2015

Optimizing Antiplatelet Therapy in ACS after PCI

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Introduction

Heart disease is known to be the leading cause of death in both men and women in the United States. Coronary disease accounts for over 108 billion dollars spent, including health services provided, medications, and productivity lost (Centers for Disease Control and Prevention, 2015). Acute coronary syndrome (ACS) results from atherosclerotic plaques that line the walls of coronary arteries resulting in myocardial ischemia or infarction and account for more than 700,000 hospital admissions in this country every year (Keifer & Becker, 2009). When these plaques rupture, macrophages and pre-inflammatory mediators are released in the blood, causing activation of the clotting cascade and subsequent thrombus formation (Wright & Antoniou, 2013).

Stenting or coronary artery bypass grafting is the standard of care for repairing atherosclerotic lesions. When stenting is used, it is imperative to initiate dual antiplatelet therapy after percutaneous coronary intervention (PCI) for the prevention of stent thrombosis and increased mortality (Mrdovic et al., 2013). Clopidogrel, a thienopyridine, along with aspirin have previously been the drugs of choice for the treatment of ACS and to prevent stent thrombosis. However, the drug has drawbacks. Clopidogrel has a delayed onset of action, taking two to four hours after a six hundred milligram loading dose to achieve platelet inhibition (Wright & Antoniou, 2013). Clopidogrel is a drug that is metabolized through the hepatic cytochrome P450 pathway, therefore making it susceptible to genetic polymorphisms and drug interactions (Roffman, 2010).

The limitations of colpidogrel have brought about newer, more potent antiplatelet drugs. Prasugrel, another thienopyridine, has an advanced onset of action, causing platelet reactivity in

15 to 30 minutes (Wright & Antoniou, 2013). Ticagrelor is another P2Y12 inhibitor that is taken twice a day. However, it does not metabolize in the liver, and it reversibly bonds to platelets (Wright & Antoniou, 2013). These new antiplatelet drugs, being more potent, carry a higher risk of bleeding. With the variety of antiplatelet drugs available, the question must be asked which drug should be the drug of choice for patients after PCI. The purpose of this literature review is to investigate various research and identify which antiplatelet therapies will be more beneficial for specific patient groups so that medical therapy can be optimized after stent implantation.

Method

Search for this review was limited to articles from 2001 through 2015 using CINAHL, MEDLINE, and the Cochrane Library. The following search words were used: *antiplatelet, antiplatelet therapy, stent thrombosis, clopidogrel, prasugrel, and ticagrelor.*

Clopidogrel

Several studies were reviewed that were clopidogrel specific. One trial focused on the effects of clopidogrel and aspirin, and four trials focused on the duration and dose of clopidogrel and aspirin. In the CURE trial, a randomized, double-blind, placebo-controlled study investigated clopidogrel compared with placebo in acute coronary syndrome patients without ST-segment elevation (Yusuf et al., 2001). Patients in this study were randomized and given a loading dose of clopidogrel (300 mg orally) or a placebo followed by a daily dose of clopidogrel (75 mg orally) or a placebo for three to twelve months. An aspirin daily dose of 75 to 325 milligrams was also given during the duration of the study. In this study, clopidogrel along with aspirin was shown to significantly lower the risk of myocardial infarction and ischemia. The drug, however, was associated with an increased risk of bleeding.

The GRAVITAS trial evaluated the effects of high dose clopidogrel (600 mg loading dose followed by 150 mg daily dose thereafter) and standard dose clopidogrel (300 mg standard loading dose followed by 75mg daily dose thereafter). This randomized, double-blind, active-control trial measured the responsiveness of platelet reactivity at 12 and 24 hours after the completion of PCI with drug eluding stents (DES) with the VerifyNow assay (Price et al., 2011). The VerifyNow assay is a test used to measure the level of platelet P2Y12 receptor blockade so that high residual platelet reactivity (HRPR), also known as poor responders to clopidogrel, can be identified to help reduce the risk of an adverse cardiovascular event (Accumetrics, 2015). The study concluded that high dose clopidogrel in patients with HRPR only gave a modest reduction in platelet reactivity when compared with standard dose clopidogrel, but the higher dose of clopidogrel did not prove to reduce the rate of death from cardiovascular events (Price et al., 2011).

Three other research studies investigated the optimal duration of clopidogrel. The DES LATE trial was designed to evaluate the hypothesis that 12 month dual antiplatelet therapy with clopidogrel and aspirin was just as effective as therapy that was extended past 12 months. The trial proved that an additional 24 months of antiplatelet therapy with clopidogrel compared with aspirin alone did not lower the end point of death from cardiac causes (Lee et al., 2013). Research done by Sardella et al. (2012) compared 12 month dual antiplatelet therapy after DES implantation versus prolonged therapy (less than twelve months) after DES implantation. The results of the study showed that prolonged therapy, based on physician preference, reduced the rate of major adverse cerebro-cardiovascular events (MACCE) in patients on dual antiplatelet therapy receiving DES implantation. However, a study conducted by Poorhosseini et al. (2012) investigated dual antiplatelet therapy for the prevention of stent thrombosis in patients

undergoing PCI with DES implantation. The study showed that extended therapy was not significantly more effective than aspirin alone in the prevention of death from cardiovascular causes (stent thrombosis or myocardial infarction).

Clopidogrel's antiplatelet effect is highly variable, and the pharmacokinetics and pharmacodynamics along with known factors were examined in a study by Frelinger et al., (2013). In this study, patients were confined to the research unit for 10 days while their diet, fluid, and activity were controlled, and a genotype analysis was performed. The study showed that pharmacokinetics and pharmacodynamics varied widely despite control of diet, nicotine, and medications (including proton pump inhibitors and statins), and identifiable factors only accounted for less than around 18 percent of a variation in clopidogrel (Frelinger et al., 2013). Measured platelet reactivity accounted for 35 to 65 percent of the variation. However, the remaining variations are unclear (Frelinger et al., 2013).

Prasugrel

Prasugrel is a third generation thienopyridine that is more potent, is not affected by the CYP2C19 polymorphism like clopidogrel, and has a more rapid onset of action. The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction) showed that prasugrel versus clopidogrel significantly reduced the rate of ischemic events in patients having PCI (Wiviott et al., 2007). In this study, in a double-blind manner, patients were given loading doses of prasugrel or clopidogrel after PCI, followed by daily maintenance doses of the assigned drug. Data showed that prasugrel had a more rapid onset of action, where platelet inhibition was

achieved within 30 minutes after the drug was given with a similar peak effect as clopidogrel at six hours.

In a substudy of the TRITON-TIMI 38 trial, Salisbury et al. (2012) developed risk prediction models for major ischemic complications and bleeding after PCI as a treatment plan with clopidogrel and prasugrel. These prediction models can be implemented at the time of PCI to determine the risk of complications associated with treatment of prasugrel and clopidogrel (Salisbury et al., 2013). This model can assist clinicians in assessing patients' risks for each decision made in the treatment of ACS. The study determined that multivariable risk models can help to identify patient's risk of adverse events after PCI and allow antiplatelet therapy to be tailored based on the risk profile of each patient. For example, a young diabetic male has an 11.4 percent reduction of ischemia risk if taking prasugrel, however a 66 year old female presenting with ST-elevation has a higher risk of bleeding on prasugrel and would benefit from clopidogrel.

Since prasugrel is more potent, the risk of bleeding increases when compared to clopidogrel. Patients that are low body weight (<60 kg) are at an even greater risk for bleeding. Therefore, the FEATHER trial was designed to evaluate previous data that suggested that low dose prasugrel (5 mg) in low body weight (LBW) patients was equivalent to standard dose prasugrel (10 mg) in higher body weight (HBW) patients (Erlinge et al., 2012). The study showed that LBW patients had a higher occurrence of treatment-related bleeding than HBW patients, however, the bleeding events were minor and not significant. Laboratory data proved that platelet inhibition was not compromised in LBW patients receiving lower dose prasugrel, in fact, the maintenance dose of 5 mg in LBW patients resulted in similar high on-treatment platelet (HTPR) reactivity as HBW patients taking 10 mg maintenance dose of prasugrel.

Ticagrelor

Ticagrelor is a drug that falls into a new class of P2Y12 inhibitors called cyclopentyl-triazolo-pyrimidine (CPTP) and binds to platelets reversibly (Wright & Antoniou, 2013). The PLATO study was developed to evaluate whether ticagrelor was superior to clopidogrel in acute coronary syndrome. Results showed that ticagrelor significantly reduced the rate of death from vascular causes, myocardial infarction, and stroke when compared to clopidogrel without greatly increasing the rate of major bleeding (Wallentin et al., 2009). Patients receiving stents during the study also showed a lower incidence of stent thrombosis in the ticagrelor group. Patients in the ticagrelor group experienced more episodes of dyspnea than the clopidogrel group, however, most instances lasted less than a week.

In an analysis from the PLATO trial, Steg et al. (2013) sought to examine the effects of ticagrelor on stent thrombosis in patients from the PLATO trial having PCI. The observation showed that 147 patients in PLATO had definite stent thrombosis with the majority being men, smokers, those with previous cardiovascular disease, and diabetics. Patients were randomly assigned to a study drug, and the drug was given prior to PCI. Most of the stent thrombosis cases occurred within the first thirty days after PCI. There was no statistical difference between ticagrelor and clopidogrel in acute stent thrombosis (the first 24 hours after PCI), but ticagrelor was shown to reduce the incidence of stent thrombosis in patients within the first 30 days of PCI.

The RESPOND study was aimed at investigating the antiplatelet effects of ticagrelor (dosed according to the PLATO trial) and platelet function when switching patients from

clopidogrel to ticagrelor and vice versa (Gurbel et al., 2010). To assess clopidogrel responsiveness, patients were given 300 mg clopidogrel, and platelet aggregation was assessed at six and eight hours after dosing. The study showed that ticagrelor has greater platelet inhibition on those who are on clopidogrel and that ticagrelor overcame clopidogrel nonresponsiveness. When therapy was switched, ticagrelor was shown to have rapid platelet inhibition, but when switching to clopidogrel patients were shown to have a reduction in platelet inhibition. Ticagrelor was also shown to be highly effective in lowering the HTPR, proving that patients benefit from ticagrelor therapy.

Wallentin et al. (2013) conducted a substudy from the PLATO trial by identifying biomarkers that might identify different patient groups with different effects of ticagrelor compared to clopidogrel. The study observed these biomarkers: high-sensitivity troponin T hs-TnT), N-terminal probrain natriuretic peptide (NT-proBNP), and growth differentiation factor-15 (GDF-15) in treatment. Patients that were found to have elevated levels of hs-TnT showed a benefit of having ticagrelor over clopidogrel. The study found that the benefit of ticagrelor is correlated to the elevation of GDF-15 and NT-proBNP. With this information, treatment may be tailored to patients.

The ONSET/OFFSET study compared the onset and offset of platelet inhibition in patients using 180 mg loading dose of ticagrelor and the 600 mg loading dose of clopidogrel (Gurbel et al., 2009). This study showed that ticagrelor has a more rapid onset (observed effect within 30 minutes of loading) of antiplatelet effect than high dose clopidogrel. The antiplatelet effect was greater and better maintained for the duration of therapy with ticagrelor than with clopidogrel, and the offset of the drug occurred much more rapidly with ticagrelor than with

clopidogrel. Data was also given that bleeding risk was less in patients when therapy was terminated 48 to 120 before surgery.

Prasugrel vs Ticagrelor

Two studies investigated the newer antiplatelet drugs. In ST-elevation myocardial infarction (STEMI) patients, rapid platelet effect is imperative, so the RAPID primary PCI study was conducted to compare prasugrel and ticagrelor in STEMI patients (Parodi et al., 2013). Results showed that prasugrel was noninferior to ticagrelor two hours after the loading dose, but it took four hours to achieve a sufficient drug effect. Morphine delayed the action of prasugrel and ticagrelor.

Diabetic patients tend to have increased platelet reactivity and are usually found to be less responsive to clopidogrel (Alexopoulos et al., 2013). Alexopoulos et al. (2013) set out to evaluate the antiplatelet effect of prasugrel and ticagrelor in patients with diabetes mellitus. VerifyNow testing was used to show that ticagrelor gave patients a stronger platelet inhibition but prasugrel and ticagrelor showed an adequate treatment of HPR.

Tailoring Antiplatelet Therapy

Dual antiplatelet therapy is the treatment of choice for patients with acute coronary syndrome that have undergone PCI. Several studies were investigated to determine if tailored therapy is beneficial to patients and whether or not it is cost effective. Since hyporesponsiveness to clopidogrel after drug-eluding stent placement is predictor of stent thrombosis, research was conducted by Sharma et al. (2013) to investigate the use of platelet function testing to predict hyporesponsiveness to clopidogrel when patients present with chest pain to the emergency department. Based on platelet function assays, this study determined that diabetics and African

Americans were more likely to be platelet reactive and less likely to be respondent to antiplatelet therapy. The study concluded that patients presenting with chest pain who are currently taking clopidogrel may benefit from platelet function testing to screen for hyporesponders and nonresponders as well as identify medication noncompliance.

Tailored antiplatelet therapy in patients may be a better alternative to standard therapy with clopidogrel and aspirin after stent implantation. A large number of the population seem to have HTPR, and experience adverse events due to stent thrombosis (Li et al., 2013). Antiplatelet resistant patients were shown to have a reduced rate of stent thrombosis and death when their therapy was personalized. The study also found that patients with tailored therapy did not have an increased risk of bleeding when compared to conventional therapy in resistant patients.

The cost effectiveness of genotype-guided therapy was reviewed in two studies investigated. Patel et al. (2014) determined that clopidogrel was less costly and was less effective when compared to prasugrel and genotype-guided therapy. Clopidogrel was found to be cheaper but may not be appropriate due to drug interactions, genetic polymorphisms, and delayed onset of action. It was determined that genotyping therapy is cost effective when compared with clopidogrel and prasugrel, but when genotype therapy is not available, clopidogrel is less costly. Patient characteristics and economic conditions should be considered when selecting antiplatelet therapy (Patel et al., 2014). Kazi et al. (2014) evaluated the cost-effectiveness of genotype-guided therapy after stent implantation in ACS patients where clopidogrel, prasugrel, and ticagrelor along with genotype-guided strategies were used. Direct medical costs (inpatient admissions, procedures, outpatient visits, and drugs) and cost associated with complications, loss of wages and caregiver costs were assessed when determining cost-effectiveness. They confirmed that genotyping patients with CYP2C19 alleles and those that are

clopidogrel non-responders is an economically attractive option, but treating all patients with ticagrelor may be a better alternative and economically reasonable.

Results

Aspirin and clopidogrel are accepted as the regimen of choice in patients with acute coronary syndrome after PCI. The CURE trial showed that clopidogrel, along with aspirin, significantly reduces the risk of death from cardiovascular causes (Yusuf et al., 2001). Treatment with high dose clopidogrel (600 mg loading dose and 150 mg thereafter) in patients with HTPR is not necessary. The GRAVITAS trial proved that standard dose clopidogrel (300 mg loading dose and 75 mg thereafter) was equal to high dose clopidogrel, and high dosing did not reduce the incidence of death from cardiovascular events, myocardial infarction, or stent thrombosis (Price et al., 2011). Prolonging therapy with clopidogrel and aspirin for longer than twelve months did not significantly reduce adverse cardiac events and may increase the risk for bleeding (Lee et al., 2013; Poorhosseini et al., 2012). Various factors contribute to the variability of platelet inhibition with clopidogrel and despite controlling diet, medication compliance, nicotine, the pharmacokinetics and pharmacodynamics still had significant differences (Freelinger et al., 2013).

The TRITON-TIMI 38 trial was designed to compare prasugrel and clopidogrel in patients with acute coronary syndrome. Wiviott et al. (2007) proved that prasugrel was better at reducing the rates of stent thrombosis when compared to clopidogrel but it increased bleeding rates. The FEATHER trial showed that prasugrel dosing should be reduced in patients under 60 kilograms (from 10 mg daily to 5 mg daily) to reduce bleeding in low body weight patients. Evidence shows that this does not reduce the amount of platelet inhibition (Erlinge et al., 2012).

It should also be noted that the use of prasugrel is contraindicated in patients with a history of previous stroke or TIAs and is not recommended for patients over the age of 65 years of age.

Ticagrelor is a new non-thienopyridine drug that is reversible and provides faster platelet inhibition. The PLATO study compared clopidogrel with ticagrelor and showed that ticagrelor significantly reduced the risk of cardiac events and death from vascular causes when compared to clopidogrel but did increase the incidence of bleeding (Wallentin et al., 2009). Storey et al. (2013) pinpointed stent thrombosis, showing that ticagrelor reduced the incidence of stent thrombosis in ACS patients following PCI when compared to clopidogrel. A substudy from the PLATO trial by Wallentin et al. (2014) determined that hs-TnT, NT-proBNP, and GDF-15 can be predictors of adverse cardiac events such as cardiovascular death, myocardial infarction, and stroke. The RESPOND study showed that ticagrelor overcomes clopidogrel nonresponsiveness and has a better antiplatelet effect in patients previously treated with clopidogrel that are switched to ticagrelor (Gurbel et al., 2010). The ONSET/OFFSET trial proved that ticagrelor has a faster antiplatelet effect than clopidogrel and a shorter duration after discontinuation (Gurbel et al., 2009).

Both prasugrel and ticagrelor are new generation antiplatelet drugs that have proved to be superior to clopidogrel. The RAPID PCI study tested the effects of prasugrel and ticagrelor, and both drugs proved to be equal in platelet reactivity. Both drugs showed that they needed at least four hours for optimal effect in ST-elevated patients (Parodi et al., 2013). Alexopoulos et al. (2013) found that both prasugrel and ticagrelor provided adequate platelet inhibition in HPR patients, but ticagrelor achieved a much greater platelet inhibition in diabetic patients that had previously been treated with clopidogrel and had previously undergone stent implantation.

There is a large percentage of the population that does not respond to platelet inhibition from clopidogrel. Nonresponders are more likely to be African American and diabetic (Sharma et al., 2013). Tailored antiplatelet therapy has proven to be associated with a reduced rate of stent thrombosis and adverse events without adversely effecting bleeding risks (Li et al., 2014). Genotype-guided antiplatelet therapy has shown to be cost-effective and may improve the cost effectiveness of prasugrel and ticagrelor (Patel et al., 2014; Kazi et al., 2014). However, ticagrelor across the board may be a more cost effect treatment for ACS patients undergoing PCI (Kazi et al., 2014).

Conclusion

Clopidogrel is an acceptable and proven strategy for preventing stent thrombosis in patients with ACS receiving PCI and continue to be used as a cost effective treatment. However, the new generation antiplatelet agents prasugrel and ticagrelor have shown to be more potent and produce a more rapid onset of platelet inhibition, especially in individuals with the reduced function allele CYPC19, in African Americans, and in those with diabetes mellitus. Tailored antiplatelet therapy is a cost-effective way to optimize outcomes and reduce adverse cardiac events. Ticagrelor is a more superior option because of its reversibility and faster onset of action, but the twice a day dosing may cause noncompliance.

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