Coming safely to a stop: a review of platelet activity after cessation of antiplatelet drugs

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Abstract: The platelet P2Y₁₂ antagonists are widely used, usually in combination with aspirin, to prevent atherothrombotic events in patients with acute coronary syndromes during percutaneous coronary intervention and after placement of arterial stents. Inhibition by clopidogrel or prasugrel lasts for the lifetime of the affected platelets and platelet haemostatic function gradually recovers after stopping the drug, as new unaffected platelets are formed. The optimal durations for dual antiplatelet therapy are prescribed by clinical guidelines. Continuation beyond the recommended duration is associated with an increased mortality, mainly associated with major bleeding. Fear of a 'rebound' of prothrombotic platelet activity on stopping the drug has provoked much discussion and many studies. However, review of the available literature reveals no evidence for production of hyper-reactive platelets after cessation of clopidogrel in patients who are stable. Any increase in acute coronary and other vascular events after stopping seems most likely therefore to be due to premature discontinuation or disruption of treatment while thrombotic risk is still high. No difference in rebound was found with the newer P2Y₁₂ inhibitors, although ticagrelor and prasugrel are more potent platelet inhibitors than clopidogrel. Recent randomized controlled trials confirm it is safe to stop the thienopyridine and continue with aspirin alone in most patients after the duration of treatment recommended by the guidelines. Decisions on when to stop therapy in individuals, however, remain challenging and there is a growing rationale for platelet testing to assist clinical judgement in certain situations such as patients stopping dual antiplatelet therapy before surgery or in individuals at highest bleeding or thrombotic risk.

Keywords: antiplatelet therapy, cessation, clopidogrel, P2Y₁₂ inhibitors, platelet activation, rebound

Background

Medical therapy to reduce platelet activation is a mainstay in prevention of atherothrombotic events in cardiovascular disease. For many years aspirin was the drug of choice, but randomized controlled trials from the 1990s onwards demonstrated the efficacy of clopidogrel in reduction of major acute coronary and cerebrovascular events and vascular deaths [CAPRIE Steering Committee, 1996]. Clopidogrel in combination with aspirin improved outcomes after acute coronary syndrome (ACS), and after percutaneous coronary intervention (PCI) with or without placement of stents [Bhatt *et al.* 2006; COMMIT

collaborative group 2005; Steinhubl *et al.* 2002; Yusuf *et al.* 2001].

Two newer P2Y₁₂ inhibitors are in clinical use. Prasugrel, another irreversible thienopyridine inhibitor [Wiviott *et al.* 2007], and ticagrelor, a reversible, noncompetitive inhibitor [Wallentin *et al.* 2009], are now preferred over clopidogrel for acute myocardial infarction for their more rapid and more potent antiplatelet action [Windecker *et al.* 2014]. However, the association with higher bleeding risk, contraindication in certain categories of patient, and higher cost, mean that clopidogrel is still widely used throughout

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the world, and following PCI in stable coronary artery disease. For the purposes of this review I will concentrate on clopidogrel.

Action of clopidogrel

Clopidogrel is a prodrug of the thienopyridine class. Conversion to the active metabolite in the liver is dependent on cytochrome P450 isoforms including CYP3A and CYP2C19. There is well recognized variability in responsiveness to clopidogrel, which is at least partly attributable to polymorphisms of these genes [Simon *et al.* 2009], as well as to drug interactions and adherence to treatment. The main therapeutic target for the active molecule is the platelet P2Y₁₂ receptor for adenosine diphosphate (ADP). Through a Gi-coupled signalling pathway, receptor occupancy induces activation of the α IIB β 3 integrin receptor (also known as glycoprotein IIb-IIIa), exposing the receptor for fibrinogen and resulting in platelet aggregate formation [Braun *et al.* 2007; Schror, 1998]. Inhibition of the P2Y₁₂ is irreversible and so, as with aspirin blockade of cyclooxygenase, this pathway of activation is inhibited for the lifetime of the platelets [Schror, 1998]. Function gradually recovers after stopping the drug because of new, unaffected platelets being produced from megakaryocytes, while ageing platelets are gradually removed. Normal platelet lifespan is 7–10 days, but disease and ageing may influence turnover times and therefore affect the time to recovery of platelet function after a single antiplatelet dose.

Duration of dual antiplatelet therapy

Evidence-based, national and international clinical guidelines prescribe the optimum durations for antiplatelet therapy, and these have evolved considerably over the past decade as more trial results emerge [Jneid *et al.* 2012; Windecker *et al.* 2014]. The European Society of Cardiology [Windecker *et al.* 2014] currently states that after acute myocardial infarction, ST-elevation myocardial infarction or non-ST-elevation myocardial infarction, dual antiplatelet therapy (DAPT) with aspirin plus a P2Y₁₂ inhibitor be continued for 12 months after the acute event; whereas for patients with stable coronary artery disease who receive PCI and a drug-eluting stent (DES), clopidogrel is recommended for 6 months, and for a minimum of 1 month after placement of a bare metal stent. It is usually recommended that patients continue on aspirin for life, unless

contraindicated, for example by drug intolerance or bleeding.

Because of the pivotal role of platelets in haemostasis and thrombosis, maintenance of the balance between inhibition and activation is essential. Thus, all antithrombotic agents introduced to date carry the side effect of increased bleeding risk. As the thrombotic risk diminishes over time, for example after successful PCI to unblock the diseased coronary artery, or healing of the vessel wall after placement of stents, the risk of mortality from bleeding becomes disproportionately higher with continued use of DAPT. However, the European guidelines [Windecker *et al.* 2014] also state that a longer duration can be used in those at high ischaemic risk and low bleeding risk, and a shorter duration in people at lower risk of recurrence or higher bleeding risk. In addition, the need may arise to withdraw antiplatelet drugs earlier than recommended, before surgery for example, or if there is intolerance to the drug, or bleeding events.

What happens clinically on stopping clopidogrel?

The publication of a series of case reports and retrospective studies sounded the alarm over an apparently increased rate of ischaemic events in the period after withdrawal of clopidogrel [Ong *et al.* 2005; Pfisterer *et al.* 2006; Ho *et al.* 2008, 2010]. Ho and colleagues [Ho *et al.* 2008] reported a clustering of adverse events in patients with previous ACS in the first 90 days after stopping clopidogrel. Despite the observational and retrospective nature of these studies, an 'Advisory' statement was issued on premature stopping of DAPT [Grines *et al.* 2007] (see Gaglia and Waksman for systematic review) [Gaglia and Waksman, 2011].

What happens to platelets when clopidogrel is withdrawn?

These studies provoked discussion of a 'rebound' in platelet activity. The theory was proposed that suppression by clopidogrel might lead to a biological adaptation of platelets or megakaryocytes, conferring enhanced sensitivity to ADP or other stimuli. Such a change would manifest itself after cessation of the drug and recovery of a noninhibited, hyperactive platelet population [Lordkipanidzé *et al.* 2009; Sambu *et al.* 2011a]. This gave rise to some small studies that

claimed to find a rebound of platelet responsiveness at varying times after stopping clopidogrel treatment.

An observational study of 28 patients with coronary stent implantation, who had been treated with clopidogrel for 12 months, found that ADP-stimulated platelet aggregation was increased at 2 weeks after withdrawal of clopidogrel compared with on-treatment levels, and remained elevated at 6 weeks, as would be expected [Diehl *et al.* 2011]. However, on testing at 17 weeks after stopping, aggregation was lower than at the earlier time points, and was now no different from that in a group of untreated stable CAD controls.

Mylotte and colleagues (2011) studied 32 patients with DES [Mylotte *et al.* 2011]. Between on-treatment values and the sample taken at 1 week following withdrawal, there was an increase in aggregation response to a range of doses of ADP, epinephrine and thrombin-receptor-activating peptide (TRAP), but not arachidonic acid. There was a further increase in aggregation induced by the lower, but not higher, doses of ADP at 1 month. By 3 months after cessation, however, aggregation with ADP and epinephrine had decreased, returning to levels similar to those found at 7 days, and this was interpreted as a transient rebound effect occurring at 1 month post cessation.

The prospective CESSATION study enrolled 28 patients who stopped clopidogrel therapy 1 year following insertion of a DES. Using the more unusual technique of thromboelastography platelet mapping (short TEG), there was gradual recovery of ADP-induced aggregation up to 1 week, but levels remained similar at 2 and 4 weeks, and so no evidence was found for a rebound in ADP pathways of aggregation [Sambu *et al.* 2011b].

Thirty-seven patients with clinically stable coronary artery disease who had been taking clopidogrel and aspirin (for varying lengths of time) were compared with a control group of patients with stable CAD who were not taking clopidogrel [Lordkipanidzé *et al.* 2014]. There were no differences in the Verify Now P2Y₁₂ test, but there was a difference in ADP-stimulated aggregation between the clopidogrel and control groups at 7 and 28 days after stopping. Difficulties in comparing these two groups directly include the considerable individual variability in platelet response,

and the reasons for being prescribed clopidogrel or not, which most likely include severity of arterial disease and the estimated thrombotic and bleeding risk.

In contrast, in a study of 200 patients who had taken clopidogrel for 12 months after stenting, there was no evidence for rebound [Djukanovic *et al.* 2011]. Although again there was no pretreatment test, platelet aggregation by a whole blood multielectrode impedance assay (Multiplate analyzer, Roche Diagnostics GmbH, Mannheim, Germany) merely reached a plateau around 10 days after stopping and was not significantly different at 45 or 90 days.

However, as none of these studies included a pretreatment baseline measurement, it was not possible to say whether platelet responsiveness was merely returning to pretreatment levels.

Platelet studies with a pretreatment baseline

Several prospective studies have been performed that included detailed platelet function analysis at a pretreatment baseline as well as on treatment, and with follow up for at least a month after stopping clopidogrel. In a placebo-controlled crossover study of 15 healthy subjects who took clopidogrel plus aspirin or placebo plus aspirin for 7 days each, a comprehensive range of platelet measurements was made. These comprised activation markers GPIIb/IIIa and P selectin by flow cytometry, aggregometry in platelet-rich plasma and in whole blood, all with a range of doses of ADP and other agonists, counting of the immature platelet fraction, and soluble CD40 ligand assay. Once platelet function had recovered, by around 8 days after stopping, there was no further increase in stimulated platelet aggregation or activation markers and no significant differences in any of the tests at 11, 15 or 45 days post cessation compared with baseline [Frelinger *et al.* 2010]. These data showed conclusively that a short-term course of clopidogrel did not increase regeneration nor alter the reactivity of newly produced platelets, at least in healthy subjects.

In a prospective, double-blind placebo-controlled trial, Ford and colleagues randomized 171 patients with stable coronary artery disease or peripheral arterial disease to 28 days of clopidogrel (75 mg) or placebo [Ford *et al.* 2014]. Patients continued to take their 75 mg daily

aspirin therapy throughout the study. A range of platelet tests was carried out at pretreatment baseline, on treatment (just before stopping clopidogrel or placebo), and at 7, 14 and 28 days after stopping. ADP-stimulated platelet aggregation (5 and 10 micromolar ADP), platelet activation markers by flow cytometry, Verify Now P2Y₁₂ and VASP-P were all significantly lower on clopidogrel treatment compared with baseline, showing appropriate responses to the drug. Unstimulated markers of platelet activation were unchanged. Values returned to baseline levels by 7 days after discontinuation. Apart from the on-treatment measurements, there were no statistically significant differences between those taking clopidogrel or placebo at any of the follow-up timepoints. Furthermore, there was no evidence for a treatment–time interaction in any of the statistical models, thereby confirming that platelet responsiveness remained stable over time after stopping clopidogrel [Ford *et al.* 2014].

Two studies used the approach of comparing the recovery of platelet activity in patients who were allocated to abrupt cessation of clopidogrel or to a tapering regimen at the planned completion of their post-stent treatment, with the aim of attenuating any rebound. Neither study found any evidence for a difference in platelet activity after complete cessation [Sibbing *et al.* 2010; Yedidya *et al.* 2012].

In summary, in studies with adequate numbers, baseline pretreatment measurements and inclusion of a placebo arm, there has been no evidence for a rebound of platelet responsiveness to ADP after stopping clopidogrel. Instead, these studies show a gradual return to original levels of platelet activation and responsiveness. It is unlikely that any rebound effect would be missed in a 30-day follow up as this is more than adequate for a complete turnover of the platelet population. Furthermore, most of the reported excess of thrombotic events occurs within the first 30 days of stopping [Lemesle *et al.* 2011]. It has also been argued that increased sensitivity of the P2Y₁₂ receptor may develop over longer-term therapy. However, the incidence of post-clopidogrel thrombotic events is highest in patients who discontinued the drug within 1 month of commencing [Lemesle *et al.* 2011], a finding more consistent with discontinuation before healing of the arteries was complete.

Most of the controlled laboratory studies selected patients with stable coronary artery disease, and it could be argued that a greater effect might be seen in patients with ACS or DES as they are at higher thrombotic risk. Patients with acute events would unfortunately be more difficult to study rigorously because of the expected long interval between pretreatment sample and stopping clopidogrel. Caution should of course be exercised in extrapolating the results to patients with a recent acute event.

Could there be adaptation of other platelet pathways to clopidogrel?

Reflecting the vital function of haemostasis and thrombus formation, platelets carry many different surface receptors that recognize various stimulatory agonists, and several signalling pathways for activation. As well as the established target of P2Y₁₂ it is apparent that clopidogrel may inhibit aggregation stimulated by other agonists, including arachidonic acid and TRAP [Ford *et al.* 2013]. Some studies have found that, although there was no rebound effect on ADP pathways of activation or aggregation, the ‘aspirin-specific’ tests, that is, using arachidonic acid as platelet stimulus, appeared less inhibited after stopping clopidogrel but maintaining the aspirin dose [Djukanovic *et al.* 2014; Hobson *et al.* 2009, Sambu *et al.* 2011b]. However, detection appears to be method dependent, as it is not seen with light transmission aggregometry [Ford *et al.* 2013, 2014; Frelinger *et al.* 2010], and Good and colleagues have recently shown that there is no additional suppression of thromboxane B₂ production when clopidogrel is added to aspirin therapy [Good *et al.* 2015]. Nevertheless, such synergistic effects probably contribute to the efficacy of dual compared with single antiplatelet therapy.

Reactive inflammation following cessation of clopidogrel has also been proffered as an explanation for an increase in major acute coronary events (MACE) [Angiolillo *et al.* 2006]. The results are conflicting, however, and are likely to reflect changes in disease state rather than an association with stopping clopidogrel [Sambu *et al.* 2011a; Wykrzykowska *et al.* 2009]. It is unclear in any case whether clopidogrel therapy directly affects any inflammatory markers, although, in common with aspirin, appearing to be associated with lower C-reactive protein [Woodward *et al.* 2004; Husted *et al.* 2010].

Despite lacking a nucleus, platelets contain the translational mechanisms needed to manufacture proteins [Weyrich *et al.* 1998], and so an adaptation response of either megakaryocytes or platelets to chronic antiplatelet therapy is not implausible [Lordkipanidzé *et al.* 2009]. However, there is no evidence to support any prothrombotic changes in receptor number or signalling capacity of platelets in the weeks after antiplatelet therapy in humans, and in any case this would not explain why any such changes were not detectable by the range of functional tests employed in the controlled research studies.

Newer P2Y₁₂ inhibitors and platelet activity

Ticagrelor (a reversible inhibitor) and prasugrel induce more potent inhibition of platelet function than clopidogrel [Storey *et al.* 2011] and, in the case of prasugrel, a more delayed recovery of platelet function after stopping [Price *et al.* 2012]. Studies so far have found no sign of rebound on stopping either prasugrel or ticagrelor [Angiolillo *et al.* 2011; Gurbel *et al.* 2009, 2011; Jakubowski *et al.* 2011], and as their modes of action are similar this would seem rational. Reversible inhibitors of P2Y₁₂ allow more rapid return of haemostatic activity when stopped. These would be considered to be beneficial properties if urgent surgery or intervention were required, or if bleeding problems arose. However, issues of poor compliance could be more serious as a missed dose would produce intermittent reversal of platelet inhibition.

Is there a true clinical rebound?

A systematic review [Gaglia and Waksman, 2011] found most early studies to be flawed and more recent detailed analyses have cast doubt on the existence of a clinical rebound particular to clopidogrel. A retrospective analysis [Collet *et al.* 2009] of the CHARISMA trial data [Bhatt *et al.* 2006] found that in almost 3000 patients who stopped taking medication before the end of the study, there were increased rates of ischaemic events and overall mortality, but the rate was actually lower in the clopidogrel plus aspirin group compared with the placebo plus aspirin group [Collet *et al.* 2009]. Bleeding events were higher than in those who completed treatment, but no different between those who had been taking clopidogrel or placebo. The investigators concluded there was no evidence for a clinically detectable rebound.

Controversy still remains over the ideal duration, but the data now emerging from randomized trials demonstrate that extending the recommended time might be of no overall benefit and even detrimental [El Hayek *et al.* 2014; Mauri *et al.* 2014; Schulz-Schüpke *et al.* 2015; Valgimigli *et al.* 2013]. In the DAPT Trial [Mauri *et al.* 2014], the risk of stent thrombosis was reduced but all-cause mortality and the incidence of severe or moderate bleeding were significantly higher in the group that continued thienopyridine to 30 months. Interestingly the rate of stent thrombosis increased in the 3 months after stopping treatment in both the group that continued on clopidogrel and the group that had changed to placebo.

Are the reasons for stopping antiplatelet drugs important?

In most studies, the timing and the reasons for stopping antiplatelet therapy were unknown. The PARIS registry study (patterns of nonadherence to antiplatelet regimens in stented patients) [Mehran *et al.* 2013] followed patients for 2 years and analysed the outcomes according to prespecified reasons for stopping:

- (1) 'discontinuation', defined as physician-recommended cessation;
- (2) 'interruption', defined as temporary cessation of DAPT of less than 14 days due to surgical procedures;
- (3) 'disruption', defined as withdrawal of antiplatelet treatment due to bleeding or noncompliance.

In 5031 patients, the rate of DAPT cessation by 24 months was 57.3%, mostly as physician-recommended discontinuation (40.8%), with disruption in 14.4% and interruption in 10.5%. Three-quarters of all events occurred in patients while still taking DAPT, but compared with those on treatment, the interruption and disruption group had a higher risk of MACE. In contrast, those with physician-recommended cessation had lower MACE risk than those who remained on DAPT at 24 months. The highest risk ratio in the disruption group occurred in the first 7 days after stopping. This is consistent with the study of Lemesle and colleagues who found that those stopping earliest had the highest risk of death, myocardial infarction, and stent thrombosis at 30 days [Lemesle *et al.* 2011].

The evidence gives reassurance that discontinuation of DAPT in low-risk patients should be considered safe, especially after 6 months from stent implantation [Franchi and Angiolillo, 2014]. Unanticipated premature disruption of treatment, however, is likely to place the patient at higher risk. Patients in this latter group are more likely to have stopped because of drug intolerance, bleeding issues or illness. Although there is no sign that clopidogrel leads to production of hyper-reactive platelets, after drug withdrawal uninhibited platelets in circulation will become activated by encountering areas of atherosclerotic vessel wall, or by increased shear stresses in narrowed arteries, or by the prothrombotic stimulus of unhealed stents.

The future of platelet testing to assess risk and guide therapy

Determining the right time to stop antiplatelet therapy in individuals remains a major issue for clinical judgement. The case for routine platelet testing at the time of PCI to guide therapy has not been supported by the recent GRAVITAS and TRIGGER-PCI trials [Price *et al.* 2011; Trenk *et al.* 2012], although in the study of Aradi and colleagues, switching those with highest on-treatment platelet reactivity from clopidogrel to prasugrel appears more promising [Aradi *et al.* 2014]. Testing to stratify those patients at higher risk for either bleeding or thrombotic events could be more useful [Collet and Montalescot, 2013] and there is proven value in specific situations, such as when surgery is required.

In the perioperative period, decision making on interruption of DAPT and removal of cardioprotection is complicated by the increase in both bleeding risk and hypercoagulability [Patel and Fleisher, 2014]. When it is deemed safe to do so, discontinuation of P2Y₁₂ inhibitors 5 days before cardiac surgery is advised to allow recovery of platelet function, although it is generally accepted that aspirin can be continued [Ferraris *et al.* 2012]. Marked individual variability in return of adequate haemostatic activity is evident however [di Dedda *et al.* 2014] and time to recovery is determined, *inter alia*, by the level of platelet reactivity before drug exposure and the extent of platelet inhibition immediately after discontinuation [Price *et al.* 2012]. A strong rationale is emerging for platelet testing; particularly suitable are the rapid whole blood methods requiring minimal sample preparation, such as the Multiplate (multielectrode impedance aggregometry, Roche

Diagnostics GmbH, Mannheim, Germany) and the point of care test, Verify Now (Accumetrics Inc, San Diego, Ca, USA) (reviewed by Petricevic, Kong and colleagues) [Petricevic *et al.* 2015; Kong *et al.* 2015]. In addition, when surgery cannot be delayed, testing may be used to predict the need for blood products [Emeklibas *et al.* 2013].

Conclusion

'Drug discontinuation effects are part of the pharmacology of a drug' [Reidenberg, 2011] and as such are an important part of safety evaluation. The term 'rebound' has been applied to denote an unexpected increase in adverse clinical events at the end of a course of treatment, and has been applied to a range of drugs [Graves *et al.* 1997]. There has also been some misuse of the term 'rebound' in the literature to denote simply a return to the status quo of the predrug state. The current evidence indicates that there is nothing unusual about clopidogrel in this regard: platelet responsiveness gradually recovers to the predrug levels after stopping. The most likely explanation for post-clopidogrel ischaemic events is premature withdrawal of required protection while the damaged vessels continue to present a highly prothrombotic stimulus. A role exists for platelet testing to assist in clinical decision making.

Conflict of interest statement

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