Clinical Considerations with the Use of Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Despite the proven benefits of using antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI), a number of key questions remain to be answered. In recent years, clopidogrel dosing strategies among such patients have evolved considerably, with newer approaches involving loading doses prior to PCI and increases in the time interval and loading dosage in an effort to overcome variable responsiveness/hyporesponsiveness to platelet inhibition. Further, the role of glycoprotein (GP) IIb/IIIa antagonists in elective stenting continues to be defined, with recent evidence suggesting that most appropriate use of these agents is in high-risk patients with elevated troponin levels. There appears to be a relationship between the use of GP IIb/IIIa antagonists with clopidogrel loading and attenuation of early inflammatory and cardiac marker release. Strategies to minimize the chance of late stent thrombosis in patients who receive drug-eluting stents (DES) are also under intense investigation. Among some patients receiving sirolimus and paclitaxel DES, current standard long-term antiplatelet strategies may be insufficient. Patient nonadherence to treatment and premature discontinuation and underutilization of antiplatelet therapies by physicians remain important clinical problems with potentially dire consequences.

Key words: catheterization/diagnostic interventional—cardiac, platelets, thrombosis/hypercoagulable states, acute coronary syndromes—ischemic heart disease, myocardial infarction—ischemic heart disease

Introduction

Platelet inhibition is an important part of standard medical management to prevent further thrombotic events and improves outcomes in patients with acute coronary syndromes (ACS) or in those who are undergoing percutaneous coronary intervention (PCI). Important considerations concerning the use of these compounds in patients undergoing PCI currently include interindividual variability in response to platelet inhibitors, optimal loading and maintenance doses, preprocedure timing of antiplatelet therapy, the role of glycoprotein (GP) IIb/IIIa antagonists in elective stenting, strategies to minimize the chance of late stent thrombosis in patients who receive drug-eluting stents (DES), and premature discontinuation/underutilization of post-PCI dual antiplatelet therapy. In this article, these topics and the recent investigations surrounding them are reviewed.

Optimizing Clopidogrel Dosing

Variability in response to clopidogrel: In managing patients with ACS who undergo PCI, rapid and predictable platelet inhibition for all patients is an important therapeutic goal. Determining the optimal dose of antiplatelet therapy to achieve this goal has been hampered by considerable interpatient variability in response to clopidogrel. In an initial study designed to examine the uniformity of platelet inhibition by a clopidogrel 300 mg loading dose followed by a 75 mg/day maintenance dose in patients undergoing stenting, platelet function was measured by aggregation and the expression of activation-dependent receptor expression.1 A
normal distribution of response was demonstrated for both measurements. Using a cutpoint of <10% absolute change in aggregation for resistance, the prevalence of resistance was about 50%–60% at 2 h; about 30% at 1 and 5 days; and 15%–21% at 30 days after stenting. This study highlighted the significant prevalence of resistance and the importance of the time when platelet studies are conducted in relation to the time of stenting when the load was administered in these patients. In another study involving a heterogeneous population of 544 patients and healthy volunteers evaluated in a post hoc analysis, platelet response to clopidogrel was also found to follow a normal distribution; the mean change in platelet aggregation was 41.9% (SD 20.8%) from baseline after clopidogrel was initiated. In that study, hypo- and hyper-responsiveness were defined as two standard deviations below or above the mean, respectively; 4.2% of patients were hypo-responsive and 4.8% were hyper-responsive by these definitions. In contrast to the prior study, this investigation suggests that a smaller but significant proportion of patients receive inadequate protection from thrombotic adverse events despite treatment with antiplatelet therapy. The results may have been affected by the heterogeneity of the population and the lack of prespecified times when platelet function was measured. Therefore, there remains a need for platelet function tests that can consistently measure platelet inhibition, and correlate those findings to adverse clinical outcomes.

Modification of clopidogrel loading doses: Antiplatelet treatment failure due to variability in response to platelet inhibition and delayed onset of antiplatelet effect remains problematic. A number of trials have been conducted in an attempt to establish the most optimal loading dose and timing of clopidogrel administration prior to PCI. The Clopidogrel for the Reduction of Events During Observation (CREDO) randomized trial was the first to establish the benefit of a longer time interval between loading dose administration and PCI. However, adverse thrombotic events continued to occur despite the use of the standard 300 mg loading dose of clopidogrel. One obvious method proposed to achieve higher platelet inhibition is to increase the clopidogrel loading dose. Indeed, the findings from the aforementioned landmark second antiplatelet therapy for reduction of myocardial damage during angioplasty (ARMYDA-2) study were the basis for the change in practice pattern currently being observed from a 300 mg loading dose to a 600 mg loading dose of clopidogrel.

Another recent trial evaluated 2 clopidogrel loading doses greater than 300 mg. The Assessment of the best Loading dose of clopidogrel to Blunt platelet activation, Inflammation, and Ongoing Necrosis (ALBION) trial was a randomized, multicenter, parallel-group study that compared a 300 mg loading dose of clopidogrel with two higher doses (600 and 900 mg) in 103 patients with non-ST-segment elevation (NSTE) ACS. Patients were randomized to the three clopidogrel loading doses, followed by 75 mg/day of maintenance clopidogrel, which was administered in addition to other standard therapy (including aspirin [ASA] therapy and low molecular weight heparin). The higher loading doses of clopidogrel were associated with significantly greater inhibition to adenosine diphosphate (ADP)-induced platelet aggregation; dose-effect relationships were observed for onset of action (within the first 6 h at 3 time points: p < 0.05 for 600 and 900 mg versus 300 mg), maximal inhibition of platelet aggregation, 24-h areas under the curve for inhibition of platelet activation (IPA), and rates of low IPA (<10% at 6 h) (Figure 1). This trial was significant because it evaluated multiple time points during the first 24 h after clopidogrel loading dosing and demonstrated the ability of a 900 mg clopidogrel loading dose to provide greater platelet inhibition within 1 h and for at least 24 h. Bleeding rates were similar in the 3 groups. Future trials will be needed to determine whether these pharmacodynamic findings translate to improvements in clinical endpoints.

Use of a 150 mg clopidogrel maintenance dose: Another possible method to achieve better platelet inhibition, particularly in high-risk patients, is to increase the clopidogrel maintenance dose. Given the significantly better platelet inhibition demonstrated with a 600 mg loading dose of clopidogrel in patients with coronary artery disease...
(CAD) already receiving standard 75 mg clopidogrel maintenance dosing,⁶ the impact of higher maintenance doses on platelet inhibition was evaluated by von Beckerath and colleagues.⁷ That double-blind study randomized 60 patients taking chronic ASA therapy who had undergone PCI and received a 600 mg loading dose to a clopidogrel maintenance dose of 75 or 150 mg/day. At 30 days following randomization, maximal 5µM ADP-induced platelet aggregation was significantly reduced, albeit with a large variability in platelet aggregation data, in patients treated with a 150 mg maintenance dose of clopidogrel (45.1% ± 20.9%) compared with the conventional dose (65.3% ± 12.1%, p<0.001) (Figure 2).⁷ Similarly, significantly greater inhibition of platelet function was observed in the 150 mg group, when platelet function was measured with the VerifyNow P2Y12 assay (p = 0.004) (Accumetrics, San Diego, Calif., USA).

Patients with type 2 diabetes have reduced responsiveness to antiplatelet agents,⁸–¹⁰ and may be at increased risk because standard maintenance doses of clopidogrel may not provide adequate protection from adverse thrombotic events. A recently published pilot study was conducted in patients with type 2 diabetes and CAD who were receiving standard clopidogrel maintenance dosing.¹¹ Angiolillo and colleagues randomized 40 clopidogrel hyporesponders (out of 64 type 2 diabetic patients) to 30 days of therapy with clopidogrel 75 mg or clopidogrel 150 mg. The degree of platelet inhibition was assessed at baseline, 30 days, and 30 days after resuming clopidogrel 75 mg dosing. At 30 days, a significant reduction in maximal ADP-induced platelet aggregation was observed in the 150 mg group compared with the 75 mg group (p = 0.002) (Figure 3).¹¹ A return to baseline values was observed in the 150 mg group at 30 days following reestablishment of 75 mg clopidogrel maintenance dosing, confirming the transient nature that the pharmacodynamic effect of high clopidogrel dosing confers and the persistency of high-platelet reactivity in this high-risk group. Notably, despite the doubling of clopidogrel dose in the 150 mg group, more than half of those patients still demonstrated suboptimal clopidogrel response, further demonstrating the effect that diabetes may have on platelet reactivity and aggregation.

A potential drawback to pushing maintenance doses of clopidogrel to 150 mg is the potential for increases in bleeding complications. However, in the recent Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, safety analyses suggested that symptomatic patients (those with documented cardiovascular disease [CVD]) were at lower risk for severe bleeding with combined clopidogrel and ASA therapy than asymptomatic patients at high atherothrombotic risk. In CHARISMA, severe bleeding occurred in 2.0% of asymptomatic patients treated with combined clopidogrel and ASA; the corresponding rate of severe bleeding among symptomatic patients was 1.6%. While certainly not proven, the authors postulate that established CVD may be a “crude proxy” for hyperactive platelets, meaning that these patients may have a lower risk for bleeding from dual antiplatelet administration.¹² Given that the target group for higher maintenance dosing with clopidogrel would likely be such higher-risk patients, the risk for bleeding complications may ultimately be deemed acceptable in this group of patients. However, this remains entirely speculative at the present time and requires future confirmation.

Ongoing investigation of higher maintenance dosing with clopidogrel loading doses: Higher maintenance doses of clopidogrel are also being evaluated in the ongoing Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS) 7 clinical trial which will be powered to detect clinical events.¹³ The CURRENT/OASIS 7 is a clinical-end point trial with a composite primary outcome measure of first occurrence of cardiovascular death, myocardial infarction (MI), or stroke within 30 days; the co-primary outcome is a 30-day occurrence of cardiovascular death, MI, stroke, or recurrent ischemia. Patients with ACS undergoing an early invasive strategy with intent for PCI are being randomized to two different clopidogrel regimens: (1) 600 mg loading dose, followed by 150 mg/day for a week and then 75 mg/day thereafter; and (2) 300 mg loading dose, followed by 75 mg/day maintenance therapy. Additionally, patients will be randomized to receive high (≥ 300 mg) versus low-dose (< 100 mg) ASA. This prospective international trial has a planned enrollment of 14,000 patients.
with unstable angina (UA) or non-ST-segment elevation MI (NSTEMI) treated with an early invasive strategy.

**Timing of Clopidogrel Therapy**

Administration of clopidogrel prior to PCI has been shown to improve post-PCI outcomes, and is widely accepted in clinical practice. The aforementioned CREDO trial was the basis for which 6 h of pretreatment was proposed to provide the full clinical benefit of clopidogrel loading. More recently, another analysis of the CREDO population was conducted in the 1,815 patients (1,762 analyzable) who underwent PCI shortly after enrollment to identify the optimal duration of treatment with a 300 mg clopidogrel loading dose. Again, a longer duration of clopidogrel pretreatment was related to a reduction in the occurrence of the combined primary endpoint (death, MI, or target vessel revascularization). However, 10–12 h of pretreatment was necessary before a difference occurred between placebo and treatment groups; and the difference between the 2 groups did not achieve statistical significance until after 15 h of pretreatment. Patients who began clopidogrel at least 15 h before PCI had a 58.8% reduction in the relative risk of the composite end point compared with placebo patients (p = 0.028); whereas the occurrence of the primary endpoint was similar in patients who received placebo and clopidogrel initiated less than 15 h prior to PCI (Figure 4).

These results suggest that patients receiving a 300 mg clopidogrel dose approximately 12 h or less prior to the procedure are not adequately protected from PCI-related thrombotic events. Moreover, identical 28-day event rates were found in patients receiving clopidogrel up to 10 h prior to PCI, regardless of whether a 300 mg or 75 mg dose of clopidogrel was administered. Accordingly, these results suggest that if a 300 mg loading dose is to be used prior to PCI, it should be initiated at least 15–24 h prior to the procedure. If this duration of pretreatment is not realistic, Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial results support the use of 600 mg of clopidogrel at least 2 h before PCI. In fact, ISAR-REACT demonstrated no further clinical benefit with clopidogrel pretreatment with this dose beyond 2–3 h prior to PCI.

**Figure 3:** The Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study shows that maximal ADP-induced platelet aggregation was significantly reduced in a group of diabetic patients who had suboptimal response to clopidogrel given a higher dose (150 mg/day) of the drug. Maximal platelet aggregation after stimulus with 20 µmol/L ADP assessed at study time points 1 (T1: baseline), 2 (T2: 30 days after randomization to either 150 or 75 mg/day), and 3 (T3: 30 days after resuming the standard dose of 75 mg/day). Values are expressed as percentage (%) of maximum platelet aggregation. Boxes represent individual measurements; bars denote means ± SD. Reproduced with permission from Angiolillo DJ et al.

**Eiective Stenting: Combining Glycoprotein IIb/IIIa Antagonists with Clopidogrel**

The AHA/ACC guidelines for management of UA/NSTEMI recommend a GP IIb/IIIa antagonist for high-risk patients undergoing planned PCI. A number of studies have focused on how adding a GP IIb/IIIa antagonist to clopidogrel pretreatment would affect inflammation and cardiac marker release in the setting of elective stenting. The Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study demonstrated that, compared with clopidogrel loading alone, administration of the GP IIb/IIIa inhibitor eptifibatide with either a 300 or 600 mg loading dose of clopidogrel was associated with superior platelet inhibition and decreased cardiac marker release.

More recently, the CLEAR PLATELETS 1b trial evaluated the effect of combining eptifibatide with clopidogrel loading (300 or 600 mg) versus clopidogrel loading alone on early inflammation and cardiac marker release in 120 patients after elective cardiac stenting. Compared with clopidogrel pretreatment alone, the combination reduced the release of CK-MB, myoglobin, and troponin-I (p = 0.03, p = 0.007, and p = 0.07, respectively). The combination group also demonstrated significant reductions in ADP-induced platelet aggregation and GP IIb/IIIa expression (p < 0.001). The majority of patients with lower platelet inhibition compared with patients with the least CRP release (p < 0.0003). Accordingly, an association can be drawn between the use of eptifibatide and a lower degree of inflammation and myocardial necrosis in patients receiving clopidogrel loading. Although the clinical implications of
the attenuation of these early cardiac and inflammatory markers requires further study, these findings suggest that early potent platelet inhibition protects against myonecrosis and inflammation in the first 24 h following stenting.

**Prevention of Late Stent Thrombosis with Drug-Eluting Stent Placement**

The optimal duration of clopidogrel treatment following stent placement is unknown. Late thrombotic events have been reported to occur among patients who receive DES, and challenge whether current recommended postprocedural antiplatelet regimens are sufficient.

A meta-analysis of 14 randomized clinical trials involving 6,675 patients who received sirolimus and paclitaxel DES or bare metal stents (BMS) suggested that there may not be a safe interval after which clopidogrel may be discontinued. In that analysis, 8 trials had more than 12 months of follow up. The incidence of late thrombosis occurring >1 year per 1,000 patients after the index procedure was substantially higher in DES patients compared with patients who received BMS (Figure 5).

An observational analysis from the BAseL stent Kosten Efektivitats Trial-Late Thrombotic Events (BASKET-LATE) trial identified 746 patients who were without major adverse events 6 months after DES or BMS placement, and had discontinued clopidogrel. Although there were no differences in cumulative rates of death or MI between patients who received DES (versus BMS), higher rates of death and MI were observed after clopidogrel discontinuation in patients receiving DES (versus BMS; 4.9% versus 1.3%, respectively) at 18-month follow-up. Additionally, a recently reported observational study in 4,666 patients who were event-free at 6- and 12-month follow-ups showed that clopidogrel use was a significant predictor of lower adjusted rates of death (2% versus 5.3%; p = 0.03, and 0% versus 3.5%, p = 0.004, respectively) and death or MI (3.1% versus 7.2%; p = 0.02, and 0% versus 4.5%, p<0.001, respectively) among patients with DES at 24 months; whereas patients who received BMS demonstrated no differences in these outcomes at 12- and 24-month follow-up. These data suggest that extended clopidogrel therapy can reduce the incidence of late thrombotic events in patients who have DES placement.

However, since this has not been studied in the setting of a large randomized clinical trial, the extent to which the duration of clopidogrel therapy should be extended remains unknown.

**Underuse of Antiplatelet Strategies Postpercutaneous Coronary Intervention: The Problem of Premature Discontinuation**

Undertreatment of outpatients with atherothrombosis has been problematic, as was highlighted in a recent review of data from an international atherothrombosis registry in which widespread underutilization of proven therapies for management of cardiovascular risk factors was identified. In that review of 67,888 patients in 44 countries with CAD, cerebrovascular disease, peripheral arterial disease, or ≥ 3 risk factors for atherothrombosis, there was a 78.6% overall utilization rate for antiplatelet agents; rates of use ranged from 53.9%
for patients with $\geq 3$ risk factors to 85.6% for patients with CAD.

Dual antiplatelet therapy with ASA and clopidogrel is currently recommended following PCI as follows:23

- In appropriate patients, ASA 325 mg/day is recommended for at least 1 month after BMS placement, 3 months after sirolimus-eluting stent placement, 6 months after paclitaxel-eluting stent placement; subsequently ASA 75 to 162 mg should be continued indefinitely.

- Clopidogrel 75 mg/day is recommended for at least 1 month after BMS placement (at least 2 weeks in patients at increased risk for bleeding), 3 months after sirolimus-eluting stent placement and 6 months after paclitaxel-eluting stent placement; however, it should ideally be continued up to 12 months in patients who are not at high risk for bleeding.

Given the recent findings of late stent thrombosis even with the use of guideline-recommended post-PCI dual antiplatelet therapy, early discontinuation of this important post-PCI adjunctive strategy by patients or health care providers is especially troubling. A study conducted by Eisenstein and colleagues suggests that the extension of providers is especially troubling. A study conducted by Eisenstein and colleagues suggests that the extension of

post-procedure antiplatelet duration of therapy is completed (12 months following Drug-eluting stent placement) or postoperative bleeding until appropriate recommended duration of thienopyridine therapy is completed (12 months following Drug-eluting stent placement if not at high risk for bleeding and a minimum of 1 month for bare metal stent placement)

- Greater effort required by health care professionals concerning discharge education about the rationale for thienopyridine therapy and the significant risks of premature discontinuation of therapy

- Specific instruction to contact treating cardiologist before stopping antiplatelet therapy, even if instructed to do so by another health care provider

- Educate healthcare providers who perform invasive or surgical procedures concerning the potential catastrophic risks of premature discontinuation of thienopyridine therapy. These professionals should be instructed to contact the patient’s cardiologist if issues concerning any patient’s antiplatelet therapy are unclear.

- Defer elective procedures with significant risk of perioperative or postoperative bleeding until appropriate recommended duration of thienopyridine therapy is completed (12 months following Drug-eluting stent placement if not at high risk for bleeding and a minimum of 1 month for bare metal stent placement)

- If thienopyridine therapy must be discontinued in patients treated with DES, aspirin should be continued (if possible) and the thienopyridine restarted as soon as possible postprocedure.

- Specific instruction to contact treating cardiologist before stopping antiplatelet therapy, even if instructed to do so by another health care provider

- Health care industry, insurers, the US Congress, and the pharmaceutical industry should ensure issues such as drug cost do not cause patients to prematurely discontinue thienopyridine therapy.

**TABLE 1: Recommendations to eliminate the chance for premature discontinuation of thienopyridine therapy.** Adapted with permission from Grines CL et al.28

| Recommendation                                                                 | 
|--------------------------------------------------------------------------------|---|
| Strong consideration of drug-eluting stent avoidance in patients not expected to comply with 1 year of therapy | Educate healthcare providers who perform invasive or surgical procedures concerning the potential catastrophic risks of premature discontinuation of thienopyridine therapy. These professionals should be instructed to contact the patient’s cardiologist if issues concerning any patient’s antiplatelet therapy are unclear. |
| Consider use of BMS or performance of balloon angioplasty with provisional stent implantation in patients likely to require invasive or surgical procedures within 1 year | Defer elective procedures with significant risk of perioperative or postoperative bleeding until appropriate recommended duration of thienopyridine therapy is completed (12 months following Drug-eluting stent placement if not at high risk for bleeding and a minimum of 1 month for bare metal stent placement). |
| Greater effort required by health care professionals concerning discharge education about the rationale for thienopyridine therapy and the significant risks of premature discontinuation of therapy | If thienopyridine therapy must be discontinued in patients treated with DES, aspirin should be continued (if possible) and the thienopyridine restarted as soon as possible postprocedure. |
| Specific instruction to contact treating cardiologist before stopping antiplatelet therapy, even if instructed to do so by another health care provider | 
| Health care industry, insurers, the US Congress, and the pharmaceutical industry should ensure issues such as drug cost do not cause patients to prematurely discontinue thienopyridine therapy |
A number of patient-related factors may cause inappropriate early discontinuation of dual antiplatelet therapy including: cost, lack of patient education concerning the importance of these therapies, older age, lack of formal education, inadequate discharge instructions, and lack of referral for cardiac rehabilitation. However, health care providers may also place patients at risk for late stent thrombosis by interrupting antiplatelet therapies prior to invasive or surgical procedures. Even though it is usually safe for patients to continue their antiplatelet therapy during minor routine procedures such as dental cleanings and extractions, physicians and dentists may nevertheless broadly instruct their patients that “blood thinners should be stopped” without distinguishing between warfarin and platelet inhibitors or considering the critical rationale for dual platelet inhibition in this patient subset. Indeed, it is especially important to promulgate practices that reduce the chance for premature discontinuation of clopidogrel. A number of recommendations were recently published in a science advisory by Grines and colleagues with the goal of eliminating premature discontinuation of thienopyridine therapy, and these are summarized (Table 1). Notably, although this recent publication recommends dual antiplatelet therapy for 12 months post-DES placement, the fact that the optimal duration of therapy in this setting has not been determined remains an important clinical consideration.

Conclusion

A number of important topics continue to dominate the literature concerning the contemporary use of antiplatelet therapies in patients undergoing PCI. Clopidogrel dosing strategies have evolved in recent years—first with the introduction of the standard practice of loading doses prior to PCI, and more recently by increasing the time interval and loading dosage of clopidogrel in an attempt to overcome variable responsiveness/hyporesponsiveness to platelet inhibition. The role of GP IIb/IIIa antagonists in this setting continues to be clarified, but it currently appears that their most appropriate use is in high-risk patients with elevated troponin levels; recent findings suggest an association between the use of GP IIb/IIIa antagonists with clopidogrel loading and attenuation of early inflammatory and cardiac marker release. Another critical consideration concerns DES placement and an observed excess occurrence of late thrombotic events, an issue suggesting that current standard long-term antiplatelet strategies post-PCI may be inadequate in some patients who receive sirolimus and paclitaxel DES; also that extension of dual antiplatelet therapy and measures to prevent its early discontinuation following PCI are necessary. Premature discontinuation of recommended thienopyridine therapy in patients treated with coronary artery stents remains an important clinical problem with potentially catastrophic risks.

References


