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Post percutaneous coronary intervention antiplatelet therapy: Current perceptions, prospects and perplexity

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Abstract

Dual antiplatelet therapy (DAT) has become standard care for patients undergoing percutaneous coronary intervention (PCI). Following balloon injury and stent placement, the intima at the site is distressed, resulting in the activation of coagulation cascade and platelets. In the case of bare metal stents (BMS), it takes six to eight weeks for the stent surface to be covered with neointima. However, in the case of a drug-eluting stent (DES), the process of healing is delayed and neointima may not form for months or even years. To prevent the formation of platelet thrombi, dual antiplatelet therapy is given as a combination of aspirin and clopidogrel for three months in a case of BMS and for a minimum of one year in a case of DES. A prolonged duration of therapy is often required for a subset of patients who are highly prone to thrombus formation. During most non-cardiac surgeries, dual antiplatelet therapy should be continued if bleeding can be directly controlled and excessive bleeding will have no adverse effect on the outcome of surgery. Prasugrel, another thienopyridine, is more potent and faster acting than clopidogrel, and is therefore of great value in cases of acute coronary syndrome during PCI, particularly in diabetics. Triple drug therapy, by adding cilastozol, is reserved for some selected thrombotic lesions. Ticagrelor and cangrelor are two new antiplatelet agents undergoing various clinical trials. (Cardiol J 2011; 18, 6: 712–717)

Key words: percutaneous coronary intervention, dual antiplatelet therapy, restenosis

Introduction

Percutaneous coronary intervention (PCI) using a bare metal stent (BMS) or a drug-eluting stent (DES) has become a widely accepted treatment for obstructive coronary artery disease (CAD). The procedure of PCI inflicts balloon injury to the site of the lesion, leading to activation of the coagulation cascade which may lead to acute and subacute thrombosis (SAT) [1]. Placement of the stent further complicates the local coagulation process with higher chances of thrombosis over the metal surface. Aggressive anticoagulation regimens have been shown to minimize the stent thrombosis rate. However, such an approach can also result in higher rates of vascular complications, in particular bleeding [2]. There has been ample clinical research in the last decade to unravel the optimal antiplatelet therapy, their dosage, the duration of such therapy and related issues in order to reduce the thrombotic complications of PCI.

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Thrombotic complications of PCI

The most dreaded complications following PCI are SAT, late stent thrombosis (LST) and very late stent thrombosis (VLST). Thrombosis occurring within 30 days is called SAT; thrombosis occurring after 30 days to one year is called late stent thrombosis; and that occurring more than one year later is called very LST [3, 4].The complication can result in fatal myocardial infarction (MI) in as many as 45% of cases [5]. Vascular injury caused by high pressure balloon dilatation and deployment of a stent leads to adherence of activated platelets at the site of injury. There is release of adenosine diphosphate (ADP), tromboxane A2 and other procoagulative factors. Release of these factors further leads to platelet aggregation and the formation of platelet-rich thrombi. The process starts almost simultaneously with balloon dilatation and stent placement. Exposure of blood coagulation components, particularly activated platelets, to the bare metal surface of the stent makes the area vulnerable to thrombosis until the stent surface gets covered with a neointima [6]. In a case of BMS, the neointima begins to form within a couple of weeks and the chances of thrombus formation keep on reducing until the stent is fully covered with neointima within eight to ten weeks. In a case of BMS, it is very uncommon to encounter thrombosis beyond this period [7–9]. DESs are very effective in reducing the chances of restenosis and thereby the need for reintervention. They do so by reducing neointimal proliferation. However, the process of stent endothelialization also gets delayed by several months or years [6]. Furthermore, sirolimus and paclitaxel induced expression of tissue factor in the DES stented lesion may kick off the coagulation cascade [6]. Finally, the polymer coating on the DES can provoke infiltration of eosinophilic cells in the vessel wall suggestive of hypersensitivity reaction, and this might contribute to a prothrombotic milieu [10].

In autopsy specimens taken from patients who have died of LST or VLST, the stents have been found to be inadequately covered with neointima with thrombi over bare metal surface of the stent [10, 11].

Evolution of dual antiplatelet therapy

In previous decades, aspirin alone in small to large doses, and subsequently in combination with coumadin, was tried but found to be ineffective in terms of reducing the incidence of SAT [12, 13]. A dual antiplatelet combination with ticlopidine, a thienopyridine derivative, proved reasonably effective in reducing the incidence of SAT compared to aspirin alone [12, 13]. However, the bone marrow suppression associated with ticlopidine clearly required another effective agent to replace ticlopidine in the combination. Clopidogrel was introduced in the late 1990s. Higher efficacy and diminished likelihood of bone marrow suppression made this new thienopyridine compound very popular. Soon, clopidogrel with aspirin became the standard care for patients undergoing PCI [14–17].

Concerns regarding clopidogrel use

Duration of use

Current guidelines of clopidogrel use in BMS patients are clear and robust (Grade 1A evidence). Clopidogrel 75 mg a day, along with aspirin 150 mg, is given for a minimum of one month and ideally up to 12 months, unless the patient is prone to bleeding [18, 19]. In patients who undergo PCI for ACS, a minimum 12 month duration is recommended (Grade 1B evidence) [18, 19]. The recommendations for DES have varied over the last few years. The earliest studies recommended only three months of dual antiplatelet therapy (DAT) following a sirolimus coated stent and six months following a paclitaxel coated stent [20]. However, several case reports of LST and VLST due to delayed healing, and autopsy confirmations of inadequate neointimal coverage for several months and years have led to confusion regarding the period for which DAT should be continued following DES implantation [18, 19]. The ACC/AHA guidelines recommended a minimum of 12 months of DAT for patients who receive DES (Grade 1B evidence) [18, 19]. DAT for longer than 12 months, and perhaps indefinitely, after DES is considered necessary in a subset of patients when antithrombotic benefit appears to exceed the risk for bleeding. This subset includes patients with minimal risk of gastrointestinal or cerebral bleeding and at increased risk of late stent thrombosis (such as those with prior brachytherapy, reduced left ventricular systolic function, complex PCI, or suboptimal procedure outcome), or in whom stent thrombosis could be catastrophic (PCI of left main or proximal left anterior descending coronary arteries). Aspirin at a dose of 75 to 162 mg/day should be continued indefinitely in all stented patients (Grade 1A evidence) [18, 19].

Clopidogrel resistance

Depending on the definition used and the laboratory assay employed to measure resistance, between 4% and 68% of patients do not show adequate

Table 1. GRAVITAS: Primary end-point.

End-point	High-dose clopidogrel	Standard-dose clopidogrel	Hazard ratio (95% CI)	P
CV death/MI/stent thrombosis	2.3%	2.3%	1.01 (0.58–1.76)	0.98

CV — cardiovascular; MI — myocardial infarction

Table 2. GRAVITAS: Bleeding results.

Outcome	High-dose clopidogrel	Standard-dose clopidogrel	P
GUSTO severe/moderate bleeding	1.4%	2.3%	0.10
Any GUSTO bleeding	12.0%	10.2%	0.18

Table 3. GRAVITAS: Percentage of patients with persistently high platelet reactivity at 30 days.

Platelet reactivity units (PRU)	High-dose clopidogrel	Standard-dose clopidogrel	P
≥ 230	62%	40%	< 0.001

response to platelet [21–27]. Clopidogrel resistance has been attributed to variation in gut absorption, variation in metabolism via CYP450 enzyme, variation in the combination with its platelet P2Y12 receptor, and possibly interaction with other drugs, especially proton pump inhibitors (PPIs) [25]. Because of partial or complete resistance, various dose schedules, particularly the administration of loading dose, have been recommended. A 600 mg loading dose of clopidogrel produces a greater maximal antiplatelet effect, an earlier antiplatelet effect, and reduces the likelihood of clopidogrel resistance [28––34]. There was no benefit found on cardiovascular (CV) outcomes or stent thrombosis with a double dose of clopidogrel in patients receiving DES with high residual platelet activity on a regular clopidogrel dose in the GRAVITAS trial [35]. In this trial, 5,429 patients on a regular dose of clopidogrel underwent platelet-function tests with the VerifyNow assay (Accumetrics, San Diego, CA, USA) 12 to 24 hours after PCI; 41% of the patients from this pool had high residual platelet reactivity (platelet reactivity units or PRU ≥ 230). They were randomized to continue on the 75 mg regular clopidogrel dosage arm or to receive another 600 mg loading dose and a higher maintenance dose of 150 mg daily arm. Baseline characteristics of the samples revealed that most patients were at relatively low risk, with 80% having stable CAD. There was an identical composite end-point of CV death/MI/stent thrombosis in both the groups (2.3%) at six month follow-up (Table 1).

Stent thrombosis occurred in 0.5% of the high-dose group compared to 0.7% of the standard-dose group but the difference was not statistically significant. There was also no difference in bleeding between the two groups (Table 2).

The absolute platelet reactivity was reduced from an average of about 280 PRU at baseline to 200 PRU in the high-dose clopidogrel group, in comparison to 240 PRU in the standard-dose group at 30 days. This was a modest, albeit statistically significant, reduction in PRU. Results at six months were virtually the same as those at three months (Table 3) [36].

TRIGGER-PCI had a similar trial design to GRAVITAS but compared clopidogrel with prasugrel based on platelet-reactivity testing in stable CAD patients post-stenting. The trial was halted prematurely and hence could not render any noteworthy information on whether a significant gain in primary CV outcome could be achieved by adding more effective antiplatelet therapy.

Finally, another trial, TRILOGY AS, comparing clopidogrel and prasugrel, is still ongoing in patients with acute coronary syndrome (ACS).

Interaction with proton pump inhibitors

Patients who are on DAT are prescribed PPI because aspirin can be responsible for gastritis and, in combination with clopidogrel, there are concerns

about gastrointestinal bleeding. A possible but unproven clinical effect of PPIs on the protection afforded by clopidogrel has been evaluated in a large number of studies, with varying and often conflicting conclusions [36–43]. The only large scale randomized trial of omeprazole *vs* placebo in clopidogrel users, the CONGENT trial, showed no significant difference in CV events (HR 0.99; 95% CI 0.68–1.44) along with a significant reduction in GI events (HR 0.34; 95% CI 0.18–0.63). However, this trial had to be terminated early because of lack of availability of continued funding by the sponsor. As a result, only 3,873 of the planned sample size of 5,000 were enrolled and there were only 109 primary CV end-points [44]. In November 2009, the US Food and Drug Administration stated that the concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel metabolism and therefore its antiplatelet activity [45]. Since the level of inhibition among other PPIs varies, it is unknown to what extent other PPIs may interfere with clopidogrel. However, esomeprazole, a PPI that is a component of omeprazole, inhibits CYP2C19 and should also be avoided in combination with clopidogrel. While the current state of knowledge does not validate the statement that PPIs are associated with clinical CV events among clopidogrel users, further randomized trials are clearly needed to draw up more concrete evidence-based guidelines.

Dual antiplatelet therapy during non-cardiac surgery

For elective non-cardiac surgery, DAT should be continued for at least the minimum duration recommended for each stent type. However, in cases where surgery is emergent, one has to evaluate the risk of bleeding during the surgical procedure. In most surgery where the chances of bleeding are less, or the bleeding can be controlled directly during surgery, it is advisable not to discontinue DAT [46]. In some procedures, such as hip, brain or spinal surgery, if needed as emergency procedures when bleeding may be difficult to control and could have adverse effects on the surgical outcomes, it may be better to discontinue one of the two agents. Thienopyridine may be discontinued for as brief a period as possible and aspirin may be continued uninterrupted if the 12 month period of DAT is not finished [46]. It is recommended that for any dental treatment, including extraction, or any other major surgery including open abdominal surgery where there is direct access to control bleeding, DAT may be continued weighing the risk of some extra bleed that one may encounter [46]. The concept of bridging a gap in thienopyridine therapy using an intravenous glycoprotein IIb/IIIa inhibitor such as tirofiban is under investigation [47].

Future paradigms in antiplatelet therapy

Triple antiplatelet therapy

Triple antiplatelet therapy i.e. aspirin, clopidogrel and cilostazol, compared to dual antiplatelet therapy i.e. aspirin and clopidogrel, has shown a lower rate of adverse CV outcomes after stent placement in patients with either stable or unstable coronary disease in several studies [48–51].

This holds true for both short- and long-term outcomes without significant difference in the rate of bleeding. In the recent CILON-T study, a combination of aspirin, clopidogrel and cilastozol in PCI for acute MI was not associated with a significant reduction in clinical outcomes after DES placement compared to the standard DAT [52]. However, the addition of cilostazol did improve post-treatment platelet reactivity as measured by P2Y12-receptor reaction units (PRU). Multiple studies have shown an association between platelet activity and outcomes. Even in the CILON-T trial, patients in the lowest tertile of platelet reactivity (PRU values of 0 to 184 U) had zero clinical events (cardiac death, non-fatal MI, ischemic stroke). We are yet to see if changing therapy based on the functional platelet knowledge changes clinical outcomes, and whether platelet reactivity is a better guide to monitoring therapy among post-PCI patients.

Newer antiplatelet agents

Prasugrel is a newer drug which binds irreversibly to the P2Y12 platelet receptor, as does clopidogrel. However, it has several distinct advantages over clopidogrel. It has a more rapid onset of action (an incredibly beneficial property whenever emergency PCI is contemplated) and is able to achieve higher degrees of platelet inhibition than clopidogrel, while having a comparable rate of significant bleeding [53]. Furthermore, human polymorphisms in gene encoding CYP450 system affect prasugrel therapy to a lesser extent; hence, platelet activity is suppressed in a larger number of patients than clopidogrel.

TRITON-TIMI 38, a pivotal trial for prasugrel, analyzed 13,608 patients with moderate to high risk ACS undergoing PCI randomized to receive prasugrel with aspirin in one arm and standard DAT in the other [54]. At an average follow-up of 14.5 months, prasugrel was associated with a significant 2.2%

absolute reduction and a 19% relative reduction in death, non-fatal MI and non-fatal stroke. Diabetics appear to derive greater benefit. The *post hoc* analysis revealed three subsets of patients who showed less net clinical benefit and increased risk of bleeding. These include patients with a history of stroke or transient ischemic attack, those above 75 years, and those weighing less than 60 kg. Based on the TRITON-TIMI 38 results, patients in whom prasugrel should be considered include those with STEMI and NSTEMI in whom a decision has been made to withhold thienopyridine therapy until after diagnostic coronary angiography. Further, it may be considered an alternative to clopidogrel in moderate or high risk ACS undergoing PCI without the aforementioned contraindications [54]. Overall, prasugrel appears to be an important advance in antiplatelet therapy.

Ticagrelor and cangrelor: Two newer antiplatelet agents

Ticagrelor differs from the thienopyridines in that it binds reversibly, rather than irreversibly, with the P2Y12 platelet receptor and has a more rapid onset of action than clopidogrel [55]. It belongs to a new chemical class of antiplatelet agents, the cyclopentyltriazolopyrimidines. In a similar fashion to prasugrel, treatment with ticagrelor leads to more intense platelet inhibition than clopidogrel [56]. In the original PLATO trial of dual antiplatelet treatment in ACS, ticagrelor significantly reduced the primary outcome of vascular death, non-fatal MI, and non-fatal stroke compared to clopidogrel (absolute risk 9.8% *vs* 11.7%; hazard ratio 0.84, 95% CI 0.77–0.92) [56]. Further, in a subgroup analysis of 5,216 (28%) PLATO recruits who were intended for non-invasive management at the time of admission, James et al. [57] found no higher risk of bleeding. Ticagrelor now has a class 1 recommendation in the European revascularization guidelines for use in combination with aspirin for the invasive management of ACS [58]. A similar recommendation will perhaps soon follow for non-invasive management [59]. Cangrelor is an intravenous non-thienopyridine P2Y12 receptor blocker that has not been shown to be superior to clopidogrel in patients with ACS undergoing PCI [37, 60].

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