Evaluating the duration of dual antiplatelet therapy in ACS patients post-PCI: A literature review

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ABSTRACT

Background

Acute coronary syndrome (ACS) patients who undergo percutaneous coronary intervention (PCI) with stents require downstream dual antiplatelet therapy (DAPT) to reduce the rates of stent thrombosis and ischemic events.(1) According to multiple guidelines, this is recommended for 1 year.(1–3) The use of dual antiplatelet therapy longer than 1 year is still debatable on whether the benefits of ischemic protection outweigh the risks of bleeding.

Objective

To evaluate randomized controlled trials (RCT) that assess downstream prolonged dual antiplatelet therapy (>12 months) in acute coronary syndrome patients treated with PCI and drug-eluting stents (DES).

Methods

A literature review by utilizing an online PubMed database for randomized controlled trials was conducted. Keywords used were "dual antiplatelet therapy" "dual antiplatelet treatment" "drug-eluting-stent". Only studies conducted in the last 15 years that met the inclusion criteria were chosen. A total of 5 randomized controlled trials were selected for review.

Results

One of the 5 RCT determined that prolonged dual antiplatelet therapy (>12 months) significantly reduces the rates of major cardiovascular events (MACE) such as all-cause mortality, myocardial infarction (MI), and cerebrovascular accident (CVA), as well as significantly reduces rates of stent thrombosis.(4) However, 3 of the 5 RTC determined that

prolonged dual antiplatelet therapy will significantly increase the rates of moderate to severe bleeding in patients.(4–6)

Conclusion

ACS patients who undergo PCI with drug-eluting stent implantation can benefit from the use of prolonged dual antiplatelet therapy to reduce major cardiovascular events, however, this would be at the cost of moderate to severe bleeding. More large scale RCT with longer follow-up are needed to determine the definitive duration of prolonged dual antiplatelet therapy.

INTRODUCTION

Ischemic heart disease is the second leading cause of death in Canada, so as physician assistants there is a high probability that we will have patients whose health is impacted by coronary artery disease (CAD)(7). There is currently high prevalence of CAD in men than women, however women ages 45 to 75 are approximately 30 times more likely to die from an acute myocardial infarction than men(8). Overall, heart disease is the leading cause for hospitalization in Canada and the federal government spends over $20 billion a year on treating cardiac patients.(8,9) Patients with ACS who undergo percutaneous coronary intervention will be prescribed by their cardiologist dual antiplatelet medications to prevent recurrent thrombotic events. This is reflected in the 2018 Canadian Cardiovascular Society (CCS) guidelines that recommend the 1-year duration of dual antiplatelet therapy(1). The beneficial use of antiplatelet medications has prompted researchers to evaluate if treatment exceeding 1 year will reduce late stent thrombosis, myocardial infarction, and revascularization. Unfortunately, increase use of antiplatelet medications will predictably increase the risk of bleeding in patients. Currently, the CCS guidelines have not set a definitive timeline for dual antiplatelet therapy exceeding 1 year in ACS patients with PCI. Ultimately, this review will examine the rates of cardiovascular events and bleeding incidences of ACS patients post-PCI on dual antiplatelet therapy for >1 year versus a shorter duration.

BACKGROUND

The most common cause of ischemic heart disease is from the rupture of an unstable atherosclerotic plaque in the coronary arteries leading to thrombus formation.(10) Plaque is made of lipoproteins, a fibrous cap, and inflammatory cells found in the intimal of the arteries.(11) Once this plaque ruptures it causes a cascade of events leading to recruitment, activation, and aggregation of platelets creating fibrin-rich thrombus.(10) The narrowing of the

coronary artery due to the formed thrombus results in decreased blood flow to the heart causing an imbalance of oxygen supply and demand(11). This results in ACS which represents life-threatening events such as unstable angina, non-ST segment elevation myocardial infarction, or ST-segment elevation myocardial infarction.(11) On the other hand, a dislodged thrombus can also decrease blood supply to the brain resulting in a stroke.(11) The primary management of a serious myocardial infarct requires revascularization by percutaneous coronary intervention or coronary artery bypass graft.(10) In percutaneous coronary intervention, a catheter and guidewire are inserted into the radial or femoral artery and fed through the arterial vasculature until it reaches the heart.(12) From there a balloon is inflated in the stenotic artery allowing a stent to be implanted, therefore opening up the artery to increase perfusion to the myocardial cells.(12) After stent placement, a possibility of re-occlusion of the culprit vessel can occur resulting in stent thrombosis and MI.(12) Thus, the use of dual antiplatelet therapy is needed to prevent clot formation and ischemic events. Initially, bare-metal stents (BMS) and early DES had high rates of restenosis and stent thrombosis, but with improved widely adopted newer DES the rates of stent thrombosis are now rare.(13)

ANTIPLATELET DRUGS

Dual antiplatelet therapy is the combination of an oral P2Y12 inhibitor plus aspirin, and as mentioned has been extensively studied in ACS patients undergoing PCI(14). Aspirin works by irreversibly inhibiting cyclooxygenase synthase, an enzyme that presents in two forms known as COX-1 and COX-2.(14) The interaction with the enzymes is dose-dependent, for instance, a low dose like “baby aspirin” (81 mg) can inhibit COX-1, while a higher dose of aspirin can inhibit both COX-1 and COX-2.(14) This is relevant since COX-1 regulates platelet and clotting effects, while COX-2 is associated with inflammatory and pain responses in the body.(14) The

majority of aspirin is absorbed through the stomach and binds to COX-1 and COX-2 which prevents the conversion of arachidonic acid to prostaglandin H.(14) The prostaglandin H substrate is needed to create a platelet activator known as thromboxane A_2.(14) In the end, through a cascade of processes, aspirin inhibits thromboxane A_2 preventing platelet activation and thrombus formation.(14)

The $P2Y_{12}$ inhibitors focused on this review are clopidogrel, prasugrel, and ticagrelor. Their mechanism of action works by binding to the $P2Y_{12}$ receptor on the platelet and inhibiting ADP activation preventing thrombus formation(14). These $P2Y_{12}$ inhibitors differ slightly from each other, for example, clopidogrel is a second-generation medication in the thienopyridine drug class.(14) It is a prodrug requiring two-step oxidation in the hepatocytes of the liver utilizing CYP isoenzymes such as CYP219.(14) Furthermore, it is an irreversible $P2Y_{12}$ inhibitor that is dose-dependent and takes up to 10 days for patients to return to baseline platelet reactivity once it is discontinued.(14) Meanwhile, prasugrel is a third-generation thienopyridine and a more potent antiplatelet medication. It is also a prodrug that irreversibly inhibits $P2Y_{12}$ receptor and is metabolized in the liver. A major difference from clopidogrel is that prasugrel only requires single-step oxidation by the CYP isozymes in the liver.(14) Lastly, ticagrelor is from a new drug class known as cyclopentyltriazolopyrimidines and reversibly inhibits $P2Y_{12}$ receptor with a fast onset of action and potent antiplatelet effect.(14) It is different from the other drugs since it does not require the liver to be activated, and it immediately inhibits platelets once absorbed through the stomach.(14) Also, ticagrelor has reversible inhibition requiring 2 doses daily, whereas clopidogrel and prasugrel have irreversible inhibition requiring 1 dose daily.(14)

GUIDELINE RECOMMENDATIONS

According to the 2018 Canadian Cardiovascular Society, 2016 American Heart Association (AHA), and 2017 European Society of Cardiology (ESC) guidelines approximately 1-year duration of DAPT is needed in ACS patients after PCI to reduce rates of cardiovascular events(1–3). For extended DAPT use the CCS guidelines states that DAPT >1 year may be favorable in high-risk ACS patients undergoing PCI, and ranks this level of evidence as a "strong recommendation".(1) These high-risk individuals include prior MI or stent thrombosis, current smokers, diabetics, chronic kidney disease, multiple coronary lesions or left anterior descending lesions(1,2). On the other hand, the AHA and ESC guidelines state that extended DAPT "may be reasonable/considered" in the same patient population but individuals must be at low risk for bleeding complications (2,3) Thus, patients who are at high risk for bleeding should avoid prolonged DAPT include: >75 years old, low body weight, anemic, previous bleeding events or coagulopathies, regular non-steroid anti-inflammatory drug use, chronic steroid use, or require oral anticoagulants.(1) The AHA and ESC guidelines rank prolonged dual antiplatelet therapy in ACS patients with PCI a class of recommendation IIb which is slightly lower than the CCS guidelines.(2,3) This is due to the lack of consensus on the efficacy of prolonged DAPT.(2,3) However, one statement that AHA, ESC, and CCS guidelines all agree on is that ticagrelor is the preferred $P2Y_{12}$ inhibitor over clopidogrel in ACS patients.(1–3) Furthermore, all 3 guidelines emphasize the need for personalized medicine when evaluating the prolonged use of dual antiplatelet therapy in each patient.(1–3)

OBJECTIVE

This literature review aims to evaluate randomized controlled trials for a prolonged duration of DAPT in post-PCI patients with ACS. Besides, discuss available online clinical tools

to help primary care clinicians determine the risk and benefit of prolonged DAPT in ACS patients.

METHODS

INCLUSION CRITERIA

The primary question for this literature review was evaluating the extended duration (>1 year) of dual antiplatelet therapy in ACS patients post-PCI. This included studies that met the following criteria: 1) prospective randomized controlled trials in multiple centres; 2) published in English; 3) Adult ACS and CAD patients who had PCI with DES implantation that occurred ≤12 months; 4) downstream use of DAPT defined as clopidogrel, prasugrel, or ticagrelor in addition to aspirin given after PCI with stenting; 5) studies that examined DAPT duration of >12 months; For example studies evaluating patients who were started on DAPT upstream (prior to PCI), or selected based on a myocardial infarction that occurred >1 year ago were excluded from the review.

PRIMARY OUTCOME MEASURES

The primary outcome measured was major adverse cardiovascular events defined as a composite of all-cause mortality, myocardial infarction, or cerebrovascular accident such as stroke. Secondary outcomes of interest included stent thrombosis or urgent revascularization. The primary safety outcome was moderate to severe/major bleeding, or fatal bleeds defined by Thrombolysis in Myocardial Infarction (TIMI), Global Use of Strategies to Open Occluded Arteries (GUSTO), Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients: an International Randomized Evaluation (STEEPLE), or International Society on Thrombosis and Hemostasis (ISTH) bleeding criteria. The intervention evaluated was the

prolonging of dual antiplatelet therapy duration by >12 months with the use of the comparator group defined as aspirin preferably with a placebo.

SEARCH STRATEGY

A search was completed using the PubMed database with filters for: randomized controlled trials from 2004 to 2019, conducted on humans, in adults ≥19 years old, and written in English. The search words utilized for the preliminary query were "dual antiplatelet therapy" "dual antiplatelet treatment" "drug-eluting-stent".

A total of 151 randomized controlled trials were retrieved from the search, and 136 out of 151 were immediately excluded since they did not meet inclusion criteria. Next, the abstract of 15 RCT was screened that led to 12 out of 15 being reviewed in full-text. Some of the RCT were excluded due to a variety of reasons like the use of dual antiplatelet therapy before PCI and the exclusion of all acute coronary syndrome patients. Finally, 5 RCT met the inclusion criteria and were selected for review (Figure 1.)

DATA EXTRACTION

The following data were extracted from the articles: year of publication, patient population, number of patients in DAPT and monotherapy aspirin group, type of $P2Y_{12}$ inhibitor used, duration of DAPT, follow-up timeline, primary outcome rates, secondary outcome rates, and bleeding event rates. (Table 1.)

RESULTS

SEARCH RESULTS

The 5 studies selected were DAPT, PRODIGY, ARTIC-Interruption, OPTIDUAL, and DES-LATE, and were completed from 2012 to 2016.(4–6,15,16) All studies utilized multiple

sites to evaluate data from 19,620 patients who completed PCI <12 months before randomization. (4–6,15,16) The population for each cohort ranged from 624 to 5020 and were pooled from the United States(4), Europe(4–6,16), Korea(15), and New Zealand(4). Four out of the 5 studies, ARCTIC-Interruption, PRODIGY, DES-LATE, and OPTIDUAL were open-labeled and evaluated the outcomes for patients with prolonged dual antiplatelet therapy from 18, 24, 24, and 48 months respectfully.(5,6,15,16) While only the DAPT trial was double-blinded with placebo and assessed outcomes for patients on dual antiplatelet therapy at 30 months.(4) Drug-eluting stents were the most common stent used.

ELIGIBILITY CRITERIA

The patient eligibility criteria were similar in each study. It included acute coronary syndrome patients over 18 years old who received a DES in 12 months or were indicated to receive a DES based on ≥1 coronary lesion with >50% stenosis of standard artery ≥2.25mm diameter.(4–6,15,16) Patients were given downstream dual antiplatelet therapy for at least 12 months as recommended by the guidelines, and during this time must have no cardiovascular events, stent thrombosis or bleeding incidences. The PRODIGY study varied from the other studies, as it included shortened dual antiplatelet therapy of 6 months or even 1 month if patients were implanted with a bare-metal stent.(5) Patients who were excluded from the studies were individuals with: poor life expectancy of >1 to 3 years, contraindications to antiplatelet therapy, gastrointestinal ulcers, bleeding disorders, pregnant, upcoming surgeries requiring DAPT cessation, or on anticoagulants. Another notable exclusion was that the ARTIC-Interruption study excluded ST-segment elevation myocardial infarction patients from enrollment.(6)

DESCRIPTION OF STUDIES

The most informative RCT in this review was the double-blind DAPT study by Mauri et al.(4) This trial evaluated 9,961 ACS and CAD post-PCI patients with DES implantation who were given dual antiplatelet therapy of clopidogrel or prasugrel with aspirin for the recommended standard 12-months. Patients were then randomized and double-blinded into two cohorts. One cohort was assigned continued DAPT for 18-months, while the second cohort had their DAPT immediately discontinued and given a placebo with aspirin. The total duration of treatment downstream from PCI was 30-months in both cohorts. For follow-up patients were reassessed 3 months after their therapy was discontinued to determine if any outcomes occurred from stopping the dual antiplatelet therapy.

The results of Mauri et al study showed that the 30-month DAPT provided a significant decrease in major cardiovascular events of 4.3% versus the standard 12-month DAPT with 5.9% ($P<0.001$). This was driven by a significant reduction in myocardial infarction in the longer DAPT group with a 2.1% decrease versus 4.1%($P<0.001$). Moreover, stent thrombosis was significantly reduced in the prolonged dual antiplatelet therapy by 0.4% versus the standard therapy of 1.4% ($P<0.001$). In contrast, there was a significant increase in death for the prolonged dual antiplatelet therapy group by a difference of 0.5% ($P<0.002$). As for the safety outcomes, a significant increase in GUSTO bleeding occurred in the extended dual antiplatelet therapy by 2.5% versus 1.6 % by standard DAPT ($P=0.001$). This was driven by moderate bleeding with a 0.7% ($P=0.004$) difference between the 30-month versus 12-month dual antiplatelet therapy groups. It was noted that both groups did not show a significant difference in severe fatal bleeds ($P=0.15$).

The second randomized controlled trial reviewed was PRODIGY by Valgimigli et al and conducted in Italy.(5) Approximately 1,970 post-PCI patients with DES and BMS implantations

were randomized into a 4 by 2 factorial open-labeled study. Initially, ACS patients were separated based on stent type inserted then randomized into two cohorts using DAPT of clopidogrel plus aspirin. One cohort was given downstream short-DAPT at 6-months while the other cohort was given prolonged-DAPT at 24-months. Patients who had implanted BMS and stable CAD were allowed to discontinue their 6-month DAPT to an even shorter period of <1 month.(5) The follow-up for the trial occurred at 1 month, then every 6 months for the full 2 years of therapy.

The results of the Valgimigli et al study determined that there was no significant difference in primary outcomes of MACE between short and prolonged dual antiplatelet therapy (10.0% versus 10.1%, P=0.91), and no significant difference in rates of stent thrombosis in either cohort (P=0.53). However, there was a significant increase in safety outcomes of TIMI major bleeding of 1.6% for 24-month DAPT versus 1.0% in the short-DAPT cohort (P=0.041).

The third randomized controlled trial reviewed was a Korean open-labeled study called DES-LATE by Lee et al.(15) It enrolled 5,045 acute coronary syndrome patients who recently had PCI with drug-eluting stent implantation and on dual antiplatelet therapy of clopidogrel plus aspirin for 1 year. If the enrolled patients had any cardiovascular or bleeding events during this period they were excluded from the randomization step in the trial. One group was assigned continued DAPT for another 12 months which made 24-months in total on DAPT, while the second group had their clopidogrel immediately discontinued. The baseline characteristics of the study were equivalent in both groups, however, there was a slight 3.4% increase in patients with multiple vessel disease in the dual antiplatelet therapy group.(15)

The results of the Lee et al study determined no significant difference in primary outcomes of major cardiovascular events for 24-month versus 12-month DAPT (2.4% vs 2.6%, P=0.75). Similarly, there was no significant difference in TIMI major bleeding between the two cohorts (1.4% vs 1.1%, P=0.20).

The fourth study was ARTIC-Interruption by Collet et al which was completed in France.(6) A total of 1,259 patients post-PCI with DES placement were on downstream DAPT of clopidogrel or prasugrel with aspirin for 1 year, and then randomized into two groups. One group was continued on DAPT for an additional 6-months and the second group had clopidogrel or prasugrel discontinued. As mentioned the trial looked at ACS patients but excluded ST-segment elevation myocardial infarction patients.(6)

The results of Collet et al determined that both cohorts experienced a primary outcome of major adverse cardiovascular events of 4%, however, statistical significance was never reached (P=0.58). On the other hand, there was a significant increase in STEEPLE bleeding in the prolong DAPT group with 12 patients (2%) experiencing events versus the discontinued DAPT group only had 3 patients (1%) with bleeding incidences (P=0.04).

The final randomized controlled trial reviewed was another open-labeled trial from France called OPTIDUAL by Helft et al.(16) The study looked at 1,385 ACS and CAD post-PCI patients with DES insertion and were on DAPT (clopidogrel and aspirin) for at least 1 year without any cardiovascular or bleeding events. These patients were then randomized into two cohorts, one with aspirin monotherapy and the other with continued DAPT for an additional 36 months. This totaled 4 years on dual antiplatelet therapy post-PCI for the prolonged cohort.

The results of the OPTIDUAL trial determined no significant difference in major cardiovascular events (P=0.17), and no significant difference in bleeding events between the prolonged and short DAPT cohorts(P=0.95).

All values were recorded in Table 1.

DISCUSSION

PRIMARY OUTCOMES

Overall out of the 5 randomized controlled trials reviewed, only the Mauri et al trial was able to determine significant findings on the benefits of prolonged DAPT. For example, maintaining dual antiplatelet therapy for 30 months decreased the rates of all-cause mortality, myocardial infarction, and stroke.(4) As mentioned the primary outcome was driven by decreasing myocardial infarction rates by 2% in the extended DAPT group.(4) (Figure 2.)

Although the Mauri et al study had patient characteristics that were fairly balanced in both cohorts, it was noted that 111 patients were diagnosed with cancer in the extended DAPT group in comparison to 65 patients in the placebo group(17). The study noted that these patients were not diagnosed with cancer before enrollment. Thus, the higher number of cancer patients in the extended DAPT group would have influenced the significant increase in non-cardiovascular death (P<0.002).(4) Therefore, it would have been advantageous to get a thorough family medical history detailing cancer as one of the variables before randomization.

Interestingly, another outcome from the DAPT study was that during the 3-month observational period after clopidogrel or prasugrel was discontinued, there was an increase in stent thrombosis by 1% (P<0.001%).(4) (Figure 3.) Evidence has shown that first-generation DES had high rates of stent thrombosis, but with second-generation DES being the preferred

device now, these rates have decreased and are presently a rare occurrence(18). A study known as the PARIS registry evaluated the rates of cardiovascular events after stopping $P2Y_{12}$ inhibitors, and a determined majority of stent thrombosis occurred in the first 6-months after DES implantation while patients were actually on dual antiplatelet therapy.(19) Given that the rates of stent thrombosis are low with the popular use of second-generation DES, and the likelihood that stent thrombosis will occur in the first 6-months after PCI, one can conclude that the use of DAPT >12 months would not be beneficial to prevent stent thrombosis. But although the risk of stent thrombosis is low, it is still fatal and prolonged DAPT needs to be carefully assessed.(14) (Figure 4)

BLEEDING OUTCOMES

As for safety outcomes 3 out of 5 trials, DAPT, PRODIGY, and ARTIC-Interruption, all resulted in statistically significant increased bleeding rates for the prolonged dual antiplatelet therapy arms (4–6).(Figure 3). These rates all ranged from moderate to severe bleeding incidences while none of these studies had significant fatal bleeding events.(4–6). There is overwhelming evidence that prolonged DAPT causes increased bleeding risk.(1) It is important to note that for ethical considerations all 19,620 patients from the 5 studies did not have any bleeding events before being randomized for prolonged DAPT use.

Another factor influencing bleeding rates were the type of bleeding criteria used. Various bleeding definitions such as GUSTO, TIMI, ISTH, and STEEPLE were used and because of the multiple definitions discrepancies in results can occur(20). The PRODIGY and DES-LATE used the TIMI bleeding definition which defines events related to hemoglobin value drops instead using a clinical assessment of the patient.(5,15,20) For example, a TIMI major bleeding is considered when hemoglobin decreases by >5 g/dl.(20) Thus, the timing of the hemoglobin

drop may not have occurred due to dual antiplatelet therapy(20), but possibly due to other causes like anemia of chronic disease or hemolysis. On the other hand, the DAPT study used GUSTO bleeding criteria that heavily used clinical assessments for bleeding events.(4,20) For instance, a GUSTO moderate bleed is recorded if a blood transfusion is needed but without any hemodynamic changes in the patient.(20) Therefore the bleeding outcomes may not be consistent among the sites in each trial since it is based on the physician's assessment which can vary due to clinical experience, regional practices, and their threshold for the use of blood transfusions.(20) Overall, an internationally adopted bleeding definition is needed for a concise study of prolonged DAPT to compare outcomes from different trials. In the end, it is important to balance hemoglobin lab values and take into account clinical assessment when evaluating a patient for prolonged DAPT.

A second factor that influences bleeding is the type of vascular access site used during PCI which none of the RCT commented on. Vascular access sites are relevant since they have changed rates of major cardiovascular events and bleeding outcomes for ACS patients who underwent PCI.(21) According to the MATRIX trial, patients who had radial access sites had significantly lower rates of major bleeds compared to femoral access sites during PCI.(21) Therefore, if more femoral sites were used in patients from the prolonged DAPT cohort than that factor would increase the rates of adverse events. Thus, it would have been informative to remark on the percentage of patients who had radial versus femoral access in each of the studies.

Moreover, a third factor that alters bleeding outcomes was the utilization of proton-pump inhibitors which are a common treatment for gastrointestinal bleeds.(22) ACS patients are prescribed lifelong aspirin to reduce mortality rates, however, aspirin can put patients at a higher risk of gastrointestinal bleeds.(22) This results in treatment with proton-pump inhibitors like

omeprazole to reduce the rates of hemorrhage.(3) The AHA and ESC guidelines both give use of proton pump inhibitors in patients with dual antiplatelet therapy a class of recommendation I.(2,3) Proton-pump inhibitors and clopidogrel compete for the same CYP2C19 hepatocyte isoenzyme for metabolization, therefore it is proposed that the use of proton-pump inhibitors may reduce the efficacy of clopidogrel but was only determined in pharmacological studies and not through randomized controlled trials.(3) Only 3 out of the 5 randomized controlled trials, ARTIC-Interruption, PRODIGY, and OPTIDUAL, included proton-pump inhibitor usage in baseline patient characteristics.(5,6,16). Overall, due to strong guideline recommendations, this warrants the tracking of proton-pump inhibitors usage in each cohort as it would affect bleeding rates.

PATIENT POPULATIONS

The randomized controlled trials selected for this review had enrolled a low-risk ischemic patient population and would have altered MACE outcomes. This was done by excluding individuals who had a cardiovascular ischemic event during the first 12-months after PCI.(6) Moreover, ARTIC-Interruption excluded patients who had a prior ST-segment elevation myocardial infarction.(6) Nonetheless, it is important to remark all the studies included patients who had comorbidities that would increase their risk of atherosclerotic events such as diabetes, current smokers, hypertension, and hyperlipidemia(1).

Another interesting factor about patient populations was the DES-LATE trial had selected an Asian patient population. Utilizing a Korean patient population may have altered the incidences of MACE to show no significant difference between the two groups regardless of the beneficial use of prolonged DAPT against cardiovascular events (2.4% vs 2.6%, P=0.75).(15) Multiple studies have shown there is a high rate of clopidogrel-resistance in Asian populations

that can reach up to 70% versus a range from 4% to 55% in a Western population.(23) This is due to genetic polymorphisms in the CY2C19 hepatic isoenzyme that is used to metabolize clopidogrel to its active form(23). Furthermore, other evidence has shown that patients with a CY2C19 polymorphism are 3 times more likely to have increased rates of stent thrombosis. (2.6% vs 0.8%, P=0.02).(23) Also, these polymorphisms can significantly increase MACE by 53% (P=0.01).(24) Hence, the Asian population may have increased the rates of cardiovascular events in the prolonged DAPT cohort in the DES-LATE trial. Therefore being cognizant of genetic variations in individuals is important when assessing the efficacy of $P2Y_{12}$ inhibitors in the use of prolonged DAPT.

TRIAL DESIGN

Regrettably, PRODIGY, DES-LATE, ARTIC-Interruption, OPTIDUAL were all underpowered thus the results from these studies were unreliable and possibly due to chance. For instance, the reason for the small patient population in the OPTIDUAL trial was due to financial issues from a lack of funding which resulted in slow patient enrollment.(16) Another limitation in the trial design is that these 4 out of the 5 RCT were open-labeled and did not use a placebo in the short DAPT cohort. This would have created bias in the patients and physicians conducting assessments during follow-up.

Furthermore, there were issues with adherence in the trial design. The PRODIGY trial had inconsistency in the duration of the 6-month DAPT cohort, since individuals with BMS and stable ischemic heart disease were allowed to discontinue clopidogrel early at 1-month based on the physician's recommendation and guidelines(2,5) Consequently, the altering of the short-DAPT duration to 1-month would have decreased the risks of bleeding in that cohort. Besides, the DES-LATE trial also had adherence issues in both cohorts. For instance, the prolonged

DAPT group only had a 79.4% adherence rate to the clopidogrel plus aspirin regimen. While 8.1% of patients in the monotherapy aspirin group ended up taking dual antiplatelet therapy instead of adhering to their aspirin only treatment.(15) In the end, not adhering to the study medications can alter the outcomes that are being monitored.

Another design issue was the selection of $P2Y_{12}$ inhibitor prescribed in the dual antiplatelet therapy cohorts. All 5 of the randomized controlled trials in this review, DAPT, PRODIGY, OPTIDUAL, DES-LATE, and ARTIC-Interruption only included patients on clopidogrel or prasugrel. The selection of antiplatelet medication is not in line with the contemporary practice of $P2Y_{12}$ inhibitors since according to the CCS, AHA, and ESC guidelines ticagrelor is the preferred agent for ACS patients undergoing PCI(1–3). This was determined by an RCT known as PEGASUS-TIMI 54 that evaluated prolonged dual antiplatelet therapy using ticagrelor.(25) This trial was excluded from this review because the patients were enrolled if they had a prior myocardial infarction within the last 3 years.(25) Whereas this review only looked at studies where ACS patients recently underwent PCI in the last 1 year.

Another trial design limitation was the follow-up timeline. As previously mentioned, the rates of stent thrombosis slightly increased following cessation of dual antiplatelet therapy in the DAPT trial and were determined by the 3-month follow-up.(4) Three out of the 5 randomized controlled trials, OPTIDUAL, DES-LATE, and PRODIGY, had no additional follow-up with patients once the dual antiplatelet therapy was discontinued. It would have been informative to add another 3-month surveillance to evaluate if stent thrombosis occurred after the discontinuation of dual antiplatelet therapy similar to the DAPT trial.

CLINICAL RESOURCES

Online calculators are available to help clinicians assess the benefit-to-risk ratio of dual antiplatelet therapy including prolonged therapy (>12 months).(1) These calculators are called PRECISE-DAPT, DAPT score, and CALIBER.(26–28) Each differs based on the required information of patient variables needed to calculate risks. For example, the PRECISE-DAPT score requires values of hemoglobin, white blood cell count, and creatinine clearance.(26) While the CALIBER score requires information on prior ischemic events, anemia, and smoking history.(28) On the other hand, the DAPT score requires the diameter of the stent and history of peripheral artery disease.(27) All 3 calculators have obvious limitations such as the PRECISE-DAPT and CALIBER scores do not take into account procedure characteristics like the type of stent used in PCI, while the DAPT score does not assess patients on ticagrelor or take into account history of bleeding incidences.(1) Furthermore, no prospective randomized controlled trials are assessing the validity of dual antiplatelet risk score calculators.(1,3) Hence, calculators are an additional tool to help with the assessment of prolonged DAPT but should not be the main decisive factor.

CONCLUSION

In summary ACS patients who undergo PCI with stent implantation can benefit from the use of prolonged DAPT to reduce major cardiovascular events, however, this would be at the cost of moderate to severe bleeding trade-off. Although there is over a decade of research on DAPT, it remains a debatable topic. One point every clinician can agree on is that the benefit-to-risk ratio of DAPT must be assessed on a case-by-case basis. With new devices and medications entering the field of cardiology, more large scale randomized controlled trials and research is needed to assess the optimal duration of dual antiplatelet therapy.

FIGURES AND TABLES

FIGURE 1. STUDY SELECTION

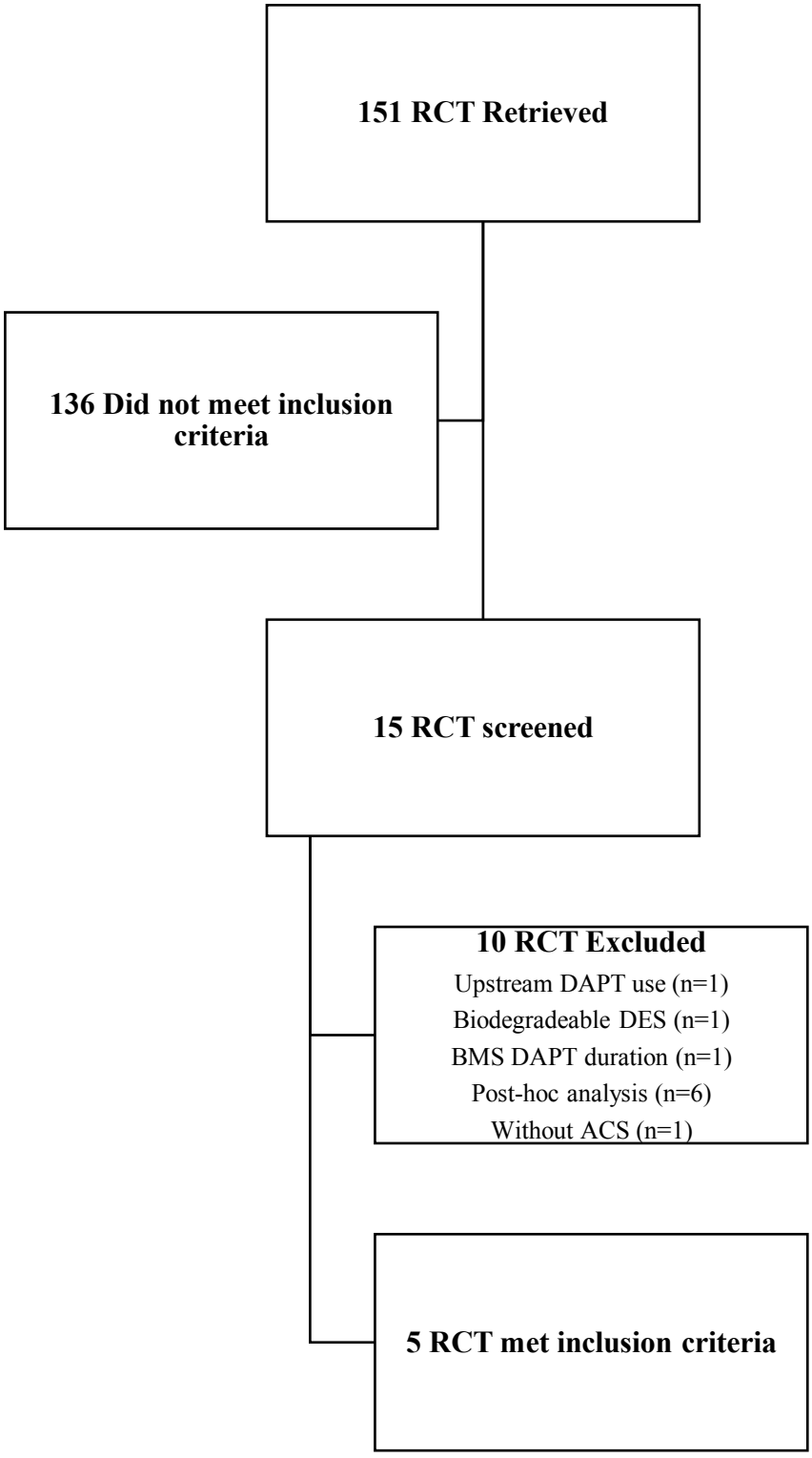

FIGURE 2. HAZARD RATIOS FOR MACE OF PROLONGED VERSUS DISCONTINUED DAPT

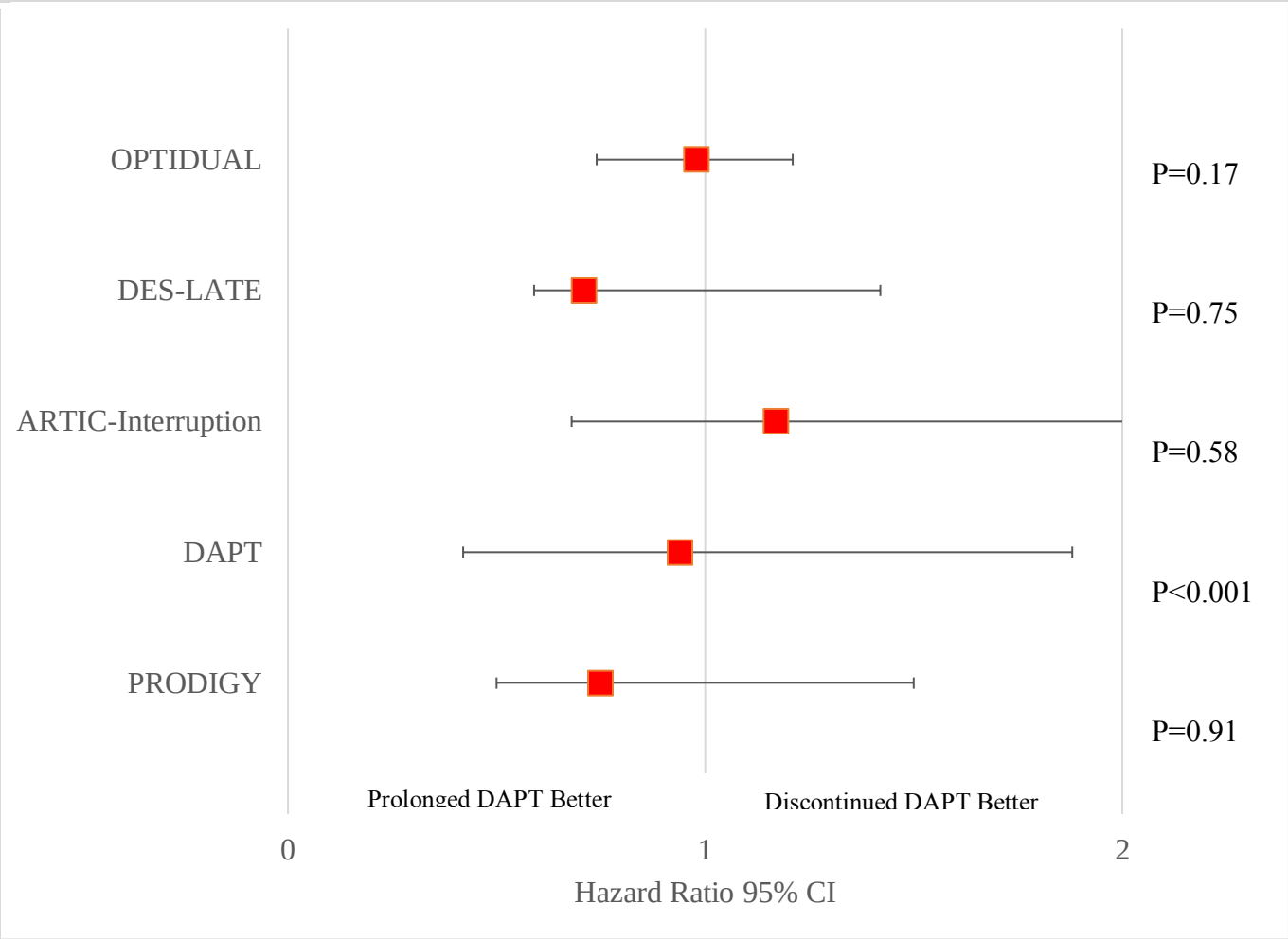

FIGURE 3. COMPARISON OF BLEEDING RATES OF PROLONGED VERSUS DISCONTINUED DAPT.

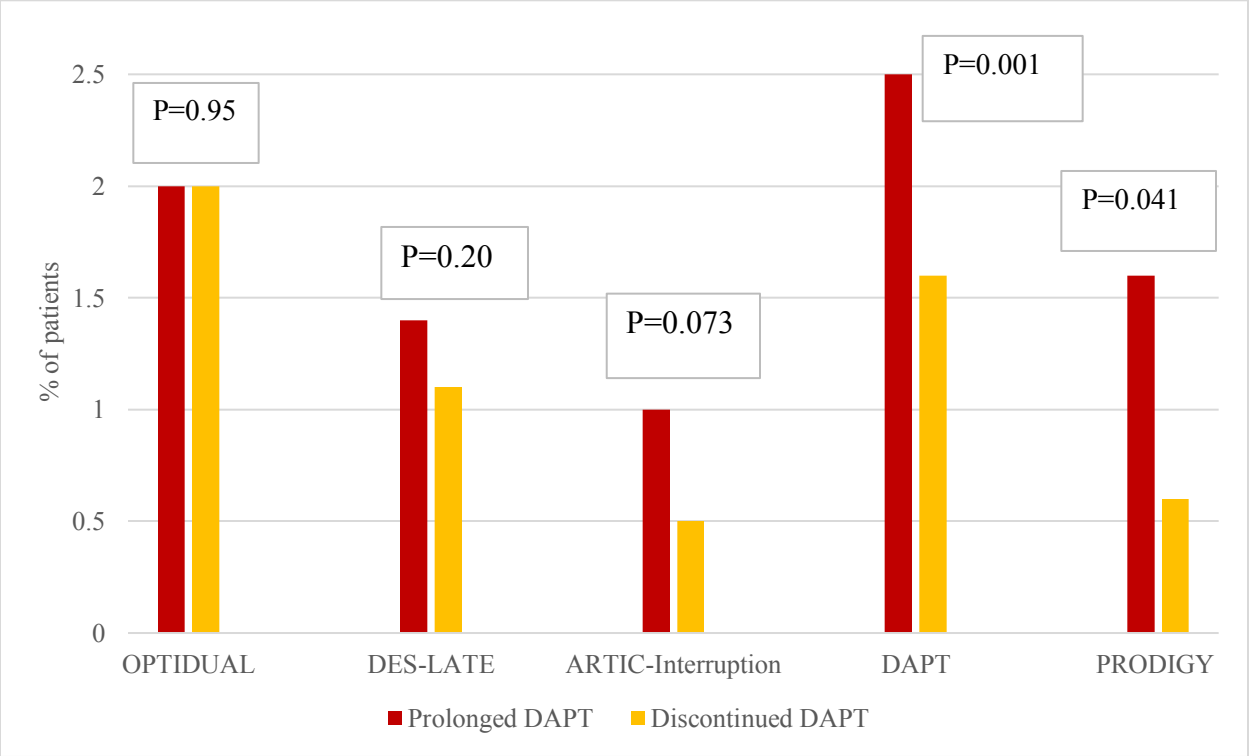

FIGURE 4. COMPARISON OF STENT THROMBOSIS RATES OF PROLONGED VERSUS DISCONTINUED DAPT.

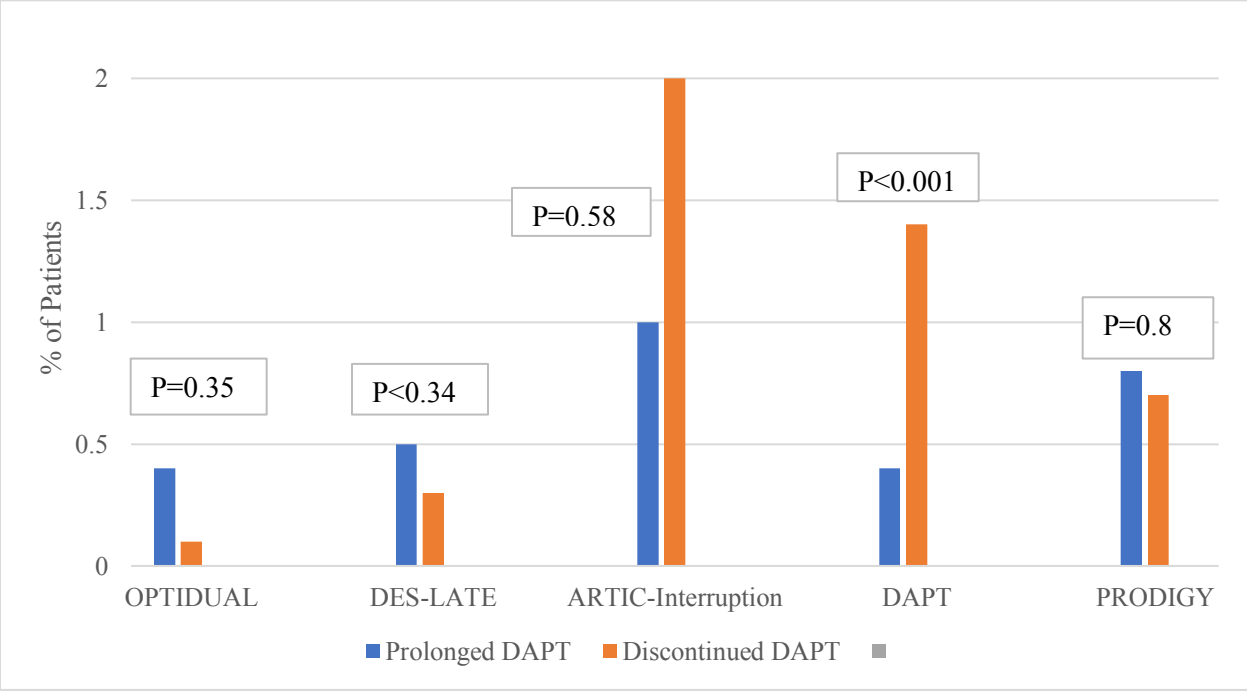

TABLE 1. SUMMARY OF RCT

Trials	Population	Number of Patients	Drug	Months and Follow-up	Primary and Safety Outcome
PRODIGY(5) 2012	PCI for ACS	1,970	Clopidogrel	6 vs 24 Follow-up 24	MACE: All-cause mortality, myocardial infarction, or stroke 24-month=100 (10.1%) 6-month= 98 (10.0%), HR 0.98 (0.74-1.29), P=0.91 ST Definite (Late, Very Late): 24-month 8 (0.8%) vs 6-month 7 (0.7%), HR 0.88 (0.32–2.42) P=0.80 TIMI Bleeding Major: 24-month=16 (1.6%) 6-month=6 (0.6%), HR 0.38 (0.15-0.97), P=0.041 Minor: 24-month=11(1.1%) 6-month=9 (0.9%), HR 0.82 (0.34-1.94), P=0.66 Major or Minor: 24-month=27(2.7%) 6-month=15 (1.5%), HR 0.55 (0.30-1.04), P=0.063
DAPT(4) 2014	PCI for ACS and CAD	9,961	Clopidogrel or Prasugrel	12 vs 30 Follow-up 36	**Co-primary:** All-cause mortality, myocardial infarction, or stroke 30-month=211 (4.3%) placebo=285 (5.9%), HR 0.71 (0.59-0.85), P<0.001 All cause death: 30-month= 98 (2.0%) vs placebo 74 (1.5%), HR 1.36 (1.00-1.85), P=0.05

					Cardiac death: 30-month= 40 (0.9%) vs placebo=47 (1.0%), HR 1.00 (0.66–1.52), P=0.98 Non-cardiac death= 30-month= 48 (1.0%) vs placebo=22 (0.5%) HR 2.23 (1.32–3.78) P=0.002 MI: 30-month=99 (2.1%) vs placebo=198 (4.1%), HR 0.47 (0.37–0.61), P<0.001 Stent-thrombosis: 30-month=19 (0.4%), placebo=65 (1.4%) HR 0.29 (0.17-0.48), P=<0.001 GUSTO Bleeding: Severe or moderate 30-month 119 (2.5%) vs placebo 73 (1.6%), HR 1.0 (0.4-1.5), P=0.001 Severe: 38 (0.8%) vs placebo 26 (0.6%), HR 0.2 (-0.1-0.6), P=0.15 Moderate: 81 (1.7%) vs placebo 48 (1.0%), HR 0.7 (0.2-1.2), P=0.004
ARTIC-Interruption(6) 2014	PCI for ACS (excluding STEMI)	1,259	Clopidogrel or Prasugrel	12 vs 18 Follow-up 33	MACE: All-cause mortality, MI, stroke or TIA, urgent coronary revascularization, stent thrombosis:18-months=24 (4%) vs 12-months=24 (4%), HR 1.17 (0.68-2.03), P=0.58 Secondary outcome=ST: 18-month=8 (1%) vs 12-month=10(2%) HR 1.30 (0.51–3.30), P=0.58 STEEPLE Bleeding:

					Major: 18-months=7 (1%) vs 12-onth=1 (<0.5%), HR 0.15 (0.02-1.20); P=0.073 Major and minor: 18-months 12 (2%) vs 12-month=3 (1%), HR 0.26 (0.07-0.91) P=0.04
DES-LATE(15) 2014	PCI for ACS	5,045	Clopidogrel	12 vs 24 Follow-up 24	MACE: Cardiovascular death, MI, stroke: 24-months=61 (2.6%) vs 12-month=57 (2.4%), HR 0.94 (0.66–1.35); P=0.75 ST: 24 month=11 (0.5%), p12=7 (0.3%) HR 1.59 (0.61–4.09), P=<0.34 TIMI Bleeding: Major bleeding: 24-month=34 (1.4%) vs 12-months=24 (1.1%), HR 0.71, (0.42–1.20); P=0.20
OPTIDUAL(16) 2016	PCI for ACS and CAD	1,385	Clopidogrel or Prasugrel	12 vs 48 Follow-up (average) 17	MACE: Composite of all-cause mortality, non-fatal myocardial infarction, stroke. 48-month= 40 (5.8%) vs 52(7.5%); HR 0.75, (0.50–1.28); P=0.17 All-cause mortality: 48-month=16 (2..3%)vs 12-month=24 (3.5%), HR 0.65, (0.34–1.22); P = 0.18. MI: 48-month=11 (1.6%) vs 12-month= 12(2.3%), HR 0.67 (0.31-1.44) P=0.31 Stroke: 48-month=5 (0.7%) vs 12-month= 7 (1.0%), HR 0.69 (0.22–2.18) P=0.53 ST: 48-month=3 (0.4%) vs12-month=1 (0.1%), HR 2.97 (0.31–28.53), P=0.35

					ISTH Bleeding: Major: equivalent in both groups=14 (2.0%), HR 0.98 (0.47–2.05), P= 0.95

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