Clopidogrel withdrawal: Is there a “rebound” phenomenon?

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Summary

Dual antiplatelet therapy with aspirin and clopidogrel is routinely indicated in patients with acute coronary syndromes and following percutaneous coronary intervention to reduce the risk of cardiovascular mortality and ischaemic events. Although clinical guidelines recommend aspirin lifelong and clopidogrel for between one and 12 months, some of the more scientifically accurate meaning of the term “rebound” is an increase in platelet reactivity and/or vascular responses which are, as yet, poorly characterised. Premature cessation of clopidogrel in patients receiving drug-eluting stents is a clear risk factor for stent thrombosis, but recent clinical studies have also demonstrated a link between “appropriate” cessation of clopidogrel and clustering of adverse clinical events. It has been suggested that this may be due to a “rebound” prothrombotic and/or proinflammatory response associated with clopidogrel withdrawal. This review will examine the definition and concept of a “rebound” phenomenon associated with clopidogrel cessation as well as the likely mechanisms behind this effect. Within the context of clinical event clustering after clopidogrel cessation, we will also discuss (i) the clinical importance of clopidogrel and the increasing uncertainty surrounding optimal duration of therapy, (ii) the antiplatelet and anti-inflammatory properties of clopidogrel and, in particular, its influence on arachidonic acid pathways traditionally thought to be mediated predominantly by aspirin and (iii) the role of newer, more potent antiplatelet agents and potential changes to anti-platelet therapy prescribing guidelines in the future.

Keywords

Clopidogrel cessation, rebound, platelet aggregation, stent thrombosis, inflammation

Introduction

In routine clinical cardiological practice the leading indications for dual antiplatelet therapy with aspirin and clopidogrel include acute coronary syndromes (ACS) and coronary stent placement. In both cases (which of course are not mutually exclusive) a strategy is employed that involves life-long aspirin together with clopidogrel for between one and 12 months, depending upon the indication, after which the clopidogrel is stopped. The evidence base indicating outcome benefit for clopidogrel in addition to aspirin is robust both as a medical treatment for acute coronary syndromes (1–3) and also for those patients receiving coronary stents in elective (4) and acute (5) settings.

Conventionally, it is considered that the clinical benefit of clopidogrel is due largely to its antithrombotic and antiplatelet activity. Indeed this assumption is largely supported by some of the most important beneficial effects of the drug such as (a) the reduction in the incidence of stent thrombosis (ST) in patients who have received coronary stents (5, 6) and (b) a reduction in peri-procedural myocardial infarction (MI) in patients undergoing percutaneous coronary intervention (PCI) (4, 7–9). However, it is apparent that clopidogrel also has the ability to modify vascular inflammatory responses which are, as yet, poorly characterised (10–12).

There is increasing uncertainty about the precise mechanisms by which clopidogrel achieves its anti-platelet effects. It is clear that this primarily involves occupation of the P2Y12 receptor, hence blocking ADP-induced platelet stimulation. Increasingly, however, there is evidence that clopidogrel also interferes with arachidonic acid (AA)-mediated platelet stimulation (13–16). There are therefore some important uncertainties about the intraplatelet machinery that mediate clopidogrel effects and the nature of its potential interactions with aspirin (17).

Furthermore, there remain unanswered questions about clopidogrel therapy. The duration of treatment after coronary drug-eluting stent (DES) deployment, for example, remains uncertain and contentious (18). Observation unequivocally demonstrates that stopping clopidogrel “too early” is a powerful risk factor for ST (19–21). By contrast, it is also well described that there is a clustering of adverse clinical events in the 90 days after cessation of long-term clopidogrel in populations of ACS patients treated with stenting and medical therapy (22, 23). The latter observation raises the possibility that cessation of clopidogrel may be associated with a “rebound” effect that is pro-thrombotic or pro-inflammatory or both and is directly responsible for adverse clinical events. As described in detail below, the more scientifically accurate meaning of the term “rebound” is an increase in platelet reactivity and/or vas-
cultural inflammation following clopidogrel withdrawal, to a level that exceeds what it was at baseline prior to the initiation of clopidogrel therapy. True “rebound” is thus more difficult to ascertain in clinical practice due to the lack of availability of comparative baseline (pre-treatment) levels.

An improved assessment and appreciation of the way clopidogrel works, and specifically of its anti-inflammatory and AA pathway activities, is likely to facilitate our understanding of the potential mechanisms of the “rebound” effect, which is an iatrogenic entity, and hence allow for its modification.

**Clinical indications for clopidogrel**

ST is a significant and potentially life threatening complication of PCI with an associated mortality of at least 30%. Early clinical trials using aspirin monotherapy or a combination of aspirin and warfarin to reduce the risk of thrombotic complications associated with stent implantation reported a high incidence of acute ST with rates of up to 20% in the aspirin monotherapy group. The evolution to dual antiplatelet therapy with aspirin and a thienopyridine resulted in a significant reduction in the risk of ST to approximately 1%, with a lower risk of bleeding compared to anticoagulant regimes (24–26). Although these early studies used ticlopidine, it has since been replaced by clopidogrel which is a safer and better tolerated agent with no requirement for routine haematological monitoring. Clopidogrel has been proven to be at least as effective as ticlopidine in reducing thrombotic and ischaemic complications after stent implantation (27, 28).

The randomised controlled CREDO trial established the beneficial effect of clopidogrel loading followed by maintenance therapy in addition to aspirin in patients undergoing elective PCI (4). Pre-treatment with clopidogrel 300 mg at least 6 hours (h) prior to PCI was associated with a reduction in peri-procedural major adverse cardiac events, and subsequent maintenance therapy for 12 months compared to treatment for only four weeks resulted in a significant reduction in the combined endpoint of death, MI and stroke (26.9% relative risk reduction; p=0.02). Similar findings have been reported in patients undergoing PCI in the acute setting, where maintenance dose clopidogrel was continued for up to one year (5).

The beneficial effect of clopidogrel also extends to ACS patients not undergoing PCI. Thus, large randomised studies of clopidogrel therapy in addition to aspirin in patients with and without ST segment elevation managed medically, have demonstrated a significant reduction in cardiovascular mortality and ischaemic events (1–3).

Although all these early studies clearly demonstrate the importance of clopidogrel pre-loading and treatment long term, the optimal duration of therapy remains uncertain. Currently, 12 months of clopidogrel 75 mg is recommended for all ACS patients with or without ST segment elevation whether or not PCI is undertaken (29, 30), as well as in elective patients undergoing PCI with DES (31, 32). There is robust evidence to suggest that premature withdrawal of clopidogrel following PCI is associated with a substantially increased risk of adverse events and is a strong independent predictor of ST particularly after DES implantation (6, 19, 21, 33–35). In fact, early discontinuation of treatment is apparently more common than expected. For example, among 500 patients who received DES after MI, 13.6% stopped their thienopyridine therapy within 30 days (20). These patients were older with more co-morbidities, were of lower socioeconomic status and were less likely to have received discharge advice about their medication or referral to the cardiac rehabilitation services. At 11-month follow up there was a highly significant increase in death (7.5% vs. 0.7% p<0.0001) and cardiac rehospitalisation (23% vs. 14% p=0.08) in those patients who discontinued their treatment prematurely.

Table 1 summarises data on patients undergoing PCI who subsequently present with ST. In general over 30% of these patients were not on clopidogrel at the time of their presentation and the median time from clopidogrel cessation to ST varied between 5–90 days in most studies.

The data in relation to the optimal duration of clopidogrel is, however, discrepant. For example, some smaller studies and observational data on patients undergoing PCI have shown that the mortality benefit of clopidogrel extends beyond one year in patients with DES (34, 36, 37). By contrast, the combined analysis of data from two recent randomised multicentre trials (REAL-LATE and ZEST-LATE) (38), found no significant difference in the combined risk of MI and cardiac death in patients with DES who received 12 versus 24 months of clopidogrel therapy (1.2% vs. 1.8%; p=0.17; 95% confidence interval [CI] 0.8 to 3.36). Some clarity on this controversial issue may be provided from the large, prospective, randomised controlled DAPT study (39), which will assess the safety and effectiveness of 12 versus 30 months of dual antiplatelet therapy in 20,000 patients following PCI.

The optimal maintenance dosage of clopidogrel therapy is also the subject of debate (40). The recent CURRENT-OASIS 7 randomised study undertaken in 25,086 ACS patients, compared 600 mg loading dose clopidogrel followed by 150 mg maintenance therapy for seven days versus 300 mg loading dose followed by the usual 75 mg maintenance therapy (41). In the sub-group of patients undergoing PCI (n=17,263), double-dose clopidogrel was associated with a significant reduction in definite ST (0.7% vs. 1.3%, hazard ratio [HR] 0.54, 95% CI 0.39 to 0.74, p=0.0001) and cardiovascular events (3.9% vs. 4.5%, HR 0.86, 95% CI 0.74 to 0.99, p=0.039) compared to the standard dose group (42). However, more data are needed to clarify the long-term risk reduction benefit associated with high-dose clopidogrel and this would need to be weighed against the increased risk of bleeding complications. Furthermore, with the advent of newer more potent antiplatelet agents, such as prasugrel and ticagrelor, and the robust data emerging supporting their use as an alternative to clopidogrel in ACS (43–46), the focus of antiplatelet therapy prescribing is likely to shift towards selecting the most appropriate, safe and effective agent for each individual patient.
**Known pharmacological activity of clopidogrel**

Clopidogrel is an inactive pro-drug that is oxidised to its active metabolite via the hepatic cytochrome P450 system. The active metabolite irreversibly binds to platelet P2Y<sub>12</sub> adenosine diphosphate (ADP) receptors, thereby inhibiting both ADP-induced platelet aggregation as well as transformation of the glycoprotein (GP) IIb/IIIa receptor to a form that allows binding of fibrinogen to the platelet adhesion, activation and thrombosis (50–52). The well described role of clopidogrel active metabolite on P2Y<sub>12</sub> ADP receptor blockade and therefore its potential effect in inhibiting VWF-mediated pathways of platelet activation may, in part, explain the prothrombotic events that occur soon after discontinuation of clopidogrel therapy.

In addition to its anti-platelet effect, clopidogrel has also been shown to have anti-inflammatory properties. CD40 ligand (L) and CD-62 P-selectin (P) are potent stimulators of vascular inflammation expressed on activated platelet membranes and on many cells of the immune and vascular systems. They play an important role in the pathogenesis and progression of atherosclerosis (62–64). Clopidogrel inhibits the expression of these inflammatory mediators, both acutely and in patients on long term maintenance therapy (10–12).

CD40L also exists in its soluble form, almost all of which is produced and released from activated platelets. Soluble CD40L is a prothrombotic and proinflammatory molecule that plays an important role in the pathophysiology of ACS. In fact, an elevated level is a prognostic marker and predictive of subsequent cardiac events (65, 66). Studies have shown that clopidogrel pre-treatment in patients undergoing PCI attenuates the inflammatory response as evidenced by a reduction in serum levels of soluble CD40L at 24 h (67, 68). This may be one of the mechanisms behind the reduced incidence of peri-procedural ischaemic events seen in patients undergoing PCI who have received clopidogrel pre-treatment.

High sensitivity C-reactive protein (hsCRP) is another important inflammatory marker that is elevated in patients presenting for personal or educational use only. No other uses without permission. All rights reserved.
with ACS and is an independent predictor of adverse outcomes (69). A significant reduction in hsCRP levels following PCI has been reported in patients receiving clopidogrel pre-treatment (70) as well as in medically managed ACS patients. Specifically, those treated with a combination of clopidogrel and aspirin have been shown to have a more significant reduction in serum hsCRP levels compared with aspirin alone (71) which may in part explain the well documented beneficial effects of dual antiplatelet therapy in reducing ischaemic events and cardiovascular mortality in ACS patients compared with aspirin monotherapy.

Given the evidence that clopidogrel exerts anti-inflammatory effects, it is plausible to hypothesise that cessation of clopidogrel may result in a proinflammatory and atherothrombotic state due to loss of its inhibitory effect on these vascular biomarkers of inflammation. Such a mechanism may not fulfil the true definition of “rebound” but could nevertheless provide an explanation for the clustering of clinical events described after cessation of clopidogrel therapy.

The “rebound” phenomenon

How do we define “rebound”?

Although the expression “rebound” phenomenon is now relatively widely used in the context of clopidogrel therapy, its definition is unclear and is often the focus for confusion and/or misunderstanding. The two most widely accepted interpretations of “rebound” are:

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**Figure 1: Mechanism of action of clopidogrel.** Clopidogrel is a pro-drug that is metabolised by the cytochrome P450 system to generate the active metabolite which irreversibly inhibits the adenosine diphosphate (ADP) P2Y₁₂ receptor. ADP binds to the P2Y₁ and P2X₁ receptors leading to a change in platelet shape initiating a weak and transient phase of platelet aggregation. The binding of ADP to its G<sub>α</sub>-coupled P2Y₁₂ receptor liberates the G<sub>α</sub> protein subunits α<sub>Gi</sub> and βγ and this results in stabilisation of platelet aggregation. The subunit α<sub>Gi</sub> leads to inhibition of adenylyl cyclase (AC), which reduces cyclic adenosine monophosphate (cAMP) levels. This inhibits the cAMP-mediated phosphorylation of vasodilator-stimulated phosphoprotein (VASP) (VASP-P), which is known to be closely related to the inhibition of glycoprotein IIb/IIIa receptor activation. (Multiple arrows indicate that intermediate steps may be involved; dotted arrows = inhibition; solid arrows = activation. CYP450 = cytochrome P450; PGE₁ = prostaglandin E₁; PKA = protein kinase activation; PLC = phospholipase C.). Reprinted with permission from Elsevier from Nguyen et al. Resistance to clopidogrel: a review of the evidence. JACC 2005; 45: 1158.
(i) simply that an adverse clinical event occurs shortly after, and because of clopidogrel cessation,

(ii) that, as a result of clopidogrel cessation, one or more parameters of either platelet reactivity or vascular inflammation reaches a level that is higher than it was at baseline before clopidogrel therapy was ever initiated.

The latter is the stricter and more scientifically accurate definition. However, the weakness with this definition is that it demands a pre-clopidogrel baseline assessment which is unlikely to be available in routine clinical practice outside the realms of carefully designed research. The term “rebound” has been increasingly used in clinical practice and publications to indicate any clinical event that occurs after clopidogrel cessation. The term “rebound phenomenon” will encompass both definitions in this paper.

Studies have shown a clear link between cessation of long term clopidogrel therapy after PCI and adverse events including ST (18, 23, 72–74). Specifically, a significant proportion of these events occur within days or weeks after clopidogrel has been discontinued, hence fulfilling at least definition (i) of “rebound phenomenon”. This effect has not only been observed in patients with coronary stents. Thus, Ho et al. (22) reported a clustering of adverse clinical events in the initial 90 days after stopping clopidogrel in a large retrospective study of ACS patients on dual antiplatelet therapy treated either medically or with PCI and stents. In the medically treated group, death or MI occurred in 17.1% of patients with 60.8% of the events occurring 0–90 days after the cessation of clopidogrel. Similarly, in PCI-treated patients death or MI occurred in 7.9%, with 58.9% of these events taking place within the initial 90 days after clopidogrel cessation. The findings from this study potentially support the hypothesis of a prothrombotic and/or proinflammatory state precipitated by clopidogrel withdrawal, a theory that has no requirement for true “rebound”. In this study, the relative increase in adverse events in the early 90-day period after stopping clopidogrel was nearly two-fold higher than at later time periods (i.e. 91 to 360 days). This is one of the few studies that examined the pattern of events that occur with clopidogrel cessation in medically managed ACS patients without the confounding factor of previous coronary stenting.

Ho et al. have recently confirmed and expanded their findings in a retrospective cohort study in 1,656 ACS patients receiving clopidogrel therapy (23). They observed a similar two-fold increase in the risk of death or MI in the 0–90 day interval after clopidogrel cessation compared with later time intervals. These findings were consistent across all patient subgroups evaluated, specifically, males versus females, medically managed versus PCI treated patients, DES versus BMS and with clopidogrel therapy duration of ≥6 versus <6 months. Furthermore, they established that the clustering of events was specific to clopidogrel discontinuation as this was not observed among patients stopping angiotensin converting enzyme (ACE) inhibitors. Additional studies are clearly needed to explore the mechanisms behind this consistently observed effect.

With regards to definition (ii) above, there is no published data so far specifically comparing baseline pre-treatment platelet reactivity and/or inflammatory biomarker levels with post-clopidogrel cessation levels. The PACT trial (75) is an ongoing randomised controlled study that will investigate this effect by measuring platelet reactivity before, during and at various time intervals after discontinuation of clopidogrel in healthy subjects on aspirin. However, extrapolation of the results to a co-morbid patient group with cardiovascular disease or diabetes may not be justified. Further data are clearly needed.

### Potential mechanisms of clustering of events after clopidogrel cessation with or without true “rebound”

The mechanisms and pathophysiology of the observed phenomenon of a clustering of clinical events are currently matters for speculation (Fig. 2). Postulated mechanisms include:

1. **Loss of anti-thrombotic and anti-inflammatory effects**

   It has been well established that clopidogrel exhibits both anti-thrombotic and anti-inflammatory properties. The former is mediated via irreversible binding to platelet P2Y12 ADP receptors thereby inhibiting ADP-induced platelet aggregation and the latter is achieved via inhibition of vascular inflammatory biomarker expression. The adverse clinical events that have been reported not long after clopidogrel is discontinued may be simply due to a prothrombotic and/or proinflammatory effect that occurs as the level of active clopidogrel metabolite diminishes.

   Angiolillo et al. (76) investigated the effect of clopidogrel withdrawal on platelet reactivity and inflammatory biomarkers in 54 diabetic patients on long-term dual antiplatelet therapy following PCI. Blood samples were taken at 12 months post-PCI on dual antiplatelet therapy and one month after clopidogrel cessation. Platelet reactivity was measured using light transmission aggregometry (LTA). As predicted, a significant increase in ADP-induced platelet aggregation, hsCRP and surface P-selectin expression at one month was observed. Without pre-clopidogrel baseline data it is not possible to determine whether this observation is consistent with a possible rebound effect associated with clopidogrel withdrawal. However, this is a small study and the results cannot be extrapolated to the non-diabetic population. It is widely accepted...
that diabetes is associated with diffuse and accelerated progression of atherosclerosis which may be related to the prothrombotic and proinflammatory status observed in these patients (77). As a result, diabetics may potentially be more vulnerable to adverse events following clopidogrel withdrawal.

The DECADES study (78) examined the effect of clopidogrel cessation on markers of inflammation 12 months after implantation of DES in a non-diabetic population. A significant increase in the inflammatory biomarkers sCD40L and P-selectin was observed between two and four weeks after clopidogrel withdrawal. There was, however, an unexplained and apparently inconsistent decrease in hsCRP levels by 21% (p=0.008) one week after cessation of clopidogrel. The questions that arose from this study are whether the increase in these specific inflammatory biomarkers following clopidogrel withdrawal are due to a loss of the inhibitory effect of clopidogrel on platelet reactivity or whether it is due to a genuine rebound pro-inflammatory state. The latter suggestion is apparently inconsistent with the observed decline in hsCRP levels. Unfortunately, no data were obtained regarding platelet reactivity in this study.

In contrast to these results, a recent small randomised study in 64 patients undergoing PCI with DES did not demonstrate a rise in platelet reactivity following clopidogrel withdrawal. Specifically, ADP-induced platelet aggregation was measured using both LTA and multiple electrode aggregometry over various time points during treatment with clopidogrel and following cessation of therapy. They examined the effect of abrupt cessation of clopidogrel therapy versus tapered withdrawal on platelet aggregation and found no significant difference between the two groups and no significant increase in platelet reactivity from 2–8 weeks following clopidogrel withdrawal (79). Several larger studies are ongoing that will specifically address and further clarify this issue. For example, the randomised controlled PACT trial will determine the effect of clopidogrel withdrawal on platelet reactivity after 14 days of treatment in healthy subjects on aspirin (75) and the retrospective observational PRACTICE 1 study will examine whether abrupt discontinuation of clopidogrel at six and 12 months after PCI is associated with a rebound increase in platelet reactivity (80).

2. Does clopidogrel potentiate the effect of aspirin?

Thromboxane A2 (TXA2) is a potent vasoconstrictor and platelet agonist that is produced from activated platelets via the AA pathway. It is well established that aspirin exerts its anti-thrombotic ef-
effects by irreversibly blocking the enzyme cyclooxygenase-1 (COX1) which is required for the synthesis of the precursors of TXA2.

One of the possible mechanisms of a “rebound” effect of clopidogrel has only recently come to light. It is based upon the simple, but still controversial, notion that clopidogrel exerts some of its antiplatelet activity via the AA-TXA2-COX pathway, as well as via the more established P2Y12 ADP mechanism. The obvious implication of this would be that when clopidogrel stops, then both pathways would be affected and this would result in an increase in both ADP- and AA-induced platelet aggregation. This would manifest as an apparent (or perhaps genuine) reduction in the response of an individual patient to aspirin when clopidogrel is stopped as assessed by AA-induced platelet reactivity.

In fact, there is accumulating evidence to suggest that clopidogrel influences AA-TXA2-COX pathways, thereby potentiating the effect of aspirin (13, 14, 81, 82). For example, two small studies have shown that patients who were initially labelled as ‘non-responders’ to aspirin as determined by optical aggregometry (16) and thrombelastography (15) were converted to ‘normal responders’ as a result of increased inhibition of AA-induced platelet aggregation by the addition of clopidogrel. Further support of the potentiation theory is demonstrated by Angiolillo et al. (76) who reported that, following clopidogrel withdrawal, 44% of patients exhibited a ‘poor response’ to aspirin determined using the platelet function analyser (PFA)-100 system, but yet when these patients were taking aspirin and clopidogrel concomitantly their AA-induced platelet aggregation profiles were consistent with an apparent ‘normal’ response to aspirin.

These data sponsor the hypothesis that clopidogrel may influence AA-mediated platelet aggregation and its cessation could therefore lead to loss of the aspirin-synergistic effect resulting in rebound attenuation of the antiplatelet effect of aspirin. If this mechanistic theory were examined and proven in larger studies, it would mean that patients who are relatively hyporesponsive to aspirin would be at particular risk of adverse events when clopidogrel is discontinued. It would follow that all patients requiring dual antiplatelet therapy, either in the context of PCI or following an
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- CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events trial
- CLARITY: Clopidogrel as Adjunctive Reperfusion Therapy trial
- COMMIT: Clopidogrel and Metoprolol in Myocardial Infarction trial
- CREDO: Clopidogrel for the Reduction of Events During Observation trial
- CURRENT OASIS 7: Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Intervention trial
- DAPT: Dual AntiPlatelet Therapy Study
- DECADES: Discontinuation Effect of Clopidogrel After Drug Eluting Stent trial
- PACT: Platelet Activity After Clopidogrel Termination trial
- PRACTICE 1: Platelet Reactivity After Cessation of Clopidogrel in the Setting of coronary Stent Implantation 1 study
- REAL-LATE: Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombosis Events trial
- ZEST-LATE: Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions – Late Coronary Arterial Thrombotic Events trial

Conclusion

There is sufficient evidence to suggest that a pro-thrombotic phenomenon following clopidogrel withdrawal is real and may be responsible for a clustering of clinical events. Further robust data is needed from large scale randomised studies to (i) further elicit the mechanisms and pathophysiology behind the rebound effect, (ii) specifically assess platelet reactivity and vascular inflammation both pre-treatment as well as post clopidogrel cessation, (iii) determine precisely how clopidogrel achieves its effects including the extent to which it influences aspirin-specific pathways of platelet aggregation, and (iv) determine whether the rebound phenomenon is also exhibited in the newer, more potent third generation P2Y12 inhibitors.

References