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Review Article

Review of Antiplatelet Use in Percutaneous Coronary Intervention

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Abstract

Percutaneous Coronary Intervention (PCI) includes both stent and non-stent procedures. Oral antiplatelet treatment has become the mainstay of therapy for the secondary prevention of coronary ischemic episodes after PCI. The appropriate use of oral antiplatelet treatment and the proper education of healthcare providers and patients is paramount to the successful medical management of these cardiac patients. The American College of Cardiology Foundation / American Heart Association / Society for Cardiovascular Angiography and Interventions guidelines suggest that dual antiplatelet therapy (DAPT) including aspirin and a $P2Y_{12}$ receptor antagonist for a period of up to 12 months may be necessary regardless of coronary intervention.

Keywords: stents; antiplatelets; percutaneous coronary intervention; ticagrelor; prasugrel; clopidogrel

Abbreviations

ACS: acute coronary syndrome; ADP: adenosine diphosphate; ARR: absolute risk reduction; BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; CKD: chronic kidney disease; CLARITY: Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT: Clopidogrel and Metoprolol in Myocardial Infarction; CREDO: Clopidogrel for the Reduction of Events During Observation; CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV: cardiovascular; CYP: cytochrome P-450; DAPT: dual antiplatelet therapy; DES: drug eluting stent; DM: diabetes mellitus; FDA: Food Drug Administration; Hgb: hemoglobin; Hct: hematocrit; HR: hazard ratio; LD: loading dose; MD: maintenance dose; MI: myocardial infarction; NNT: number needed to treat; NR: not reported; NSTEMI: non – ST elevation myocardial infarction; PLATO: Study of Platelet Inhibition and Patient Outcomes; PPI: proton pump inhibitor; PRBC: packed red blood cells; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; RRR: relative risk reduction; STE: ST-elevation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction; TLR: target lesion revascularization; TRITON: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; TVR: target-vessel revascularization; UA: unstable angina

Introduction

Percutaneous Coronary Intervention (PCI) involves both non-stent and stent procedures with the latter being the preferred method of revascularization. A stent is a mesh-like tube of thin wire that can open within a blood vessel like a scaffold, to keep the blood vessel open. There are two types: 1) the bare metal stents (BMS) - which are made of cobolt-chromium alloy and drug-eluting stents (DES) – which are embedded with an antiproliferative agent (Table 1) [1].

Bare metal stents help to reduce restenosis rates by attenuating arterial recoil and contraction as compared to balloon angioplasty alone. The restenosis rates with BMS were reported to be between 16% and 44%, with higher rates of stenosis attributable to several risk factors, including, long lesion length and small vessel caliber [2]. Drug-eluting stents help to further reduce the rates of restenosis. Several trials have demonstrated DES reduce the 1-year incidence of restenosis requiring target-lesion revascularization (TLR) by > 70% when compared to BMS [3].

Drug eluting stent placement has been shown to increase the incidence of late stent thrombosis, particularly related to discontinuation to dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ antagonists [4-6]. Late stent thrombosis is defined as a stent thrombosis within the first years of stent placement. In 2007, an Food Drug Administration (FDA) advisory panel reviewed the data on thrombosis associated with DES using the Academic Research Consortium. They concluded that DES were associated with a small increase (1 - 5%) in stent thrombosis compared to BMS [7-9]. Predictors of late stent thrombosis may be classified as procedural, angiographic, and clinical [9]. Of particular interest, practitioners can help to mitigate some clinical factors including heart disease, renal disease, diabetes mellitus, and premature discontinuation of DAPT by providing education and proper follow - up [9-13].

With these recent findings in mind, the role of DAPT becomes a central issue in the medical management of patients undergoing PCI with stent placement.

Table 1: US FDA Approved Drug-Eluting Stents.

Cypher	Sirolimus	Cordis	April 2003
Taxus Express 2	Paclitaxel	Boston Scientific	March 2004
Taxus Liberte	Paclitaxel	Boston Scientific	October 2008
Promus (Xience V)	Everolimus	Abbot/Boston Scientific	July 2008
Promus (Element)	Everolimus	Boston Scientific	November 2011
Endeavor	Zotarolimus	Medtronic	February 2008
Resolute Integrity	Zotarolimus	Medtronic	February 2012

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Oral Antiplatelet Therapies

Aspirin

The backbone of DAPT consists of aspirin therapy, which irreversibly inactivates cyclo - oxygenase enzyme, reducing the levels of vasoactive compounds, thromboxane A2 and prostacyclin. Aspirin use has been associated with a 25% to 50% reduction of MI, stroke and vascular death when used for secondary prevention in high risk patients [14-16]. The controversy with aspirin often lies in its dosing. A large, randomized, study was conducted to determine the optimal dose of aspirin and clopidogrel, for acute coronary syndromes (ACS) patients undergoing PCI. Study results showed no difference between high-dose (300 - 325 milligram [mg]) and low-dose (75 - 100 mg) aspirin for the primary outcome of cardiovascular (CV) death, myocardial infarction (MI), or stroke at 30 days ($p = 0.61$). There was also no significant difference in major bleed ($p = 0.90$), however, minor bleeds increased by 13% ($p = 0.04$) [17]. Further details of the results of this study are discussed in the next section. Since the role of aspirin therapy in ACS has been clearly established this article will focus on the use of $P2Y_{12}$ antagonists (clopidogrel, prasugrel, ticagrelor) in this population.

Clopidogrel

Clinical pharmacology: Clopidogrel, a thienopyridine, is a prodrug that irreversibly inhibits the $P2Y_{12}$ receptor. This, subsequently, impedes adenosine diphosphate (ADP) - mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation. It is indicated to reduce the rate of atherothrombotic events, MI, stroke, and vascular deaths in patients with recent MI, stroke, or established peripheral arterial disease [18]. Clopidogrel is metabolized by several cytochrome P-450 (CYP) isoenzymes CYP2C19, CYP3A4, CYP2B6, and CYP1A2. Poor metabolizers of the CYP2C19 may have diminished antiplatelet response to clopidogrel. Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of clopidogrel [18,19]. The elimination half-life is ~6 hours and 30 minutes for the active metabolite. In ACS, clopidogrel is given at a loading dose (LD) of 300-600 mg, followed by a maintenance dose (MD) of 75 mg daily [18,20].

Clinical efficacy data: The benefit of clopidogrel therapy in ACS was first established in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and PCI-CURE trials [21,22]. The CURE study was a large, randomized controlled trial (RCT) conducted in ACS patients with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI). Patients were randomized to receive clopidogrel 300 mg LD then 75 mg daily MD or matching placebo for 3 - 12 months (mean 9 months). All patients were given aspirin 75 - 325 mg daily. There were two primary outcomes: 1) a composite of CV death, nonfatal MI, or stroke, 2) a composite of CV death, nonfatal MI, stroke or refractory ischemia. The study demonstrated a 20% relative risk reduction (RRR) in the first primary outcome and a 14% RRR in the second primary outcome with clopidogrel treatment ($p < 0.001$) [21]. The subset of patients that reaped the most benefit were those who had MI, Q-wave MI, and refractory ischemia during hospitalization [21]. The PCI-CURE was a sub analysis of the CURE study to determine the benefits of clopidogrel pretreatment in patients undergoing PCI most of whom had stents deployed. After a mean of 8 months, there was a 30% RRR in the combined primary outcome of CV death, MI, or urgent target-vessel revascularization (TVR) within the first 30 days of PCI ($p = 0.03$) [22]. Long-term administration of clopidogrel after PCI (30 days to 1 year) was also associated with lower rates of the primary outcome ($p = 0.03$), and the combined endpoint of CV death or MI ($p = 0.047$) [22]. These studies revealed that DAPT in ACS patients without ST elevation (STE), ± PCI, is effective at reducing major CV events [21,22].

The Clopidogrel for the Reduction of Events During Observation trial (CREDO) was conducted to determine the safety and efficacy of long term clopidogrel and of clopidogrel pretreatment prior to PCI (± stent placement), in patients with symptomatic coronary artery disease (CAD) [23]. Patients were randomly assigned to receive clopidogrel 300 mg LD or matching placebo, in addition to aspirin 325 mg, within 24 hours of PCI. After PCI, clopidogrel 75 mg and aspirin 325 mg daily were continued for all patients for the first 28 days. Long-term (12 months) aspirin 81 - 325 mg treatment was continued in all patients, while clopidogrel treatment of 75 mg daily was only continued in patients who received the LD. At 1 year, clopidogrel therapy was associated with a 27% RRR and a 3% absolute risk reduction (ARR) in the primary endpoint of death, MI, or stroke ($p = 0.02$), with a number needed to treat (NNT) of 33 [23]. However, clopidogrel pretreatment did not significantly reduce the combined risk of death, MI, or urgent TVR at 28 days. This trial demonstrated that in patients undergoing PCI, ± stent placement, DAPT significantly reduced the risk of adverse CV ischemic events when continued for 1 year post-procedure.

The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI 28) and Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trials help to establish the use of DAPT in STEMI [24,25]. The CLARITY-TIMI 28 trial was a large, RCT conducted in STEMI patients who were randomized to receive clopidogrel 300 mg LD then 75mg MD or matching placebo. All patients received aspirin 75 - 162 mg daily. Treatment with clopidogrel resulted in a 31% RRR in the primary composite endpoint of occluded infarct-related artery on angiography, death or recurrent MI before angiography ($p < 0.001$) [24]. Clopidogrel treatment had a significant effect on occluded infarct-related artery while only a trend in benefit was observed for recurrent MI [24]. Accordingly, a subanalysis of this study CLARITY-PCI) in patients undergoing planned PCI (without stent placement) was conducted. Patients were randomized to a clopidogrel pretreatment group or standard therapy group (clopidogrel administration at PCI). Pretreatment with clopidogrel significantly reduced the incidence of the primary composite endpoint of CV death, MI, or stroke following PCI by 46% ($p = 0.008$) [26]. The incidence of the composite endpoint of MI or stroke prior to PCI was significantly reduced by 38% ($p = 0.03$). Additionally, a 41% significant reduction in CV death, MI, or stroke from randomization through 30 days, with a NNT of 23 ($p = 0.001$) was observed in this analysis [26]. Both CLARITY trials demonstrated that in STEMI patients who received aspirin, ± PCI, the addition of clopidogrel improved the patency rate of the infarct-related artery and reduced ischemic complications [24,26]. However, questions still remain on the effects of DAPT on mortality alone in STEMI patients.

The COMMIT trial was a large, multi-centered, RCT to determine

the effects of DAPT on morbidity and mortality in STEMI patients, not undergoing PCI. Patients were randomly assigned to receive clopidogrel MD 75 mg or matching placebo in addition to aspirin 162 mg daily. Assignment to clopidogrel produced a 9% RRR in death, reinfarction, or stroke (p = 0.002), corresponding to 9 fewer events per 1000 patients treated for about 2 weeks [25]. There was also a 7% significant proportional reduction in any death (p = 0.03) [25]. This study revealed that in STEMI patients undergoing medical management, adding clopidogrel 75 mg daily to aspirin and other standard treatments, safely reduced morbidity and mortality, which set the stage for the routine administration of DAPT in STEMI patients.

As discussed previously, the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial was conducted to determine the optimal dose of aspirin and clopidogrel, for ACS undergoing PCI. In a 2 x 2 factorial design, ~25,000 patients were randomly assigned to either a double dose clopidogrel group (LD: clopidogrel 600 mg on day 1, then MD 150 mg daily x 6 days, then MD 75 mg, thereafter) or standard-dose clopidogrel group (LD: clopidogrel 300 mg, then MD: 75 daily thereafter) and either a high-dose or low-dose aspirin group. The primary outcome was CV death, MI, or stroke at 30 days. There was no statistical significant difference in the primary outcome. p = 0.30. However, double-dose clopidogrel treatment resulted in a 30% RRR (p = 0.001) in the secondary outcome of stent thrombosis on those who underwent PCI [17]. This study revealed that doubling the dose of clopidogrel, therefore its' expected potency, did not result in the reduction of adverse CV ischemic outcomes; however, this dose may be beneficial in stented patients.

Clinical safety data: The primary safety endpoints of many of these trials were determined using the TIMI bleeding criteria, which categorize bleeding as major, minor, or minimal. Major bleeding is defined as follows: 1) intracranial bleeding; 2) clinically significant overt signs of bleeding associated with an absolute decrease in hemoglobin (Hgb) 5 g / dL (if Hgb not available, hematocrit [Hct] decrease > 15%); or 3) if coronary artery bypass graft (CABG) related – fatal/perioperative intracranial bleeding, reoperation following closure to control bleeding, transfusion ≥ 5 units of whole blood or packed red blood cells (PRBCs) within a 48 hour of procedure, or chest tube output > 2 L within 24 hours of procedure. Minor bleeding is defined as follows: any clinically overt signs of bleeding associated with a decrease in Hgb of 3 to ≤ 5 g/dL (or if Hgb not available, Hct decrease of 9 to ≤ 15%). Minimal bleeding is as follows: any clinical overt sign of bleeding (including imaging) associated with a decrease in Hgb < 3 g/dL (if Hgb not available, Hct decrease < 9%) [27].

In the CLARITY trial, there was no difference in the rates of TIMI-defined major bleeding (p = 0.28) and minor bleeding (p = 0.17) between groups [24]. These findings were consistent with the results revealed in the PCI-CLARITY where there was no increase rate of TIMI major or minor bleeding (p > 0.99) [26]. The COMMIT trial also revealed no increased risk in all fatal, transfused, or cerebral bleeds in patients exposed to clopidogrel (p = 0.59), who were > 70 years or in those given fibrinolytic therapy [25]. The CURE and CURE-PCI trial also found no significant difference in major bleeding in patients exposed to clopidogrel (p = 0.64) [21,22]. In the PCI-CURE trial, there was a trend but no significant increased risk of major bleeding at 1 year (*P* = 0.07) [22].

In the CURRENT-OASIS 7, bleeding was assessed according to TIMI criteria and the study's prespecified definitions. Major bleeding was defined as bleeding requiring red-cell transfusions ≥ 2 units, leading to decrease in Hgb ≥ 5 g/dL, as well as, CABG-related, symptomatic intracranial, and fatal bleeding. Major bleeding occurred more frequently in the double-dose clopidogrel group than in the standard dose group (p = 0.01) [17].

Safety data reveals that short-term and long-term exposure to clopidogrel does not significantly expose patients to harm. Other reported adverse events included rash, pruritus, purpura, bruising and epistaxis [17,21-26].

Prasugrel

Clinical pharmacology: Prasugrel is indicated to reduce the rate of thrombotic CV events, including stent thrombosis in patients with ACS who are to be managed with PCI. It is a thienopyridine prodrug like clopidogrel, however its' metabolism requires only a single step - primarily mediated by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite has an ~7 hour elimination half-life. Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the feces as inactive metabolites [28]. Prasugrel is given at a 60 mg LD, then a 10 mg MD. Patients weighing < 60 kg may be given a 5mg daily MD due to the increased risk of bleeding with standard dosing; however this dose has not been prospectively studied. Prasugrel is contraindicated in patients with a prior history of stroke or transient ischemic attack and active bleeding. In elderly patients > 75 years, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit [28-32].

Clinical efficacy data: The efficacy of prasugrel was demonstrated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON TIM I - 38) [33]. This was a large head-to-head, multicenter, RCT comparing prasugrel to clopidogrel in moderate to high risk ACS patients scheduled for PCI. Two - thirds of patients had UA/NSTEMI and 1/3 of patients had STEMI. Patients were randomly assigned to receive prasugrel 60 mg LD then a 10 mg daily MD or clopidogrel 300 mg LD then 75 mg daily MD for 6 - 15 months. All patients were concurrently taking aspirin therapy. Treatment with prasugrel resulted in a 19% RRR in the primary efficacy endpoint of death from CV causes, non-fatal MI, or non-fatal stroke (p < 0.0001) [33]. A significant reduction in the secondary endpoints of MI (p < 0.001), urgent TVR (p < 0.001), and stent thrombosis (p < 0.001) were also noted [33]. This study also found that in ACS patients scheduled for PCI, prasugrel therapy was associated with significantly reduced rates of ischemic events, however, mortality alone did not differ significantly [33]. Interestingly, the LD of clopidogrel was not one that is routinely used in practice unless there is a concern for bleeding in patients. Comparisons with the higher LD of clopidogrel (600 mg), has yet to be conducted.

In diabetic patients prasugrel may have also shown improved benefit when compared to clopidogrel. Several studies using multiple methods of measurement of platelet function have demonstrated

less inhibition and greater rates of poor antiplatelet response to clopidogrel among subjects with DM [34-37]. A subanalysis was conducted of the TRITON TIMI - 38 trial in diabetic patients, with a portion of those diabetics receiving insulin. In the prasugrel-exposed subjects, the primary efficacy endpoint of death from CV causes, non-fatal MI, or non-fatal stroke was reduced significantly by 14% in subjects without DM ($p = 0.02$), by 30% in subject with DM ($p < 0.001$) and by 37% in DM subjects on insulin ($p = 0.009$). Rates of MI were also reduced with prasugrel treatment by 18% in subjects without DM ($p = 0.006$) and by 40% in subjects with DM ($p = 0.02$). The net clinical benefit with prasugrel was more evident for subjects with DM ($p = 0.001$) than for subjects without DM ($p = 0.16$) [38]. These study results reveal that subjects with DM tended to have a greater response to prasugrel as compared to clopidogrel in reducing CV ischemic events. These data demonstrate that the more intensive oral antiplatelet therapy provided with prasugrel is of particular benefit to patients with DM.

Clinical safety data: The major safety endpoints in the TRITON TIMI-38 included TIMI-defined bleeding incidences; including, life-threatening bleed. Life-threatening bleed is defined as a TIMI major bleeding event that meets any of the following criteria: a) fatal, b) causes hypotension requiring treatment with intravenous inotropic agents, c) requires surgical intervention for ongoing bleeding, necessitates the transfusion of 4 or more units of blood (whole blood or PRBC) over a 48-hour period, d) is a symptomatic intracranial hemorrhage [39].

The rate of major and life-threatening bleeding in prasugrel-exposed subjects was increased by 32 % ($p = 0.03$) and 55% ($p = 0.01$), respectively. TIMI major bleeding was increased by 43% among subjects without DM on prasugrel ($p = 0.02$), however, in subjects with DM similar bleeding rates were observed between study groups ($p = 0.81$). Other adverse events observed in the TRITON TIMI-38 study in at least 3% of patients treated with prasugrel, and with similar frequency in the clopidogrel arm, included hypertension, hypercholesterolemia, hyperlipidemia, headache, back pain, dyspnea, nausea, dizziness, cough, hypotension, fatigue, and noncardiac chest pain [33].

Ticageclor

Clinical pharmacology: Ticagrelor, a cyclopentyltriazolo-pyrimidine, is a direct-acting, reversible oral antiplatelet agent. It is indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS; in patients treated with PCI it reduces the rate of stent thrombosis [40]. It has been shown to have a more rapid onset and offset of platelet inhibition compared with clopidogrel. Unlike clopidogrel and prasugrel, ticagrelor does not require hepatic activation [41-43]. Ticagrelor is highly plasma protein bound (> 99%). The elimination half-life of ticagrelor is 7 hours and 9 hours for the active metabolite. Pharmacokinetic parameters do not appear to be affected by age, gender, ethnicity, or renal impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events [40-43].

Ticagrelor is a CYP3A4/5 substrate and inhibitor, an inhibitor of the P-glycoprotein transporter, and a moderate inhibitor of CYP2C9. Due to its inhibitory effects on CYP3A4, patients receiving more than 40 mg daily of simvastatin or lovastatin 40 may be at an increased risk of statin-related adverse events. Digoxin levels should be monitored with initiation of ticagrelor or any changes in ticagrelor therapy. Ticgrelor is contraindicated in patients with intracranial hemorrhage, active bleeding and severe hepatic impairment. Ticagrelor is initiated with a 180 mg a LD then 90 mg twice daily MD after the initial LD of aspirin 325 mg, ticagrelor should be administered with a daily aspirin dose limited to 75 to 100 mg [40-43].

Clinical efficacy data: The study of Platelet Inhibition and Patient Outcomes (PLATO), was a large, multicenter, double-blind, double-dummy, RCT that compared ticagrelor to clopidogrel for the prevention of CV events in ACS patients [44-46,48-50]. Two-thirds of patients had UA/NSTEMI and 1/3 of patients had STEMI. Patients were randomized to receive a ticagrelor 180 mg LD then 90 mg twice daily MD or clopidogrel 300-600 mg LD, then 75mg MD for 12 months[44-46,48-50]. All patients were concurrently taking aspirin therapy. Treatment with ticagrelor resulted in 16% RRR in the primary end point of CV death, MI, and stroke ($p < 0.001$) with a NNT of ~53 patients [45]. Treatment with ticagrelor also resulted in lower incidences of the secondary outcomes including MI ($p = 0.005$), death from vascular causes ($p = 0.001$), death from any cause ($p < 0.001$), and stent thrombosis ($p = 0.01$) [45]. There was no difference in the incidence of stroke between the treatment and control groups ($p= 0.22$) [45]. In a prespecified sub-group analysis, there was a significant interaction between treatment and region, with less effect of ticagrelor in North America than internationally ($p = 0.045$) [46]. It was revealed that more patients in the United States (53.6%) than in the rest of the world (1.7%) took a median aspirin dose ≥ 300 mg / d, which provided the only explanation for a substantial fraction of regional interaction [46]. Results from this subanalysis revealed that in patients taking low MD of aspirin, ticagrelor was associated with statistical superiority compared with clopidogrel [46]. As a result, the drug labeling includes “black box” warning that higher than 100 mg / daily MD of aspirin may reduce the effectiveness of ticagrelor [40]. It has been postulated that high dose aspirin inhibits synergistic prostacyclin and $P2Y_{12}$ inhibition antiplatelet effects [47].

The primary composite efficacy end point of CV death, MI, and stroke was further analyzed in the two subgroups of the study: NSTEMI and STEMI [48,49]. In NSTEMI patients for whom early invasive strategy was planned, ticagrelor treatment resulted in 16% RRR in the primary efficacy endpoint ($p = 0.0025$) [48]. Ticagrelor also resulted in the reduction of the incidences of the various secondary outcomes including MI ($p = 0.0023$), CV death ($p = 0.025$), all cause death ($p = 0.013$) and stent thrombosis ($p = 0.0068$) in the NSTEMI cohort [48]. There was also no difference in stroke seen between the treatment and control groups ($p = 0.65$) in this cohort [48]. In STEMI patients, ticagrelor treatment resulted in a non-statistically significant 13% RRR in the primary efficacy endpoint ($p = 0.07$) [49]. When silent MI was excluded, ticagrelor treatment reduced the incidences of the secondary outcomes including CV death/MI ($p = 0.01$), all cause mortality ($p=0.05$), MI (0.03), recurrent cardiac ischemia (0.81, $p = 0.05$) and stent thrombosis ($p = 0.04$) [49]. However, there was an increase incidence of stroke - especially non-hemorrhagic strokes, in the STEMI cohort ($p = 0.02$) [49]. Ticagrelor was also associated with a lower rate of the primary outcome in patients with STE or new left bundle-branch block ($p = 0.07$), those undergoing CABG ($p =$

0.29), in patients with planned non-invasive management (p = 0.04) [48-50].

In a subanalysis of patients with DM or poor glycemic control, ticagrelor treatment demonstrated a trend for improved outcomes with non significant reductions of 12% in the primary composite endpoint (HR, 0.88; 95% CI, 0.76 to 1.03), 18% in all cause mortality (HR, 0.82; 95% CI, 0.81 to 1.12), and 35% in stent thrombosis (HR: 0.65, 95% CI: 0.36-1.17,) [50]. In another subanalysis of patients with impaired renal function, ticagrelor also demonstrated a trend for improved outcomes. In patients with chronic kidney disease (CKD, estimated creatinine clearance < 60 mL / min [Cockcroft - Gault]), there was a 23% reduction of primary endpoint (HR: 0.77; 95% CI: 0.65 to 0.90;) and 28% reduction in total mortality (HR, 0.72; 95% CI, 0.58 to 0.89) [52]. Ticagrelor does not seem to have as much of an impact in DM patients as does prasugrel, however may have some benefit particularly in patients with CKD.

Clinical safety data: The primary safety end points in PLATO were major bleeding, bleeding requiring red blood cell transfusion, and life-threatening or fatal bleeding. Rates of major bleeding were not different between groups (p = 0.43) [45,46,48-50]. Although incidence rates overall were low, in ticagrelor exposed patients, non–CABG-related bleeding was increased by 18% (p = 0.03), intracranial bleeding was increased by 55% (p = 0.06), and fatal intracranial bleeding rates were increased 10-fold (p = 0.02) [45,46,48-50]. In the diabetic patient subgroup there was no increase in major bleeding (p = not reported [NR]) [51]. In patients with chronic kidney disease major bleeding rates, fatal bleedings, and non-coronary bypass-related major bleedings were not significantly different between groups (p = NR) [52]. Dyspnea, nausea, insomnia, diarrhea, hypotension, syncope, and rash occurred more often in patients treated with ticagrelor than with clopidogrel or placebo. Serum creatinine and uric acid levels were also elevated with ticagrelor treatment [45,46,48-52].

Treatment Failures

Both clopidogrel and prasugrel require hepatic activation with CYP isoenzymes. While prasugrel is not as susceptible to drug interactions due to some of its pharmacokinetic features, clopidogrel use in certain patients poses a challenge. Clopidogrel is biotransformed mostly with CYP2C19, therefore in patients who are poor metabolizers, thus may result in a reduced antiplatelet effect. Poor metabolizers with ACS on clopidogrel treatment may be at higher risk of a CV event than do patients with normal CYP2C19 function [53]. The most recent published guidelines, do not recommend routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI. Genetic and platelet function testing may be used to help identify poor metabolizers who are at high risk for poor clinical outcomes. If a patient has been positively identified, treatment with an alternate $P2Y_{12}$ inhibitor such as prasugrel or ticagrelor may be a strong consideration [54].

Proton pump inhibitors (PPIs) are also metabolized by the CYP2C19 and competitively inhibit the metabolism of clopidogrel; however, the clinical significance of this interaction is unknown [55]**.** An FDA warning, recommends avoiding the combination of clopidogrel with PPIs and other inhibitors including azole antifungals: cimetidine, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine [56]. More recently published guidelines recommend against the routine use of PPIs for patients at low risk of gastrointestinal bleeding [54]. The antiplatelet effect of ticagrelor dosed according to the PLATO trial in patients deemed nonresponsive to clopidogrel and the effects of switching from clopidogrel to ticagrelor was investigated in the RESPOND study [57]. Both responders and nonresponders received either clopidogrel 600 mg LD , then MD 75 mg daily or ticagrelor 180 mg LD, then MD 90 mg twice daily for 2 weeks. All nonresponders and half of the responders switched therapy for an additional 2 weeks. Ticagrelor rapidly achieved greater platelet inhibition than clopidogrel after switching therapies. In clopidogrel nonresponders, switching to ticagrelor produced a significant decrease in platelet aggregation [57]. Adherence to antiplatelet treatment is paramount to successful long-term treatment with PCI. There are a number of factors that lead to premature discontinuation including older age, lower educational level, being unmarried, lack of discharge instruction for medication use, lack of referral to cardiac rehabilitation, preexisting cardiovascular disease, anemia, lack of health care due to cost, and high cost of medications [58,59]. Elective and non-elective surgeries may also pose a dilemma for practitioners and patients who've undergone PCI. A recently published FDA advisory recommends postponing elective surgery for 1 year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients [59].

American College of Cardiology Foundation / American Heart Assocation / Society for Cardiovascular Angiography and Intervention (ACCF / AHA / SCAI) 2011 Guideline Update

The ACCF / AHA / SCAI developed and published a new guideline specifically for PCI in early December 2011, highlighting the addition of the new oral antiplatelet agents in patients undergoing PCI [54]. In the preceding guideline, Class I recommendations included the following: loading doses of clopidogrel 300 to 600 mg or prasugrel 60mg were recommended for patients undergoing PCI; regardless of stent type, both of these agents were recommended to be given at maintenance doses for up to 12 months; and discontinuation of clopidogrel prior to CABG should be 5 days for clopidogrel and 7 days for prasugrel [60]. Class IIb recommendations state that for patients receiving DES stents that long term clopidogrel or prasugrel may be continued beyond 15 months [60]. In the current guidelines, a clopidogrel loading dose of 600 mg are recommended for all patients undergoing PCI. Ticagrelor has been added as a class I recommendation at a loading dose of 180 mg. This set of guidelines also highlights the need for patient education on the commitment DAPT compliance that would be required if undergoing PCI [44] (Table 2).

Conclusion

Prasugrel and ticagrelor are associated with greater platelet inhibition, faster onset of action, and better overall clinical outcomes compared with clopidogrel, but are associated with more non-surgery-related bleeding than clopidogrel. These agents may also have greater benefit in patients with DM. Current guideline recommendation suggest that all patients undergoing PCI should be on DAPT for a period of up to 12 months, although some patients may benefit from

Table 2: ACCF/AHA/SCAI guideline for oral antiplatelet therapy in patients undergoing PCI.

Class 1
Nonenteric aspirin 81mg to 325 mg daily should be given to patients prior to PCI (Level of evidence B)
Aspirin 81 mg to 325 mg should be continued indefinitely
Loading dose of thienopyridine should be given to patients undergoing PCI with stenting options include (Level of Evidence: A), options include : clopidogrel 600mg (ACS and non ACS patients) (Level of Evidence B); prasugrel 60 mg (ACS patients) (Level of Evidence: B); ticagrelor 180 mg (ACS patients)
Loading dose of clopidogrel should be 300 mg within 24 hours of fibrinolytics and 600 mg more than 24 hours after fibrinolytics
Clopidogrel 75 mg daily, prasugrel 10 mg daily and ticagrelor 90 mg twice daily should be given for at least 12months in all patients receiving stents during PCI for ACS (Level of Evidence: B)
Non-ACS patients receiving DES should receive clopidogrel 75 mg daily for at least 12 months for patients not at high risk for bleed (Level of Evidence: B)
Non-ACS patients receiving BMS should receive clopidogrel 75 mg should be given for a minimum of 1 month to 12 months, except in high risk bleed patients where clopidogrel can be given for a minimum of 2 weeks(Level of Evidence: B)
Class IIa
Aspirin 81 mg per day in preference to higher maintenance doses is reasonable
Early discontinuation of thienopyridine may be considered if the risk of morbidity from bleeding outweighs the benefit
Class IIb
DAPT may be continued beyond 12 months in patients receiving DES (Level of Evidence: C)
Class III
Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack (Level of Evidence:B)

extended therapy. The key to successful treatment is adherence to medication and education.

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