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 anti-coagulation 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.
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 late 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
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

### Table 1. GRAVITAS: Primary end-point.

<table>
<thead>
<tr>
<th>End-point</th>
<th>High-dose clopidogrel</th>
<th>Standard-dose clopidogrel</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/stent thrombosis</td>
<td>2.3%</td>
<td>2.3%</td>
<td>1.01 (0.58–1.76)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

CV — cardiovascular; MI — myocardial infarction

### Table 2. GRAVITAS: Bleeding results.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High-dose clopidogrel</th>
<th>Standard-dose clopidogrel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO severe/moderate bleeding</td>
<td>1.4%</td>
<td>2.3%</td>
<td>0.10</td>
</tr>
<tr>
<td>Any GUSTO bleeding</td>
<td>12.0%</td>
<td>10.2%</td>
<td>0.18</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Platelet reactivity units (PRU)</th>
<th>High-dose clopidogrel</th>
<th>Standard-dose clopidogrel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 230</td>
<td>62%</td>
<td>40%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

/MI/stent thrombosis in both the groups (2.3%) at six month follow-up (Table 1).
about gastrointestinal bleeding. A possible but un-
proven clinical effect of PPIs on the protection af-
forded by clopidogrel has been evaluated in a large
number of studies, with varying and often conflict-
ing conclusions [36–43]. The only large scale ran-
domized trial of omeprazole vs placebo in clopi-
dogrel users, the CONGENT trial, showed no sig-
nificant 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 pri-
mary 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 clopi-
dogrel metabolism and therefore its antiplatelet
activity [45]. Since the level of inhibition among
other PPIs varies, it is unknown to what extent oth-
er PPIs may interfere with clopidogrel. However,
esomeprazole, a PPI that is a component of ome-
prazole, inhibits CYP2C19 and should also be avoid-
ed in combination with clopidogrel. While the cur-
cent state of knowledge does not validate the state-
ment that PPIs are associated with clinical CV
events, further randomized trials are clearly needed to draw up more con-
crete 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 rec-
commended 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 dur-
ing surgery, it is advisable not to discontinue DAT
[46]. In some procedures, such as hip, brain or spi-
nal 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 den-
tal 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 con-
cept 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, clopi-
dogrel and cilostazol, compared to dual antiplatelet
therapy i.e. aspirin and clopidogrel, has shown a low-
er 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 com-
bination of aspirin, clopidogrel and cilostazol 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 out-
comes. 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 wheth-
er platelet reactivity is a better guide to monitor-
ing therapy among post-PCI patients.

**Newer antiplatelet agents**

Prasugrel is a newer drug which binds irrevers-
ibly to the P2Y12 platelet receptor, as does clopi-
dogrel. However, it has several distinct advantag-
es 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 sig-
nificant bleeding [53]. Furthermore, human poly-
morphisms in gene encoding CYP450 system affect
prasugrel therapy to a lesser extent; hence, plate-
let activity is suppressed to a lesser extent, hence, plate-
let activity is suppressed in a larger number of pa-
tients 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 prasug-
rel 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 patients followed for up to three years, J Am Coll Cardiol, 2007; 49: 1043–1051.

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References
