

Treating Clifford: When and For How Long? Clopidogrel use in ACS and Post-PCI

Considering the confusion as to the appropriate duration of clopidogrel therapy for patients with acute coronary syndrome (ACS) and post-percutaneous coronary intervention (PCI), due to differing recommendations, Dr. Hubacek and Dr. Fort outline the importance of sustained/long-term dual antiplatelet therapy.

Jaroslav Hubacek, MD, MSc, FRCPC; and Stephen Fort, MD, MRCP, FRCPC

Clifford's CAD, ACS and NSTEMI

Clifford comes to your office one week following a recent admission to the hospital due to first presentation of coronary artery disease (CAD), with acute coronary syndrome (ACS)-non-ST segment MI (NSTEMI).

Clifford underwent coronary angiogram and was found to have:

- normal left ventricular function,
- single vessel disease and
- a critical lesion in his mid-left anterior descending artery, for which he underwent percutaneous coronary intervention (PCI) with a drug-eluting stent.

Since discharged he is feeling fine, with no symptoms at rest or during exertion. He is scheduled to start a cardiac rehabilitation program.

His current medications include:

- enteric coated acetylsalicylic acid (ASA), 81 mg q.d.
- clopidogrel, 75 mg, q.d.
- metoprolol, 50 mg, b.i.d.
- rosuvastatin, 20 mg, q.d.

**What can you do to help Clifford?
Read on to find out how to treat him.**

Antiplatelet therapies are the mainstay in the treatment of ACS and following PCI. Both ACS and PCI are associated with atherosclerotic plaque rupture, with subsequent platelet activation and thrombus formation.

Activation of the platelets is achieved via several pathophysiological pathways and can be inhibited by multiple drugs (Figure 1). Use of the antiplatelet therapies, especially clopidogrel in the outpatient setting, is confusing due to conflicts between the duration of clopidogrel therapy currently recommended by international guidelines and guidelines funded through provincial drug programs.

The objective of this review is to highlight the importance of sustained/long-term dual anti-platelet therapy in patients with ACS and post-PCI.

When can Clifford stop taking clopidogrel?

In this case, it would be essential to continue treatment with clopidogrel ideally for nine months to 12 months.

What is the evidence for this recommendation?

Clopidogrel is one of the essential antiplatelet medications used following ACS and coronary stenting. It has additive benefit in patients with coronary artery disease (CAD) to the use of acetylsalicylic acid (ASA) as a single therapy.

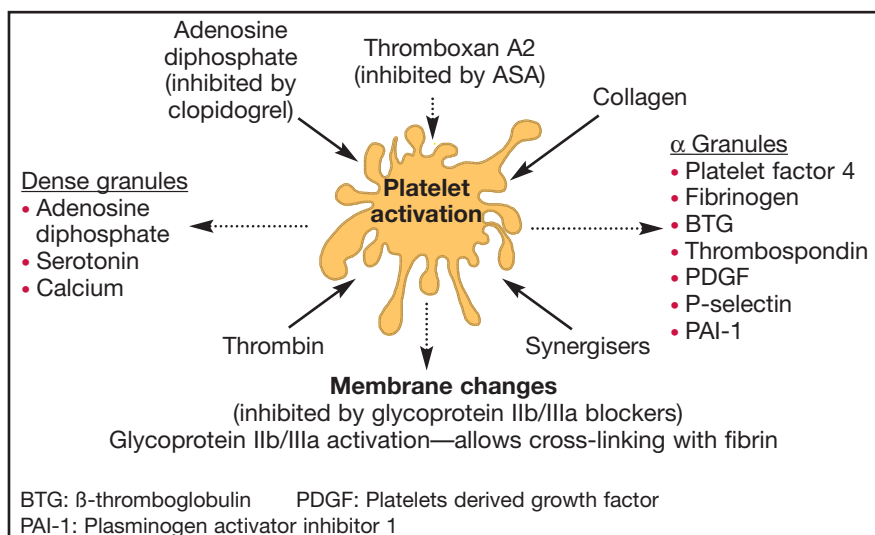


Figure 1: Platelets: A pivotal role in thrombosis.

The CURE trial

The role of clopidogrel in ACS was assessed in the randomized controlled trial (RCT) Clopidogrel in Unstable angina to prevent Recurrent Events (CURE),¹ which enrolled patients with ACS (non-ST segment MI and unstable angina) within 24 hours of presentation of symptoms. Patients were assigned to receive ASA alone, or clopidogrel plus ASA for three months to 12 months (mean of nine months).

The combination therapy reduced composite end-points of cardiovascular death, non-fatal MI and stroke by an absolute risk reduction (ARR) of 2.1% and relative risk reduction of 20% ($p = 0.001$). This benefit was achieved at the expense of increased risk of major bleeding (number needed to harm of 166), especially GI tract bleeding, mainly due to the co-prescription of 325 mg, or higher doses, of ASA.

The CURE-PCI study

The CURE-PCI study (a substudy of CURE) assessed the efficiency of clopidogrel in the patients undergoing PCI.² It demonstrated an ARR of 1.9% in primary end-points ($p = 0.03$).

In this PCI population, clopidogrel with low-dose ASA was not associated with an increased risk of major bleeding; however, minor bleeding did increase by 1.4% ($p = 0.03$).

The CREDO trial

Another RCT, the Clopidogrel for Reduction of Events During Observation (CREDO) study, of stable patients undergoing PCI (without a known indication for long-term clopidogrel) were randomized to clopidogrel or placebo. All patients received ASA. Long-term use (one year) of clopidogrel and ASA treatment following elective PCI resulted in the significant reduction of the combined risks of death for MI or stroke ($p = 0.02$), with an ARR of 3%, compared to ASA and short-term (one month) clopidogrel therapy.³

To summarize...

Current evidence from RCT studying antiplatelet therapy with clopidogrel for at least nine months to 12 months, found that combination therapy significantly reduces adverse cardiovascular events in patients suffering from ACS and/or those undergoing PCI.

Dr. Hubacek completed his Internal Medicine training in Calgary. He is currently a Cardiology Fellow at Dalhousie University and the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia.

Dr. Fort is Director, Cardiac Catheterization Laboratory and Assistant Professor of Medicine at Dalhousie University and Queen Elizabeth II Health Sciences Centre. He is also an Interventional Cardiologist with more than 10 years experience in clinical trials in ACS and PCI.

Table 1

Clopidogrel guidelines

	Indication	Recommendation
ACS	<ul style="list-style-type: none"> • Conservative management • Undergoing PCI (bare-metal stent) • Undergoing PCI (drug-eluting stent) • Patients with indication for warfarin • STEMI and fibrinolytics 	<ul style="list-style-type: none"> • 9 to 12 months • 9 to 12 months • 9 to 12 months • 9 to 12 months* • 8 days/in-hospital
Elective PCI	<ul style="list-style-type: none"> • Bare-metal stent • Drug-eluting stent (sirolimus) • Drug-eluting stent (paclitaxel) 	<ul style="list-style-type: none"> • 1 month • > 3 months • > 6 months
Non-ACS/PCI perioperative period	<ul style="list-style-type: none"> • Primary/secondary prevention • Coronary artery bypass graft surgery 	<ul style="list-style-type: none"> • Not indicated • Stop 5 to 7 days prior to OR


* Caution/avoidance of triple therapy (ASA + clopidogrel + warfarin) is recommended in patients with high-risk of bleeding complications.

In addition to ASA, when compared to the risk of bleeding⁴ in patients at either high-risk of CAD or in those with established CAD, results of the recent Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study showed little, or no benefit with > 12 months use of clopidogrel.

Is there any harm to stopping Clifford's clopidogrel use early, before nine months or 12 months, after ACS and PCI, respectively?

There are multiple case studies and anecdotal reports of patients that have been re-admitted with ACS and acute in-stent thrombosis within days of premature discontinuation of clopidogrel following recent ACS and/or PCI.

So far, the best evidence of adverse events after early discontinuation of clopidogrel, comes from the PREMIER registry.⁵ The

PREMIER registry was one in which patients who had stopped thienopyridines (clopidogrel or ticlopidine) by day 30, following PCI, with drug-eluting stents, were more likely to die within the next 11 months (7.5% vs. 0.7%; $p < 0.0001$) and/or to be re-hospitalized (23% vs. 14%; $p = 0.08$), than compared to patients who continued the treatment. 

References

1. Yusuf S, Zhao F, Mehta SR, et al: 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. The CURE study. *N Engl J Med* 2001; 345(7):494-502.
2. Mehta SR, Yusuf S, Peters RJ, et al: Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators: Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet* 2001; 358(9281):527-33.
3. Steinhubl SR, Berger PB, Mann JT III, et al: CREDO investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. *JAMA* 2002; 288(19):2411-20.
4. DL Bhatt, KAA Fox, W Hacke, et al: Clopidogrel and aspirin vs. aspirin alone in the prevention of atherothrombotic events (CHARISMA). *N Engl J Med* 2006; 354(16):1706-19.
5. Spertus JA, Kettelkamp R, Clifton Vance DO, et al: Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement results from the PREMIER Registry. *Circulation* 2006; 113(24):2803-9.