Clopidogrel in acute coronary syndromes: Where are we now?

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Introduction

Acute coronary syndromes (ACS) are the most common cause of death worldwide. In the United States, over 1,500,000 patients with an ACS are discharged annually (1). ACS is caused by disruption of an atherosclerotic plaque with superimposed thrombotic occlusion of the coronary artery, resulting in myocardial ischaemia or infarction. Platelets play a central role in the initiation and propagation of this process. As a result, effective anti-platelet therapy has become a cornerstone of ACS treatment. The objective of this article is to review the evidence regarding clopidogrel and its impact on the treatment of ACS in contemporary practice.

Clopidogrel: Mechanism of action

Platelet adhesion, activation and aggregation play an important role in the pathophysiology of atherothrombosis. Under healthy conditions, vascular endothelium releases prostacyclins and nitric oxide, which attenuate platelet response. In acute plaque rupture, injury to vascular endothelium occurs, thereby exposing subendothelial proteins, including collagen and von Willebrand factor that recruit localised platelet-rich thrombi and promote platelet activation (2, 3). Tissue factor is released resulting in coagulation activation (4). Degranulation of platelets promotes further activation and aggregation through release of thromboxane A2, adenosine diphosphate (ADP) and serotonin. ADP binds to the P2Y12 receptor and in part promotes a conformational change in platelet morphology (due to accumulation of intracellular calcium) leading to expression of glycoprotein IIb/IIIa receptors on the cell membrane. Activation of these receptors allows for formation of fibrinogen crosslinks among platelets providing the scaffold for platelet-rich thrombus formation (5).

Clopidogrel is a platelet P2Y12 ADP-receptor antagonist that inhibits platelet activation and aggregation. It is a prodrug which requires metabolic activation in the liver using the cytochrome P450 pathway. The active metabolite forms an irreversible ligand with the P2Y12 receptor preventing the binding of ADP and thereby inhibiting the expression of glycoprotein IIb/IIIa receptors and platelet aggregation (6).

Clinical evidence for clopidogrel as an antiplatelet agent

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial provided some of the earliest evidence for clinical benefit of clopidogrel (7). Clopidogrel was directly compared with aspirin for secondary prevention of ischaemic events in patients with prior myocardial infarction (MI), stroke / transient ischaemic attack (TIA) or peripheral arterial disease. At a mean of 1.9 years follow-up, clopidogrel monotherapy modestly reduced the primary outcome of cardiovascular death (CV) death, MI or stroke favouring clopidogrel (9.3% vs. 11.4%; RR 0.80; 95% CI 0.72–0.89, p<0.001). In the 2,658 patients undergoing PCI, there was a 31% relative reduction in CV death or MI (12.6% vs. 8.8%; RR 0.69; 95% CI 0.54 to 0.87, p=0.002) (5). At 30 days, a pretreatment strategy with a clopidogrel loading dose (versus initiating therapy after the PCI) did not significantly reduce events, however, in a pre-specified subgroup analysis a benefit of clopidogrel loading dose (300 mg) was observed when administered >6 hours before PCI.

Clopidogrel in unstable angina / NSTEMI

The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial examined the effects of clopidogrel (300 mg immediately, followed by 75 mg once daily) versus placebo for up to 12 months, in addition to aspirin and standard therapies, in patients with unstable angina or non-ST-segment elevation MI (NSTEMI) (9). In the 12,562 patients randomised, there was a 20% relative reduction in the primary outcome of cardiovascular death (CV) death, MI or stroke favouring clopidogrel (9.3% vs. 11.4%; RR 0.80; 95% CI 0.72–0.89, p<0.001). In the 2,658 patients undergoing PCI, there was a 31% relative reduction in CV death or MI (12.6% vs. 8.8%; RR 0.69; 95% CI 0.54 to 0.87, p=0.002) (5). At 30 days, there was a 44% relative risk reduction favouring clopidogrel pre-treatment (i.e. before PCI), indicating the value of early initiation of clopidogrel at the time of first medical contact and before coronary angiography.
Benefits were observed in addition to proven medical therapies (aspirin, beta-blockers, ACE inhibitors, lipid-lowering therapy) or revascularisation procedures (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]). Given these results, expert consensus guidelines from the American College of Cardiology/American Heart Association (10) and the European Society of Cardiology (11) recommend early initiation of clopidogrel (i.e. at the time of first medical contact), followed by up to one year of therapy in patients with ACS.

**Clopidogrel in STEMI**

More recently, the role of dual antiplatelet therapy has been extended to patients with ST-segment elevation myocardial infarction (STEMI). The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 study randomised patients with STEMI receiving fibrinolysis to clopidogrel (300 mg load followed by 75 mg daily) versus placebo for 30 days, in addition to aspirin (12). The primary endpoint of occluded infarct-related artery at angiogram or death or recurrent MI before angiography was reduced by 36% in favour of dual antiplatelet therapy (15% vs. 21.7%; 95% CI 0.53–0.76; p<0.001). There was also a 20% RR reduction in CV death, recurrent MI or recurrent ischaemia requiring urgent revascularisation at 30 days (11.6% vs. 14.1%; 95% CI 0.65–0.97; p=0.03). In the 1,863 patients receiving PCI, improvements in CV death, recurrent MI or stroke were also observed (3.6% vs. 6.2%; adjusted odds ratio [OR] 0.54; 95% CI 0.35–0.85; p=0.008) with clopidogrel pre-treatment versus placebo (Fig. 1) (13).

The Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial conducted in over 1,000 centres in China, enrolled 45,852 patients with STEMI and randomised them to clopidogrel (75 mg daily) or placebo in addition to aspirin until discharge or up to four weeks in hospital (14). Approximately one-half of patients were treated with fibrinolysis while the remaining patients received medical therapy alone. A 9% relative reduction in the primary endpoint of in-hospital death, re-infarction or stroke was observed in patients receiving clopidogrel (9.2% vs. 10.1%; 95% CI 0.86–0.97; p=0.002). Importantly, there was also a 7% RR reduction in death from any cause (co-primary endpoint) favouring clopidogrel (7.5% vs. 8.1%, 95% CI 0.87–0.99; p=0.03).

**Variability to clopidogrel response**

Despite impressive reductions in major CV events across the spectrum of ACS and in patients undergoing PCI, inter-individual variations in clopidogrel responsiveness have been reported using different laboratory assessments of platelet function (15–18). Some observational studies have correlated a lower platelet response to clopidogrel with adverse cardiovascular events, including stent thrombosis (19–22). Yet, it is unknown whether tailored therapy based on platelet function testing alone improves clinical outcomes. Recently, the Gauging Responsiveness With a VerifyNow Assay Impact on Thrombosis and Safety (GRAVITAS) trial presented in abstract form at the American Heart Association 2010 Scientific Sessions evaluated higher dose clopidogrel (150 mg daily) compared to standard dose clopidogrel (75 mg daily) in hypo-responders identified using a point-of-care platelet assay (VerifyNow P2Y12 test) receiving PCI with drug-eluting stents and treated for six months. Although high-dose clopidogrel reduced platelet reactivity, no difference in the primary endpoint of CV death, non-fatal MI or stent thrombosis was seen (2.3% vs. 2.3%; hazard ratio [HR] 1.01; 95% CI 0.58–1.76; p=0.98). High dose clopidogrel did not increase GUSTO severe or moderate bleeding (1.4% vs. 2.3%, p=0.10) (23). The main limitation of this trial was that it was underpowered, with too few patients to adequately evaluate the primary objective. It also questions the role of point-of-care testing to guide antiplatelet therapy. Based on the results of the trial, routine use of point-of-care testing cannot be recommended. Additional trials are underway, evaluating more potent antiplatelet regimens in patients with high residual platelet reactivity on clopidogrel (TRIGGER-PCI, ARCTIC, TARGET-PCI).

**Double-dose clopidogrel regimen**

Doubling the loading dose of clopidogrel from 300 mg to 600 mg and the maintenance dose from 75 mg to 150 mg daily results in greater platelet inhibition (24–31). Recently, this was evaluated in the multi-national Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNts-Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 trial (32). This double-blind, multi-national trial of 25,086 patients with ACS (with and without ST segment elevation) and intent for PCI were randomised to receive either a...
double-dose regimen of clopidogrel (600 mg/day then 150 mg/day for 7 days then 75 mg/day) or the standard dose regimen (300 mg/day then 75 mg/day). In a factorial design, patients were also randomised to receive high-dose aspirin (300–325 mg daily) or low-dose aspirin (75–100 mg daily). Overall, there was no significant difference in the two clopidogrel dose regimens for the primary outcome of CV death, MI, or stroke at 30 days (4.4% vs. 4.2%; adjusted HR 1.36; 95% CI 1.07–1.74; p=0.039) (Table 1, Fig. 2) (33). As well, there was an impressive 46% relative reduction in definite stent thrombosis (academic research consortium [ARC] definition) with the double-dose clopidogrel regimen (1.3% vs. 0.7%; adjusted HR 0.54; 95% CI 0.39–0.74; p=0.0001) (Table 1, Fig. 2) (33). In patients who did not undergo PCI, there was no significant difference in the primary endpoint between dosing regimens (4.3% vs. 4.9%; HR 1.14; p=0.22) (32). In PCI, higher rates of CURRENT-defined major bleeding were observed with double-dose clopidogrel (1.1% vs. 1.6%; adjusted HR 1.41; 95% CI 1.09–1.83; p=0.009) but was not seen with using TIMI-defined major bleeding (0.7% vs. 1.0%; adjusted HR 1.36; 95% CI 0.97–1.90; p=0.074). There was no significant increase in fatal bleeds, intracranial haemorrhages or CABG surgery-related bleeds (33). These data suggest that all ACS patients treated with an early invasive strategy with intent for PCI should be treated with a 600 mg (as opposed to 300 mg) loading dose. After angiography, those who receive PCI should continue with the double-dose regimen, while those who do not have PCI should be treated with the standard dose regimen or the clopidogrel could be withheld altogether, depending on the clinical scenario (26).

### Genetic polymorphisms and response to clopidogrel

Genetic polymorphisms in hepatic enzymes involved with clopidogrel metabolism have been reported as a possible mechanism for sub-optimal pharmacodynamic response. Clopidogrel is an inactive thienopyridine prodrug which requires a two-step oxidation process for bioactivation. Using the hepatic cytochrome P450 pathway, CYP 2C10, CYP 1A2 and CYP 2B6 enzymes initiate the first stage of oxidation followed by subsequent activation with CYP 2C19, CYP 2C9, CYP 2B6 and CYP 3A4 isozymes (35). Polymorphisms in CYP 2C19 isozyme (particularly the loss-of-function cytochrome CYP 2C19*2 variant) have accounted for clopidogrel hypersensitivity in patients with ischaemic heart disease. The effects of the CYP2C19*2 allele was tested in an observational registry of 259 patients (<45 years) already on clopidogrel for one month after MI (36). At six months, the primary endpoint of death, MI or urgent coronary revascularisation occurred more frequently in carriers compared to non-carriers of the allele (15 vs. 11 events; HR 3.69; 95% CI 1.69–8.05; p=0.001). Higher in-stent thrombosis events were noted as well (8 vs. 4 events; HR 6.02; 95% CI 1.81–20.04; p=0.001).

In a sub-study of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel...
grel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38, subjects with CYP2C19 polymorphism had a 52.4% RR in the clopidogrel active metabolite compared to non-carriers (p<0.001) which resulted in a 53% relative increase in CV death, MI or stroke (12.1% vs. 8.0%; 95% CI 1.07–2.19; p=0.01) (Fig. 3) and a three-fold increase in in-stent thrombosis (2.6% vs. 0.8%; HR 3.09; 95% CI 1.19–8.00; p=0.02) (37). No such effect was seen in active metabolite levels, inhibition of platelet aggregation or clinical outcomes in patients assigned to prasugrel (38) (Fig. 3). However, a direct comparison of clopidogrel versus prasugrel was not made in carriers and non-carriers, so it is not clear whether using prasugrel instead of clopidogrel would overcome this effect. In addition, this study did not have a placebo control group, so the effects of residual confounding of the CYP 2C19 polymorphism could not be ascertained in this study.

The French Registry of Acute ST-Elevation and Non ST-Elevation Myocardial Infarction (FAST-MI) consecutively enrolled 2,208 patients with acute MI and observed a higher rate of all-cause death, MI, or stroke in CYP 2C19 loss-of-function allele carriers than non-carriers treated with clopidogrel at one year (21.5% vs. 13.3%; adjusted HR 1.98; 95% CI 1.10–3.58) (39). In the 1,535 patients who received PCI, the CV event rate was 3.58-fold higher in carriers of the loss-of-function alleles (95% CI 1.71–7.51; p=0.005).

The Pharmacogenomics of Antiplatelet Intervention (PAPI) study is the first to report the genome-wide association of clopidogrel response in 429 healthy Amish participants (homogeneous patient population) (40). The loss-of-function CYP2C19*2 variant was associated with reduced clopidogrel response on ADP-induced platelet aggregation. In a separate population undergoing PCI and treated with clopidogrel, patients with the CYP2C19*2 variant had a greater than two-fold risk of a CV ischaemic event or death during one year follow-up (HR 2.42; 95% CI 1.18–4.99).

A limitation of these studies is that they lack a randomised placebo control arm and are therefore subject to residual confounding. Recently published findings from the CURE ACTIVE genotype study found similar effects of clopidogrel versus placebo in reducing CV death/MI/stroke irrespective of loss-of-function CYP2C19 alleles in patients with ACS (carriers: 8.0% vs. 11.6%; HR 0.69; 95% CI 0.49–0.98, non-carriers: 9.5% vs. 13.0%; HR 0.72; 95% CI 0.59–0.8, p=0.84 for the interaction) (41). Figure 4 shows the lack of heterogeneity in the first and second primary composite outcomes of clopidogrel versus placebo, stratified according to metaboliser phenotype. Similar results were observed in the ACTIVE trial of patients with atrial fibrillation, published in the same report. These large studies (CURE and ACTIVE trials) are the only randomised comparisons of clopidogrel versus placebo in carriers and non-carriers of the loss-of-function allele. They clearly demonstrate that carriers of the allele have similar benefits with clopidogrel as non-carriers. Because the study employed a placebo group, it was able to determine the effects of the gene on clopidogrel response independent of any residual confounding due to other effects the modifier of the CYP2C19 allele could not be ascertained in this study. The findings from this large analysis are consistent with the findings of the CURE-ACTIVE genetic study.

Other genetic polymorphisms involving oral bioavailability have been described. Intestinal absorption of clopidogrel is limited by adenosine triphosphate-binding cassette (ABC) efflux transporter, a P-glycoprotein encoded by the multidrug resistance gene ABCB1. Patients with one or two variant alleles (ABCBI CT or TT genotypes) have diminished intestinal absorption of clopidogrel (43) and higher rates of death, MI or stroke (adjusted HR 1.51; 95% CI 1.09–2.10 and adjusted HR 1.72; 95% CI 1.20–2.47, respectively) than non-carriers (42). Similar findings were seen in ACS patients where TT homozygotes had a higher risk of CV death, MI or stroke compared to CC or CT patients at 15 months (12.9% vs. 7.8%; HR 1.72, 95% CI 1.22–2.44; p=0.002) (44). Patients with both CYP2C19 and ABCB1 polymorphisms are at high risk of death, MI or stroke at one year compared to homozygote wild-type alleles (adjusted HR 5.31; 95% CI 2.13–13.20) (39). Again, no placebo controls were employed in these studies and should be interpreted with caution.

**Figure 3:** Cytochrome P450 polymorphisms and response to clopidogrel (37) (left panel) and prasugrel (38) (right panel) from the TRITON TIMI 38 trial.

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**Clopidogrel and PPIs**

Recently, observational studies have suggested that proton pump inhibitors (PPI) may reduce the efficacy of clopidogrel. Pharmacodynamic data suggest an attenuated clopidogrel inhibitory effect on platelet P2Y12 when omeprazole is introduced to patients undergoing PCI (45, 46). Using the vasodilator-stimulated phosphoprotein (VASP) assay to assess platelet reactivity index (PRI), patients randomised to omeprazole along with clopidogrel showed higher PRI levels after several days compared to clopidogrel alone (45). Subsequent retrospective studies have demonstrated an association between CYP2C19-metabolised PPIs and reduced clinical outcomes in ACS (47–49). Y et, in a randomised trial to evaluate the question of drug interaction between PPI’s and clopidogrel on CV outcomes related to the use of PPIs and clopidogrel compared to PPIs alone in patients with an MI admitted to hospital (51). At 30-days after discharge, patients who received both clopidogrel and a PPI were at increased risk of CV death, re-hospitalisation for MI, or stroke (adjusted HR 1.29; 95% CI 1.17–1.42; p<0.001). Among patients without clopidogrel, PPI use was associated with similar risk (adjusted HR 1.29; 95% CI 1.17–1.42; p<0.001). No interaction was seen between groups (p=0.72). Thus, proton pump inhibitors appear to be associated with an increase risk of adverse events after discharge from an MI irrespective of clopidogrel administration.

A recent systematic review and meta-analysis was performed on 25 studies evaluating the effects of PPIs on clopidogrel therapy (52). Although there was no difference in mortality (RR 1.04; 95% CI 0.93–1.16) an increase in major cardiovascular events (RR 1.29; 95% CI 1.15–1.45) and MI (RR 1.31; 95% CI 1.12–1.53) was seen with versus without PPIs. A 50% RR in gastrointestinal bleeding was noted with omeprazole and clopidogrel (HR 0.55; 95% CI 0.37–0.69). However, selected studies in this meta-analysis included observational, post-hoc and a randomised comparisons leading to heterogeneity which may reflect inconsistencies and biased results.

Clopidogrel and Optimization of GI Events Trial (COGENT)-1 is the only randomised control trial addressing the interaction between PPI’s and clopidogrel on CV outcomes in ACS or PCI (53). Although the trial was stopped prematurely (sponsor declared bankruptcy), preliminary analysis suggests no heterogeneity in participants randomised to a single pill combination of omeprazole and clopidogrel compared to clopidogrel alone (HR 1.02; 95% CI 0.70–1.51). To add, gastrointestinal events were significantly lower in patients taking omeprazole and clopidogrel (HR 0.55; 95% CI 0.36–0.85). Thus, results for the only randomised trial to evaluate the question of a PPI-clopidogrel interaction suggests that unique data published from a nationwide cohort study in Denmark evaluated the risk of CV outcomes related to the use of PPIs and clopidogrel compared to PPIs alone in patients with an MI admitted to hospital (51). At 30-days after discharge, patients who received both clopidogrel and a PPI were at increased risk of CV death, re-hospitalisation for MI, or stroke (adjusted HR 1.29; 95% CI 1.17–1.42; p<0.001). Among patients without clopidogrel, PPI use was associated with similar risk (adjusted HR 1.29; 95% CI 1.17–1.42; p<0.001). No interaction was seen between groups (p=0.72). Thus, proton pump inhibitors appear to be associated with an increase risk of adverse events after discharge from an MI irrespective of clopidogrel administration.

**Figure 4:** Effect of clopidogrel as compared with placebo on clinical outcomes among patients with acute coronary syndromes in the CURE trial, stratified according to metaboliser phenotype (41).
PPIs do not attenuate the clinical benefits of clopidogrel and may provide additional gastrointestinal protection.

**Newer ADP-receptor antagonists**

Two additional trials evaluating more potent ADP-receptor inhibition have demonstrated superiority over standard-dose clopidogrel (54). The Trials to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI)-38 study randomised 13,602 patients with ACS to prasugrel (a known pro-drug requiring metabolic conversion) (60 mg/day then 10 mg/day) or standard-dose clopidogrel (300 mg/day then 75 mg/day) and followed for 6–15 months (55). Despite the known benefit of pre-treatment with clopidogrel in ACS and PCI (13, 56), patients with NSTEMI were randomised after completion of coronary angiography in the TRITON-TIMI-38 trial. A 19% RR reduction in the primary endpoint of CV death, MI or stroke was observed with prasugrel (9.9% vs. 12.1%; 95% CI 0.73–0.90; p<0.001). As well, a 52% relative reduction in definite or probable stent thrombosis was seen (1.1% vs. 2.4%; 95% CI 0.36–0.64; p<0.001). Effects tended to be greater in diabetics (12.2% vs. 17.0%; HR 0.70; 95% CI 0.58–0.85; p=0.001) compared to non-diabetics, although the statistical interaction was not significant (9.2% vs. 10.6%; HR 0.86; 95% CI 0.76–0.98; p=0.02) (p=0.09 for the interaction). In a prespecified analysis of STEMI patients (intended for primary PCI), a consistent benefit in the primary outcome with ticagrelor compared to clopidogrel (9.4% vs. 10.8%; HR 0.87; 95% CI 0.75–1.01; p=0.07) (60). These results were consistent irrespective of loading dose (approximately one-third of patients received a 600 mg load of clopidogrel). Reduction in total mortality was also observed with ticagrelor in STEMI (5.0% vs. 6.1%; HR 0.82; 95% CI 0.67–1.00; p=0.05). Stroke was low in both groups but was higher in ticagrelor-treated patients (1.7% vs. 1.0%; HR 1.63; 95% CI 1.07–2.48; p=0.02).

Despite its reversible properties, higher rates of study defined non-CABG related bleeding (4.5% vs. 3.8%; HR 1.19; 95% CI 1.02–1.38; p=0.03) and TIMI defined non-CABG related bleeding (2.8% vs. 2.2%; HR 1.25; 95% CI 1.03–1.53; p=0.03) were seen with ticagrelor. As well, higher rates of fatal intracranial bleeding (0.1% [11/9,325 patients] vs. 0.01% [1/9,186 patients]; p=0.02) were observed, but this was balanced by lower rates of non-intracranial fatal bleeds, such that overall there was no difference in fatal bleeding between the groups. There was a numerically lower, but not statistically significant, rate of bleeding in patients undergoing CABG (7.4% vs. 7.9%; HR 0.95; 0.85–1.06; p=0.32), such that the overall rate of major bleeding did not differ (11.6% vs. 11.2%; HR 1.04; 95% CI 0.80–1.11).
Clinical Focus

Clopidogrel reduces major adverse cardiac events across the spectrum of acute coronary syndromes, including unstable angina, NSTEMI, STEMI and PCI, and is considered standard therapy in contemporary practice. More recently, variability to clopidogrel has been demonstrated with platelet function testing, although the clinical importance of these findings, and how to change management based on these, is much less clear. Genetic polymorphisms in the cytochrome P450 CYP2C19 enzyme may explain some of the variability in clopidogrel response, yet the importance of this polymorphism on clinical events remains to be determined. In a large analysis from two randomised trials (CURRENT-ACTIVE), there was no heterogeneity in clopidogrel response versus placebo in carriers and non-carriers of the loss of function allele. At this time, use of platelet function and/or genetic testing to guide clinical practice is premature and further data are needed to validate either approach. A seven-day double-dose regimen of clopidogrel benefits patients undergoing PCI, mainly by reducing stent thrombosis, and should be considered in ACS patients who have an early invasive strategy with intended PCI. Two new ADP receptor antagonists, prasugrel and ticagrelor, have more potent antiplatelet effects than clopidogrel. Prasugrel reduces ischaemic events compared with the standard dose of clopidogrel in patients undergoing PCI who are not pre-loaded with clopidogrel. Ticagrelor reduces both mortality and ischaemic events compared with clopidogrel in a broad spectrum of patients with ACS. Both agents increase the risk of non-CABG-related major bleeding. Other novel antiplatelet agents are currently under investigation and may provide additional options for treatment of patients with ACS.

References


