**ABSTRACT**

**BACKGROUND:** We aimed to determine the efficacy and safety of different anti-platetet regimens after percutaenous coronary intervention (PCI) with drug eluting stent (DES) implantation using a network meta-analysis of randomized controlled trials (RCTs).

**METHODS:** RCTs comparing shorter duration (≤6 months) of dual antiplatelet therapy (S-DAPT) with either aspirin (ASA) or P2Y12 inhibitor monotherapy against longer duration (≥12 months) DAPT (L-DAPT) after PCI were searched in the MEDLINE, EMBASE and COCHRANE databases. End-points of interest were all-cause death, cardiovascular (CV) death, myocardial infarction (MI), stent thrombosis (ST), major bleeding and major or minor bleeding. Network meta-analyses were done using frequentist approach.

**RESULTS:** Eighteen RCTs with total of 57,942 patients met the inclusion and exclusion criteria. This included 14 RCTs (N= 28,853) of S-DAPT with ASA monotherapy and 4 RCTs (N= 29,089) with P2Y12 inhibitor monotherapy. Compared with L-DAPT, the rates of MI were significantly higher with S-DAPT with ASA monotherapy [OR 1.23; 95% CI 1.01-1.48], but not with P2Y12 inhibitor monotherapy [0.98; 0.85-1.14]. Both S-DAPT regimens lowered rates of major bleeding when compared to L-DAPT; ASA monotherapy [0.70; 0.49-1.00] and P2Y12 monotherapy [0.67; 0.45-0.98]. There were no differences in risks of all-cause or CV death with either regimen of S-DAPT and L-DAPT. However, in acute coronary syndrome subgroup, ASA monotherapy was associated with increased risk of ST [1.55; 1.021-2.36] but such effect was not apparent with P2Y12 monotherapy [0.93; 0.58-1.48].

**CONCLUSION:** Among patients undergoing DES implantation, S-DAPT with P2Y12 inhibitor monotherapy reduces bleeding without increased risk of MI or ST compared with L-DAPT. Prospective trials are needed to evaluate if S-DAPT with P2Y12 monotherapy is superior to S-DAPT with ASA monotherapy for ischemic protection.

**Keywords: Percutaneous Coronary Intervention, Drug Eluting Stents, Dual anti-platelet therapy**

**ABBREVIATIONS**

ACS:Acute Coronary Syndrome

ASA: Aspirin

CV: Cardiovascular

DAPT: Dual antiplatelet therapy

DES: Drug Eluting Stent

L-DAPT: Longer dual antiplatelet therapy

MI: Myocardial Infarction

PCI: Percutaenous Coronary Intervention

RCT: Randomized Controlled Trial

S-DAPT: Shorter dual antiplatelet therapy

ST: Stent thrombosis

TIMI: Thrombolysis in Myocardial Infarction

**INTRODUCTION**

Dual antiplatelet therapy (DAPT) with aspirin (ASA) and a P2Y12 inhibitor is recommended after percutaneous coronary intervention (PCI) to reduce risk of recurrent atherothrombotic events. Current U.S. and European guidelines recommend at least 6-12 months of DAPT after drug eluting stent (DES) implantation based on indication for PCI [1,2]. The guidelines also refer to the conundrum of balancing ischemic benefit with the increased bleeding risk that is fundamentally associated with longer DAPT. Not surprisingly, the risks of ischemic and bleeding events after PCI and their independent association with increased mortality presents a clinical challenge in optimizing DAPT duration [3].

Several randomized controlled trials (RCTs) have tested the hypothesis of abbreviated DAPT duration (≤6 months) versus longer duration (≥12 months) after PCI for stable or acute coronary syndrome (ACS) [4-8]. Pooled analyses of these RCTs have shown somewhat conflicting results with regards to ischemic risk with shorter DAPT (S-DAPT), however with a consistent reduction in bleeding events compared with longer DAPT (L-DAPT) [9-12]. Importantly, contemporary RCTs were designed to withdraw P2Y12 inhibitor while continuing ASA therapy after 3-6 months in the S-DAPT arm. Furthermore, while extended duration (>12 months) of DAPT has shown ischemic benefit in selected patients after PCI, this strategy has been fraught with a substantial higher bleeding risk and possibly higher non-cardiac mortality [13-15- ARCTIC, DAPT, PEGASUS TIMI 54]. Recently, four RCTs have tested hypothesis of a new strategy of S-DAPT by withdrawing ASA while continuing the P2Y12 inhibitor after a period of 1-3 months [16-19]. This strategy has been postulated to provide a more favorable risk-benefit profile by reducing bleeding risk (associated with DAPT) without compromising ischemic efficacy amongst patients undergoing PCI. Accordingly, we performed this systematic review and meta-analysis to study the cumulative evidence of this novel approach of S-DAPT against L-DAPT. We also performed a network meta-analysis to compare this approach of abbreviated DAPT duration with P2Y12 monotherapy against the conventional ASA monotherapy.

**METHODS:**

The current study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [20]. We systematically searched Medline, Cochrane and Embase databases for RCTs comparing different durations of DAPT after PCI with DES implantation. Following key words were used for database search in different combinations: “aspirin”, “P2Y12 receptor inhibitor”, “clopidogrel”, “prasugrel”, “ticagrelor”, “dual antiplatelet therapy”, “DAPT”, “drug eluting stent/s”, “DES”, “randomized controlled trial”. Inclusion criteria were RCTs that compared six months or shorter duration of DAPT (S-DAPT) versus longer duration (≥12 months) (L-DAPT) after DES implantation. Studies were further characterized based on the antiplatelet treatment used after the period of mandated DAPT in the S-DAPT arm (i.e. monotherapy with ASA or a P2Y12 inhibitor) depending on trial design. We excluded studies that were either 1) non-randomized, 2) used predominantly bare metal stents, 3) compared 12 months versus extended (>12 months) duration of DAPT.

Two authors (A.G. and A.R.) independently screened the abstracts and reviewed the studies for inclusion and exclusion criteria. Relevant data collected from individual studies included baseline characteristics, indication for PCI (elective vs. ACS), duration of DAPT in each arm, antiplatelet type (ASA or P2Y12 inhibitor) in the S-DAPT arm, P2Y12 inhibitor(s) used, DES types and duration of follow up. Primary end points included all-cause death, cardiovascular (CV) death, myocardial infarction (MI), stent thrombosis (ST), major bleeding and composite of major or minor bleeding. End points were defined as per individual trial protocol. For the end point of bleeding, TIMI (Thrombolysis in Myocardial Infarction) criteria were used preferably, if reported in the studies. BARC (Bleeding academic research consortium) criteria for bleeding were utilized if an individual RCT didn’t report TIMI bleeding [21].

We used the frequentist approach for network meta-analyses to study comparisons of different DAPT regimens 1) S-DAPT with ASA monotherapy; 2) S-DAPT with P2Y12 monotherapy; and 3) L-DAPT. NMA combines multiple pairwise meta-analyses and allows for direct and indirect comparisons. Data was analyzed using 'R 3.6.1' software (R Core Team 2019) package 'netmeta' that implements network meta-analysis using graph-theoretical methods that are equivalent to the frequentist methods [22- Rücker 2012]. Odds ratios (ORs) and the 95% confidence intervals were calculated and graphed as forest plots using 'netmeta' and 'gglot2' R packages (23- Wickham 2016].

**RESULTS:**

Initial database search resulted in 1183 studies, out of which 22 trials met the inclusion criteria [4-8,13,14,16-19,24-34]. Four RCTs were excluded from the present analysis since they were designed to compare 12 months DAPT with >12 months DAPT duration [13,14,33,34]. Thus, the current study included 18 trials with total of 57,942 patients (Supplementary Figure 1). Trial design, inclusion/exclusion criteria, and primary and secondary end points of individual studies are described in Table 1. L-DAPT arm of all studies mandated DAPT with ASA and a P2Y12 inhibitor for at least 12 months. S-DAPT arm of different trials involved dual therapy (<6 months) followed by monotherapy with either ASA (14 RCTs=28,853 patients) or a P2Y12 inhibitor (4 RCTs= 29,089 patients). Baseline characteristics of patients included in RCTs are shown in Table 2. Most of the trials included patients with both elective and ACS indications, except three trials that included only ACS patients [28,29,31]. Overall, the clinical presentation was ACS in ….(%) patients and stable CAD in … (%) patients. With regards to the P2Y12 inhibitor, clopidogrel was used exclusively in 10 trials, ticagrelor in 2 trials, and combination of either clopidogrel, ticagrelor or prasugrel in 6 trials [Table 2]. Individual trial end-points definitions are described in Supplementary Table 1.

The network of treatment regimens used for analysis in the current study is depicted in **Figure 1**. We compared three DAPT regimens: S-DAPT with ASA monotherapy, S-DAPT with P2Y12 inhibitor monotherapy and L-DAPT. Table 3 summarizes the estimates for each outcome by direct and indirect comparisons using frequentist network meta-analyses. Compared to L-DAPT, both the S-DAPT with ASA [OR 0.90 (95% CI 0.75-1.08)] and S-DAPT with P2Y12 [0.90 (0.77-1.05)] monotherapy arms were associated with similar odds of all cause death (**Figure 2**). All cause death was also similar between S-DAPT with P2Y12 versus S-DAPT with ASA monotherapy arm [1.00 (0.78-1.28)]. Similarly, there was no significant difference in CV death between the 3 DAPT arms (**Figure 2**). Consistent results were noted in ACS patients with no significant heterogeneity between groups (**Figure 3**).

MI was higher amongst patients treated with S-DAPT with ASA monotherapy [1.23 (1.01-1.48)] but not with P2Y12 monotherapy [0.99 (0.85-1.14)] when compared with L-DAPT (**Figure 2**). For ACS subgroup, there was borderline trend towards increase in MI with ASA monotherapy (p= 0.07) compared with L-DAPT (**Figure 3**). Although, ST was not significantly different between DAPT regimens among entire population, there was signficant interaction between effect size and treatment arms in ACS subgroup (Figures 2,3). Specifically, compared with ACS patients treated with L-DAPT, ST was signficiantly higher among those treated with S-DAPT with ASA monotherapy [1.55 (1.02-2.36)], whereas such an effect was not apparent with P2Y12 monotherapy [0.93 (0.58-1.48)]. Using frequentist network meta-analysis, no significant differences were noted in MI or ST between S-DAPT with ASA or P2Y12 inhibitor monotherapy arm.

Major bleeding was defined as per the TIMI criteria in 8 studies, while BARC criteria were used in 7 studies (Supplementary Table 1). Major bleeding was significantly decreased in the S-DAPT with P2Y12 [0.670 (0.455-0.986); p=0.042] when compared with L-DAPT (Figure 3). There was a non-significant trend towards reduction in major bleeding amongst patients treated with S-DAPT with ASA when [0.704 (0.494-1.004); p=0.053] compared with L-DAPT. Risk of major or minor bleeding was also significantly lower in both S-DAPT strategies when compared with L-DAPT (Figure 3). Indirect comparison, showed no differences in odds of major bleeding between S-DAPT with ASA versus S-DAPT with P2Y12 monotherapy arms. Using the frequentist NMA, S-DAPT with P2Y12 was associated with decreased risk of major or minor bleeding when compared to S-DAPT with ASA monotherapy [0.736 (0.562-0.964); p=0.026]. (Table 3).

**Discussion**

In this study of over 57,000 patients pooled from 18 RCTs, we evaluated the effect of withdrawing treatment with ASA or a P2Y12 inhibitor after a shortened period of DAPT in patients who received DES. The principal findings of our network meta-analysis are: a) ASA monotherapy after S-DAPT was associated with increased rates of MI but lower rates of bleeding compared with strategy of continued DAPT for 12 months; b) S-DAPT with P2Y12 therapy was associated with significant reduction in bleeding compared with L-DAPT strategy without any significant difference in ischemic endpoints, c) No significant differences in rates of death or ST was apparent between patients treated with either S-DAPT strategy and L-DAPT. with P2Y12 monotherapy compared to S-DAPT with ASA monotherapy.

Optimal duration of DAPT after PCI remains debatable. The previous recommendations of a minimum 12 month DAPT post PCI with drug eluting stents (DES) were based on observational data [J Am Coll Cardiol. 2011 Dec 6;58(24):e44-122]. Fundamentally, all DES release pharmacologic agents to suppress neo-intimal hyperplasia, thus reducing the rate of in-stent restenosis compared to bare metal stents. However, this can also impair arterial healing leading to delay and sometimes-incomplete endothelization, hence increasing the risk of late ST [Pharmacol Res. 2015 Mar;93:22-7]. Currently used newer generation DESs with thinner stent struts (65–90μm), optimized polymer biocompatibility and improved drug delivery kinetics have been shown to result in very low rate of late (1 month to 1 year) and very late (>1 year) ST [Circulation. 2014 Jan 14;129(2):211-23]. Accordingly, several RCTs have challenged the conventional therapy with 12 months of DAPT in patients receiving DES suggesting similar safety and efficacy of S-DAPT (3-6 months). Further, meta-analyses of these RCTs have shown significant reductions in bleeding risks with S-DAPT as compared with L-DAPT (12 months or greater) without an ischemic harm, particularly in those at low risk of thrombotic events. Thus, as endorsed by the guidelines update, an abbreviated DAPT regimen might be sufficient, especially in patients with low ischemic risk and/or high bleeding risk [J Am Coll Cardiol. 2016 Sep 6;68(10):1082-115; J Am Coll Cardiol. 2015 Mar 24;65(11):1103-6; Circulation. 2014 Jan 14;129(2):211-23].

Bleeding events after PCI are associated with increased risk of mortality [JACC Cardiovasc Interv. 2016 Jul 11;9(13):1349-57]. Indeed, an analysis of the ADAPT-DES study showed a strong association of post discharge bleeding with subsequent mortality, an effect size that was greater than MI, thus. suggesting differential weight of these end-points on mortality [J Am Coll Cardiol. 2015 Sep 1;66(9):1036-45]. Further, there is a suggestion of time dependent effects of ST such that very late ST might be associated with lesser mortality risk compared with early and late ST. In addition, a

These crucial findings underpin the clinical imperative of defining newer regimens of DAPT with a more favorable balance between ischemic and bleeding complications. In this context, our pooled analysis of RCTs shows that a new strategy of abbreviated DAPT followed by monotherapy with a P2Y12 inhibitor is associated with significantly lower riskof bleeding without any increase in ischemic events including ST and MI. However, These findings are clinically very relevant for patients who had undergone PCI and are also at high risk of bleeding due to underlying comorbidities. Results of our network meta-analysis support use of either P2Y12 inhibitor or aspirin after completion of short duration DAPT. Our results revealed a clinical benefit of less bleeding without ischemic harm with shorter duration DAPT followed by monotherapy with P2Y12 inhibitor or aspirin.

Although we didn't observe a benefit for ischemic events of P2Y12 monotherapy strategy against ASA monotherapy after mandated S-DAPT, this strategy has mechanistic foundation.

This finding is in congruence with the results and analyses of recent RCTs. In sub group analysis of PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) at 2 years, Costa et al, reported that longer duration of DAPT was associated with increased risk of bleeding in without any significant difference in the primary endpoint [a composite of all cause mortality, MI, or cerebrovascular accident (CVA)] at 2 year follow up [Eur Heart J. 2015 May

21;36(20):1242-51]. Hahn et al had reported non inferiority of S-DAPT followed by clopidogrel montherapy compared to 12month DAPT in patients who were at relatively lower risk of ischemic events [JAMA 2019;321:2428-2437]. ; JAMA 2019;321:2414-2427]. Similarly, in another open-labelled RCT, Watanabe and colleagues reported significantly lower rate of a composite of cardiovascular and bleeding events similar in low risk patients population who were treated with Clopidogrel monotherapy after 1month of DAPT compared with 12 month DAPT [JAMA. 2019 Jun 25;321(24):2414-2427]. Recently, TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial compared ticagrelor monotherapy (after 3month DAPT) and 12month DAPT strategies among patients who underwent PCI with DES and were at high risk for bleeding or ischemic events. Finding of this large multicenter RCT showed 44% lower risk of BARC type 2, 3, or 5 bleeding with no difference in risk of death, myocardial infarction, or stroke among patients who received ticagrelor monotherapy after completion of 3-month DAPT compared to those continued to receive DAPT for 12 months. Results of GLOBAL LEADERS-- the largest randomized trial examining the effect of withdrawing treatment with aspirin while continuing treatment with ticagrelor alone after 1 month of dual antiplatelet therapy after PCI, were also reported recently. Investigators reported no difference in terms of the composite endpoint of all-cause mortality or new Q-wave myocardial infarction among patients who received 2 years of treatment with ticagrelor (in combination with aspirin for the first month) with 12 months dual antiplatelet therapy followed by aspirin. Interestingly, results of post hoc substudy of GLOBAL LEADERS, supported the hypothesis compared with standard 12 months DAPT long-term ticagrelor monotherapy after 1 month of DAPT might be more beneficial especially among patients who underwent multivessel PCI [J Am Coll Cardiol. 2019 Oct 22;74(16):2015-2027].

To our knowledge this is the first network meta-analysis evaluating efficacy and safety of aspirin or P2Y12 inhibitor monotherapy after brief duration of DAPT compared 1year DAPT therapy post PCI. Network meta-analyses is very helpful statistical tool to compare mixed treatment strategies and evaluate the totality of evidence from randomized trials focusing on the same clinical topics and sharing, within the network frame, a common comparator. A network meta-analysis is thus an excellent tool for head to head comparison of the different antiplatelet strategies post PCI.

However, our analysis was limited by the data included in the study and variation in duration of short DAPT prior to aspirin or P2Y12 inhibitor monotherapy. Meta-analysis of rare events can produce erroneous results. This problem is further compounded in network meta-analysis if few trials per comparison are available, as was the case with P2Y12 inhibitor monotherapy vs DAPT arms. Secondly, outcomes (e.g. definition of major bleeding) were not consistently reported across all the trials. Further, studies included in our analysis were open label and timing of randomization was not same in all studies. This could dilute the difference between various treatment arms, especially if ischemic or bleeding events have occurred before randomization or DAPT discontinuation. An individual participant meta-analysis might overcome this limitation, even if this might reduce the sample size. Third, in current study covariate-adjusted analyses for possible confounders like presence and severity of heart failure; diabetes, ischemic burden, prior history of bleeding; renal insufficiency; stroke; procedural variables (left main intervention; length, number and location of stent) could not be performed due to non-availability of patient level data. Studies included in this analysis have enrolled and randomized patients with diverse clinical presentations and characteristics, thus it is unlikely that these variables would have confounded our results due to selection bias. Fourth, due to lack of data, in this analysis we were unable to differentiate if clinical outcomes with P2Y12 inhibitor monotherapy are dependent on choice of agent (i.e ticagrelor, prasugrel or clopidogrel)

Trials investigating short duration (≤ 6 months) to longer duration (≥ 12 months) DAPT have shown controversial results. Some studies comparing 3 to 6 months vs 12 or more months of DAPT have shown no difference in ischemic events with similar or slightly higher bleeding events with longer DAPT. (3,4,5,6,7,8) While, other trials have shown trends of increased risk of ischemic events in short term compared to long term DAPT. (9) Multiple meta-analysis of trials comparing short term vs long term DAPT had shown similar efficacy between the two groups but with increased bleeding in the long term DAPT group. (10,11,12) The risk of ischemic events especially MI cannot be completely ignored as seen in some meta-analysis. (13,14,15, 16) Interestingly in some of the meta-analysis there was concern for increase in non-cardiovascular death in the long term DAPT group which was shown to be correlating with increased risk of bleeding in that group. (17, 18) The risk of bleeding remains substantial in patients on DAPT with 1-year bleeding risk in recent trials ranging from 0.3 % to 2.8 %. (3) Majority of these trials excluded high bleeding risk patients. In trials which included patients with high bleeding risk 1-year bleeding was reported somewhere between 3.5 % to 7.2 %. (19)

Whatever benefits of DAPT in reducing ischemic event is offset by increased bleeding events. In all the above trials short term DAPT vs followed by aspirin monotherapy. In order to decrease ischemic events along with bleeding events it was later proposed that a short term DAPT followed by monotherapy with a P2Y12 inhibitor might work. (20, 21,22,23) In vitro studies have reported that aspirin offers limited anti-platelet effect in the presence of strong P2Y12 receptor blockade. (24) In healthy human volunteers clopidogrel and ticagrelor monotherapy when compared to dual therapy in combination with aspirin led to comparable anti-platelet effects. (25) In a direct comparison of anti-platelet monotherapy, clopidogrel was associated with reduced ischemic risk with similar bleeding profile when compared to aspirin alone. (26, 27)

Recently few randomized controlled trials are published with short term DAPT followed by P2Y12 monotherapy at-least for 12 months compared to 12 months of DAPT therapy (28,29,30,31). Some of them have shown no difference between the two groups in ischemic events with decreased bleeding events. (29,30) Given the conflicting results we decided to do a meta-analysis to compare short DAPT therapy followed by P2Y12 monotherapy vs 12 months of DAPT therapy.

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