyridine,” “acute coronary syndrome,” “ACS,” “non-ST-elevation myocardial infarction,” “NSTEMI,” “unstable angina” and “percutaneous coronary intervention.” Abstracts were reviewed, and articles relevant to emergency department (ED) management of ACS were selected.

Pathophysiology

Over the last several years, our understanding of the pathogenesis of ACS has significantly improved, and has led to the development of new strategies for the management of these patients. The acute coronary syndromes — unstable

angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (MI) — share the same underlying pathophysiology involving platelet activation, aggregation and initiation of the coagulation cascade.^{3,4} Rupture of an unstable vascular plaque exposes its thrombogenic lipid-rich core, initiating platelet adhesion to the damaged vessel wall and local exposure of the subendothelial matrix. Platelet activation is then initiated through both mechanical and chemical mechanisms. Known chemical mediators that activate platelets include thrombin, adenosine diphosphate (ADP), thromboxane A₂ (TXA₂), serotonin, fibrinogen and von Willebrand's factor. Ultimately, platelet activation causes the conversion of glycoprotein IIb/IIIa (GP IIb/IIIa) receptors into a configuration that enables fibrinogen-mediated cross-linking of adjacent platelets, hence platelet aggregation. Simultaneous activation of the coagulation cascade may then lead to the production of a stable fibrin clot.^{5,6} Clinically, ACS differ depending on the extent of thrombus formation, thrombus stability, anatomical location, degree of coronary occlusion and extent of the myocardial damage resulting from the diminished blood flow.^{5,7}

Our increased understanding of ACS pathophysiology has led to the development of many effective pharmacological interventions. Acetylsalicylic acid (ASA) decreases platelet aggregation by inhibiting TXA₂ production, and heparin interferes with the coagulation cascade. Both have become cornerstone therapies for ACS patients. GP IIb/IIIa receptor antagonists such as abciximab, eptifibatid or tirofiban are powerful agents to further inhibit platelet aggregation in high-risk patients. Until recently, only ASA was administered past the acute period,¹ but more recently,

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evidence suggests that the ADP antagonist clopidogrel has added benefits when given in combination with ASA in reducing long-term risk of ischemic events.^{8–10}

Pharmacology and pharmacokinetics

Clopidogrel, a thienopyridine derivative, acts by preventing ADP binding to its receptor on the platelet, thus inhibiting the activation of the ADP-dependent GP IIb/IIIa complex.^{11,12}

Food or antacids do not affect the bioavailability of clopidogrel. It is 98% protein-bound and has an elimination half-life of approximately 8 hours.^{11,13} In healthy volunteers and patients with atherosclerosis, the maximal effect of a single 40-mg dose occurs after 5 hours and persists for 24 hours.¹⁴ Clopidogrel binding to ADP receptors is irreversible; therefore, platelets are inhibited for the remainder of their lifespan, about 7 days. This means that, after drug discontinuation, clinical normalization of platelet function takes approximately 5 days, until sufficient new platelets are generated.^{11–13}

In vivo, clopidogrel is converted to its active metabolite by the hepatic cytochrome P450 (CYP)-1A and -3A enzyme systems.¹³ Recent literature suggests a potential drug interaction between clopidogrel and atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor commonly used in ACS patients.¹⁵ Since atorvastatin is metabolized by cytochrome P450-CYP3A4, it has been postulated that its co-administration with clopidogrel may result in the reduced metabolism of clopidogrel to its active metabolite, thereby decreasing clopidogrel's antiplatelet effects.¹⁵ However, this drug interaction did not appear clinically significant in a trial of ACS patients who received clopidogrel and atorvastatin concomitantly for 5 weeks.¹⁶

Clopidogrel has similar structure to ticlopidine, the first thienopyridine antiplatelet agent, differing only by the addition of a carboxymethyl side group. This structural change gives rise to clopidogrel's safer side-effect profile and better tolerability.¹⁷ Clopidogrel is less likely to cause thrombocytopenia and neutropenia; therefore, its use does not mandate ongoing hematologic monitoring (unlike ticlopidine). The CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) demonstrated that the incidence of neutropenia is similar in patients receiving clopidogrel and ASA (0.1% and 0.17% respectively).¹⁸ Other clinical trials, along with a recent meta-analysis, also showed similar efficacy but fewer adverse events with clopidogrel compared to ticlopidine in preventing thrombosis following coronary artery stent implanta-

tion.^{8,9,19–22} The “ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable and Non-ST-segment Elevation Myocardial Infarction” replaced ticlopidine with clopidogrel as the antiplatelet of choice for patients who cannot tolerate ASA, and identified ASA–clopidogrel as the standard antiplatelet combination to prevent post-coronary stent thrombosis.¹

Clinical evidence

The best evidence for clopidogrel in ACS management came from the CURE trial (Clopidogrel in Unstable angina to prevent Recurrent Events), an international multicentre randomized double-blind placebo-controlled study comparing the efficacy and safety of early and long-term use of clopidogrel plus ASA versus ASA alone in patients with non-ST-elevation ACS.¹⁰ In CURE, 12 562 eligible patients with ACS (Box 1) were randomized to receive a 300-mg loading dose of clopidogrel (or matching placebo) followed by 75 mg of clopidogrel (or matching placebo) for 3 to 12 months. At the discretion of the physician in charge, all patients concurrently received ASA in a dose range of 75 to 325 mg daily.

There were 2 primary endpoints in this trial. The first was a composite of cardiovascular death, non-fatal MI or stroke; the second was a composite of cardiovascular death, non-fatal MI, stroke or refractory ischemia. Secondary outcomes included severe ischemia, heart failure, the need for revascularization and bleeding complications. Major bleeding was defined as disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding requiring transfusions of 2 or more units of blood. Bleeding was considered life-threatening if it was fatal; or led to a reduction in the hemoglobin level of at least 5 g per decilitre or to substantial hypotension requiring the use of intravenous inotropic agents; if it required a surgical intervention; if it was a symptomatic intracranial hemorrhage; or it

Box 1. Eligibility criteria for the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial²²

Eligible patients had ACS symptoms for <24 hours **AND** had either:

- ECG changes (ST-segment depression ≥ 1 mm, elevation ≤ 1 mm, transient elevation > 2 mm, or T-wave inversion) in at least 2 contiguous leads, **or**
- an elevation of serum troponin, creatinine kinase, creatine kinase MB isoenzyme or other cardiac markers to at least twice the upper limit of normal or 3 times the upper limit of normal within 48 hours after percutaneous coronary intervention.

ACS = acute coronary syndromes

necessitated the transfusion of 4 or more units of blood. Minor bleeding was defined as any hemorrhage leading to the interruption of the study medication.

After a mean of 9 months of follow-up, the incidence of the first primary outcome (cardiovascular death + non-fatal MI + stroke) was 9.3% in the clopidogrel group and 11.4% in the placebo group (absolute risk reduction [ARR] = 2.1%; relative risk [RR] = 0.80; 95% confidence interval [CI], 0.72–0.90; $p < 0.001$). This suggests that 48 people would need to be treated for 9 months to prevent 1 outcome event. The reduction in the primary endpoint was mainly driven by reduction in MI (5.2% for clopidogrel and 6.7% for placebo; RR = 0.77, 95% CI, 0.67–0.89) and there was no difference in the incidence of cardiovascular death or stroke. Similarly, the second primary endpoint was significantly lower in the clopidogrel group (16.5% v. 18.8%; $p < 0.001$; ARR = 2.3%; RR = 0.86; 95% CI, 0.79–0.94). Further analyses indicated that the benefit of clopidogrel was apparent within a few hours of randomization and achieved statistical significance by 24 hours.

Offsetting this benefit was a higher incidence of bleeding complications. Major bleeding was reported in 3.7% of clopidogrel recipients and 2.7% of placebo recipients, an ARR increase of 1.0% (RR = 1.38; 95% CI, 1.13–1.16; $p = 0.001$). This suggests that, for every 100 patients treated with clopidogrel, there is 1 extra major bleed. Patients who received clopidogrel within 5 days of coronary artery bypass grafting (CABG) were at higher risk, with major bleeding rates of 9.6% and 6.3% in the clopidogrel and

placebo arms respectively (RR = 1.53; $p = 0.06$). Clopidogrel was also associated with a higher incidence of minor bleeding (5.1% v. 2.4%; $p < 0.001$) and life-threatening bleeding (2.2% v. 1.8%; RR = 1.21; 95% CI, 0.95–1.56), although the risk of hemorrhagic stroke was the same (0.1%) in both groups. The incidence of thrombocytopenia was the same (0.004%) in both groups. The main results of CURE are summarized in Table 1.

PCI-CURE was a substudy of CURE, and it included 2658 CURE patients who underwent percutaneous coronary intervention (PCI).²³ The investigators tested the hypothesis that clopidogrel and ASA pretreatment (median 10 days), followed by long-term treatment (mean, 8 mo) was superior to ASA and short-term clopidogrel post PCI stent implementation therapy (4 wk). The primary outcome was a composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days, but the authors also tracked cardiovascular death and MI beyond 30 days to assess long-term effects.

PCI-CURE showed that clopidogrel recipients suffered 30% fewer primary outcome events (4.5% v. 6.4%, $p = 0.03$) at 30 days. Clopidogrel recipients also had a lower rate of cardiovascular death/MI (6.0% v. 8.0%, $p = 0.047$) at the end of the follow-up period. As with the main CURE study, there was no significant survival benefit, and differences were related to lower MI rates. In PCI-CURE, there was no difference in major bleeding rates between groups (2.7% for clopidogrel v. 2.5% for placebo; $p = 0.64$); however, only 24% of patients in this study received a GP

Table 1. Summary of main results from the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial²²

Outcomes	Group, no. (and %) of patients		<i>p</i> value	Relative risk (95% CI)	ARR	NNT (or NNH)
	Clopidogrel <i>n</i> = 6259	Placebo <i>n</i> = 6303				
Efficacy outcomes						
<u>Primary endpoint #1:</u>						
Non-fatal MI, stroke or CVD death	582 (9.3)	719 (11.4)	<0.001	0.80 (0.72–0.90)	2.1%	48
<u>Primary endpoint #2:</u>						
Non-fatal MI, stroke, CVD death, or refractory ischemia	1035 (16.5)	1187 (18.8)	<0.001	0.86 (0.79–0.94)	2.3%	44
MI	324 (5.2)	419 (6.7)		0.77 (0.67–0.89)	1.5%	67
Q-wave MI	116 (1.9)	193 (3.1)		0.60 (0.48–0.76)	1.2%	84
Refractory ischemia during initial hospitalization	85 (1.4)	126 (2.0)		0.68 (0.52–0.90)	0.6%	167
Bleeding outcomes*						
Life-threatening, %	2.2	1.8		1.21 (0.95–1.56)	0.4%	250
Major, %	3.7	2.7	0.001	1.38 (1.13–1.67)	1.0%	100
Minor, no. of patients (and %)	322 (5.1)	153 (2.4)	<0.001		2.7%	37

ARR = absolute risk reduction; NNT = number needed to treat; NNH = number needed to harm; MI = myocardial infarction; CVD = cardiovascular disease
 *See "Clinical evidence" section for descriptions of each category of bleeding.

IIB/IIIa receptor antagonist, and this practice contrasts with the standard of care in North America, where most patients receive a GP IIB/IIIa receptor antagonist to reduce procedure-related thrombosis.²⁴ The small number of patients who received ASA, heparin, and GP IIB/IIIa receptor antagonists in addition to clopidogrel make it difficult to extrapolate the bleeding complication rates or conclude that this relatively standard combination is safe.

Limitations of clinical evidence

Patients presenting to the ED with unstable angina or NSTEMI often require urgent medical and interventional management. Although clopidogrel has been evaluated in several large randomized trials, only the CURE trial looked at patients representative of those in the ED setting.^{10,18} Results from the CURE trial are therefore important in defining clopidogrel's role in ACS; however, they leave several unanswered questions, such as optimal dose and timing prior to PCI, optimal duration of therapy, and whether this agent can be safely combined with GP IIB/IIIa antagonists.

Other trials (e.g., TACTICS) have demonstrated the benefit of an early invasive strategy, which is the standard of care in many North American centres;²⁵ however, CURE focused on medical management, excluding centres that

employ aggressive early intervention.¹⁰ CURE's relatively conservative medical approach is most applicable to centres without access to early invasive strategies. Furthermore, only 6.5% of subjects in the CURE trial received GP IIB/IIIa inhibitors; as a result, there are limited data addressing combined use of clopidogrel, GP IIB/IIIa inhibitors, heparin and ASA, and the safety and efficacy of these combination therapies are unknown.

The CURE trial studied relatively high-risk ACS patients who had ST changes in at least 2 contiguous ECG leads or elevated serum markers; therefore, emergency physicians should, in general, limit its use to patients with these risk markers.

In patients requiring urgent revascularization, the dose and timing of clopidogrel administration may be important. The CREDO trial (Clopidogrel for the Reduction of Events During Observation) evaluated the safety and efficacy of clopidogrel loading and maintenance therapy in patients undergoing elective PCI.²⁶ Although these patients are unlike acute ACS patients presenting to EDs, the CREDO results shed light on the optimal timing of clopidogrel administration prior to PCI. In the CREDO trial, patients received a 300-mg loading dose of clopidogrel (or placebo) 3–24 hours (mean = 9.8) prior to PCI. A prespecified time analysis suggested that patients who received clopidogrel at least 6 hours prior to PCI had fewer adverse

Table 2. Evidence-based recommendations for the use of clopidogrel in the emergency department (ED)

Patients	Practice sites	Recommendations for ED
<p>Eligible</p> <ul style="list-style-type: none"> High-risk ACS patients <ol style="list-style-type: none"> presenting within 24 hours of onset of symptoms and either elevated cardiac enzymes (2× upper limit of normal) or ECG changes (ST depression ≥1mm, elevation ≤1 mm, transient elevation >2 mm or T-wave inversion) in at least 2 contiguous leads <p>Ineligible / Caution</p> <ul style="list-style-type: none"> Patients at lower risk than described above (as initially the CURE investigators²² enrolled patients >60 years of age who presented with new symptoms but no HISTORY of coronary artery disease) Patients at high-risk of bleeding (those receiving concomitant oral anti-coagulants, or GP IIB/IIIa receptor antagonists) 	<p>Suitable</p> <ul style="list-style-type: none"> Sites where medical management is the standard of care <p>Unsuitable</p> <ul style="list-style-type: none"> Sites where mechanical intervention occurs as the standard of care (i.e., hospitals with access to a catheterization lab) Where GP IIB/IIIa receptor antagonists are commonly used in combination with stent implantation Sites where emergency by-pass surgery is an option (as there was increased incidence of major bleeding in patients who could not discontinue clopidogrel within 5 days of the surgery) 	<ul style="list-style-type: none"> Consider prescribing combination ASA 75–325 mg/d plus clopidogrel 300-mg loading dose followed by 75 mg/d Consider prescribing ASA 75–325 mg/d

ACS = acute coronary syndromes; ASA = acetylsalicylic acid; CURE = Clopidogrel in Unstable angina to prevent Recurrent Events trial; GP IIB/IIIa = glycoprotein IIB/IIIa

outcomes than those who received it within 6 hours of PCI (23, -13.4%; 95% CI, -83.8% to 29.8%; $p = 0.60$). This may reflect clopidogrel's dose-dependent effect on platelet aggregation and its delayed onset, with maximal effects seen approximately 5 hours after loading.¹⁴ Although CREDO's study population was lower acuity than typical ACS patients presenting to the ED, the data suggest that, whenever possible, clopidogrel should be given at least 6 hours before PCI. It is not known whether patients with ACS requiring urgent revascularization would benefit from clopidogrel given within 6 hours of the procedure because this was not evaluated in PCI-CURE.²³

Finally, the optimal duration for clopidogrel therapy is not known. CURE and CREDO showed benefit for patients treated with clopidogrel and ASA out to 9 and 12 months respectively.^{10,26} At present, long-term data beyond 1 year are not available. The ACC/AHA 2002 Guideline Update recommends that patients receiving either a non-interventional approach or planned PCI should receive clopidogrel for at least 1 month and up to 9 months.¹

Emergency medicine perspectives

The ACC/AHA 2002 Guideline Update for clopidogrel use in ACS has considerable clinical and financial implications. These guidelines strongly recommend an early interventional strategy in ACS patients with high-risk indicators.¹ Yet most of the patients in the CURE study were not revascularized on their index visit and did not receive GP IIb/IIIa receptor antagonists.²³ Consequently, there are insufficient data to support the concomitant use of ASA, clopidogrel, heparin and GP IIb/IIIa antagonists in the acute management of ACS patients, and one must be cautious in applying the findings of the CURE trial to patients unlike those studied — notably to patients undergoing PCI and receiving GP IIb/IIIa antagonists. It is also important to re-emphasize the higher risk of bleeding in patients who receive clopidogrel within 5 days of CABG, and this certainly has implications for emergency physicians who work in settings that provide PCI and CABG on an urgent basis. See Table 2 for a summary of evidence-based recommendations for the use of clopidogrel in the ED.

Summary

Clopidogrel is a thienopyridine antiplatelet agent with a more favourable safety profile than its predecessor, ticlopidine. Clopidogrel is now the antiplatelet of choice for patients who cannot tolerate ASA, but its role in ACS is less clear. The best evidence supporting clopidogrel use in pa-

tients with ACS comes from the CURE trial. This study suggests that appropriately selected patients who have definitive ECG changes or positive cardiac markers are most likely to benefit from therapy, and that, for every 1000 such patients treated, approximately 20 outcome events (mostly MIs) will be prevented at the cost of 10 extra major bleeds.¹⁰ Extending clopidogrel use to ACS patients without the high-risk features described above is likely to result in even fewer favourable outcomes relative to toxicity. The safety and efficacy of early clopidogrel administration is unclear in patients who will undergo primary PCI and receive GP IIb/IIIa antagonists, and clopidogrel should probably be avoided in patients likely to undergo CABG within 5 days.

Clopidogrel is priced at approximately \$3 per 75-mg tablet, which means a 9-month course of therapy like that studied in CURE will cost between \$750 and \$900. A recent cost-effectiveness analysis from Sweden concluded that ASA–clopidogrel combination therapy compares favourably with other cardiovascular treatment and prevention strategies;²⁷ however, prior to declaring this a cost-effective alternative to ASA alone, a thoughtful North American pharmacoeconomic analysis is required.

Competing interests: None declared.

Key words: ACS; acute coronary syndromes; clopidogrel

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