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Duration of dual antiplatelet therapy after percutaneous coronary intervention with implantation of second-generation drug-eluting stent: A meta-analysis of randomized controlled trials

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Objective: The optimal duration of dual antiplatelet therapy (DAPT) in patients after PCI with implantation of a drug-eluting stent is still controversial. We conducted a meta-analysis to compare the efficacy and safety of short term DAPT (≤ 3 months) followed by P2Y12 inhibitor monotherapy and standard DAPT (12 months) after PCI. *Method*: Relevant studies published in Medline, Embase, CoChrane Library were searched for randomized controlled trials (RCTs) until November 2019. Studies were screened by selection criteria then quality assessed through the Cochrane Collaboration's tool. Data were extracted from the included studies and statistically analyzed by RevMan 5.3 software. *Results*: Five RCTs (n=18,357) were included. Compared with standard DAPT, the short term DAPT was associated with a significant decrease in the major bleeding [odds ratio (OR)=0.43, 95% Confidence Interval (CI):0.32-0.58, *P*<0.00001] and any bleeding [OR=0.56, 95%CI:0.47-0.66, P<0.00001]. There were no significant differences in all-cause death [OR=0.91, 95%CI:0.71-1.16, *P*=0.45], major adverse cardiac and cerebrovascular event [OR=1.01, 95%CI:0.87-1.17, *P*=0.91] and stent thrombosis [OR=0.97, 95%CI:0.61-1.54, *P*=0.91] between with the short term DAPT group and the standard DAPT group. *Conclusions:* Short term DAPT followed by P2Y12 monotherapy could reduce the risk of bleeding without increasing the incidence of ischemic events after PCI with implantation of second-generation DES compared with standard DAPT. Therefore, short term DAPT may be a promising strategy to balance ischemic events and bleeding complications in patients after PCI.

1. Introduction

Dual antiplatelet therapy (DAPT), consisting of acetylsalicylic acid (ASA) and P2Y12 inhibitor, can be considered as standard anti-thrombotic therapy after the percutaneous coronary intervention (PCI) with implantation of a drug-eluting stent (DES) (Kukreja et al. 2009). The 2016 ACC/AHA Guideline recommended that patients with acute coronary syndrome (ACS) undergoing PCI should receive a minimum of 12 months DAPT (Levine et al. 2016). However, given the long term DAPT associated with an increase in bleeding risks that could offset the anticipated benefits of reduction in ischemic events, as well as the advances in DES have led to a remarked reduction in the incidence of stent thrombosis (Palmerini et al. 2013). So multiple randomized controlled trials (RCTs) have tried to discontinue ASA properly that evaluated whether short term DAPT could provide an adequate reduction in ischemia events while decreasing the bleeding risk. Previous studies have shown that the efficacy of 6 months of DAPT followed by 6 months of P2Y12 inhibitor monotherapy is not inferior to 12 or 24 months DAPT, and reduced the risk of major bleeding (Valgimigli et al. 2017; Gilard et al. 2015; Schulz-Schüpke et al. 2015). Moreover, it was suggested that the greatest reduction in cardiovascular events with DAPT is seen in the first 3 months. So, several RCTs have attempted to compare the benefits and risks of short term DAPT (≤ 3 months) with conventional 12 months DAPT in patients undergoing PCI with new generation of DES. Thus, we sought to assess the efficacy and safety of short term DAPT (≤ 3 months) followed by P2Y12 monotherapy *versus* standard DAPT (12 months) in ACS patients.

2. Investigations and results

2.1. Study identification and selection

According to the search strategy, a total of 707 records were identified. Next, 688 records were excluded after reading titles and abstracts, and 14 records were excluded after reading the full text. Finally, a total of five studies involving 18,357 patients were included (Fig. 1). These studies included in our analysis all were RCTs, and all of the expected outcomes were obtained in these

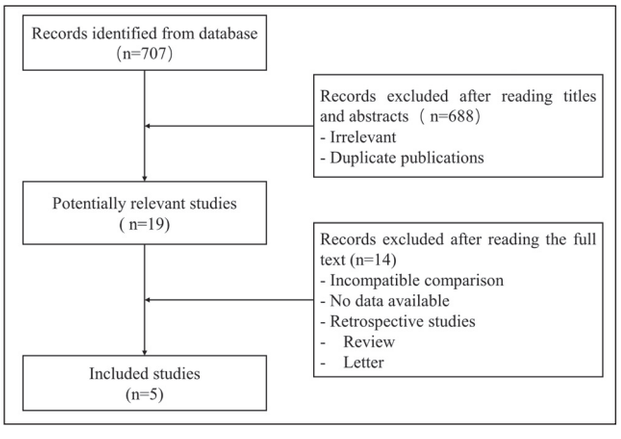

Fig. 1: Flow diagram of study selection

articles (Feres et al. 2013; Kim et al. 2012; Hahn et al. 2019; Watanabe et al. 2019; Mehran et al. 2019).

2.2. Characteristics of included studies

One RCT (STOPDAPT-2) evaluated 1 month *versus* 12 months of DAPT. Four RCTs (OPTIMIZE, RESET, SMART-CHOICE, TWILIGHT) evaluated 3 months *versus* 12 months of DAPT. In these trials, second-generation DES were used in all patients in a group of short term DAPT. And the data of renal insufficiency was missing in the RESET trial (Kim et al. 2012). The characteristics of these studies are summarized in the Table.

2.2. Quality assessment

As shown in Fig. 2, quality was assessed according to the Cochrane Collaboration's tool for assessing the risk of bias with the following factors: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; other bias. In each factor, studies were labeled as low, high or unclear risk of bias due to the presence or absence of sufficient information.

Table: Characteristics of included studies

Study	Year	Number of patients (n, T/C)	The average age (years, T/C)	Male (n, TC)	Diabetes mellitus (n, T/C)	Renal insufficiency (n, T/C)	Acute coronary disease (%, T/C)	Stent type	P2Y12 type	
									T (%)	C (%)
OPTIMIZE (3 VS. 12 mo)	2013	1563/1556	61.3/61.9	992/982	554/549	114/89	37.0%/37.7%	zotarolimus-eluting stent	clopidogrel (99.7)	clopidogrel (99.8)
RESET (3 VS. 12 mo)	2012	1059/1058	62.4/62.4	682/665	316/305	NA	RESET (3 VS. 12 mo)	Endeavor zotarolimus-eluting stent	clopidogrel	clopidogrel
SMART-CHIOCE (3 VS. 12 mo	2019	1495/1498	64.6/64.6	1087/1111	570/552	44/53	58.2%/58.2%	platinum chromium everolimus-eluting stents or sirolimus-eluting stents with biodegradable polymer	clopidogrel (76.9%) or prasugrel or ticagrelor (23.1%)	clopidogrel (77.6%) prasugrel or ticagrelor (22.4)
STOPDAPT-2 (1 VS. 12 mo)	2019	1500/1509	68.1/69.1	1183/1154	585/674	82/84	37.7%/38.6%	CoCr-EES	clopidogrel (60.2) or prasugrel (39.6)	clopidogrel (60.2) or prasugrel (39.6)
TWILIGHT (3 VS. 12 mo)	2019	3555/3564	65.2/65.1	2709/2712	1319/1301	572/673	63.9%/65.7%	Second-generation drug-eluting stents	ticagrelor (87.1)	ticagrelor (85.9)

T: test group; C: control group; mo: moths; NA: data not available

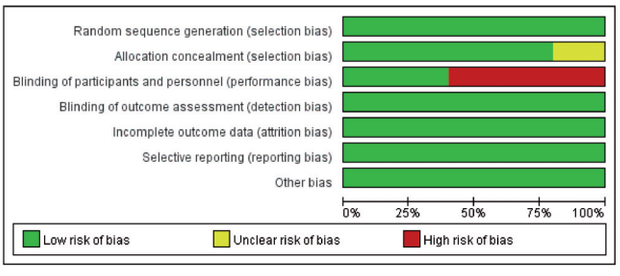

Fig. 2: Risk of bias assessment of include studies

2.4. Efficacy

2.4.1. Major adverse cardiac and cerebrovascular events (MACCE)

MACCE, as primary effective endpoints, were defined as a composite of all-cause, myocardial infarction or stroke during 12 months. Five studies reported MACCE involving 18,357 patients. The incident of MACCE in short term DAPT group and standard DAPT group was 3.94% and 3.90%, respectively. The combined of OR for MACCE showed no statistical difference between the two groups (OR=1.01, 95%CI:0.87-1.17, P=0.91; Fig. 3). And, there was no significant heterogeneity demonstrated (P=0.62, I^2=0%).

2.4.2. All-cause death

Five studies involving 18,357 patients reported all-cause death. The frequency of all-cause death in the short term DAPT (≤ 3 months) was 1.35% compared with 1.48% in standard DAPT. The combined OR for all-cause death was OR=0.91, 95%CI:0.71-1.16, P=0.45 (Fig. 4). There was no significant heterogeneity among studies (P=0.53, I^2=0%).

2.4.3. Stent thrombosis

Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium classification (Cutlip et al. 2007). Figure 5 shows the results of stent thrombosis from the 5 studies on 18,357 patients. Second-generation DES were used in all of five studies that the low incident of stent thrombosis was 0.39% (36 of 9172) and 0.4% (37 of 9185), respectively. The combined OR for short term DAPT verse standard DPAT of 1.05 (95%CI:0.78-1.42, P=0.91). There was no significant heterogeneity appeared (P=0.61, I^2=0%).

2.5. Safety

2.5.1. Major bleeding

Major bleeding was defined as BARC 3-5 what was used across five trials. Five studies reported major bleeding involving 27,206 patients. Figure 6 shows that the incidence of major bleeding was 0.72% (66 of 9172) in the short term DAPT group and 1.64% (151 of 9185) in the the standard group. The results show that short term DAPT reduced the incidence of major bleeding more than standard DAPT. The combination of OR was 0.43 (95%CI:0.32-0.58, P<0.00001). There was no evidence of heterogeneity among studies (I^2=33%, P=0.20).

2.5.2. Any bleeding

Any bleeding complications occurred in 592 of 18,357 patients, including 215 cases (2.34%) in the short term DAPT group and 377 cases (4.10%) in the standard DAPT group, as shown in Fig. 7. Among the 5 studies, the weight of TWILIGHT trial was 65.6%, which significantly affected the combination of OR. The final value of OR was 0.56 (95%CI:0.47-0.66, P<0.00001). The result showed that short term DAPT more reduce the complication of any bleeding than standard DAPT. There was no significant heterogeneity demonstrated (I^2=37%). Results showed that any bleeding occurred less frequently in the short term DAPT group than in the standard DAPT group.

3. Discussion

In this meta-analysis, we included 5 studies involving 18,357 patients. We compared the safety and efficacy between short term DAPT (≤ 3 months) and standard DAPT (12 months) after PCI with implantation of second-generation DES. The main results of this meta-analysis are as follows: 1) the short term DAPT is associated with a lower risk of major or any bleeding compared to standard DAPT; 2) the benefits of standard DAPT on MACCE,

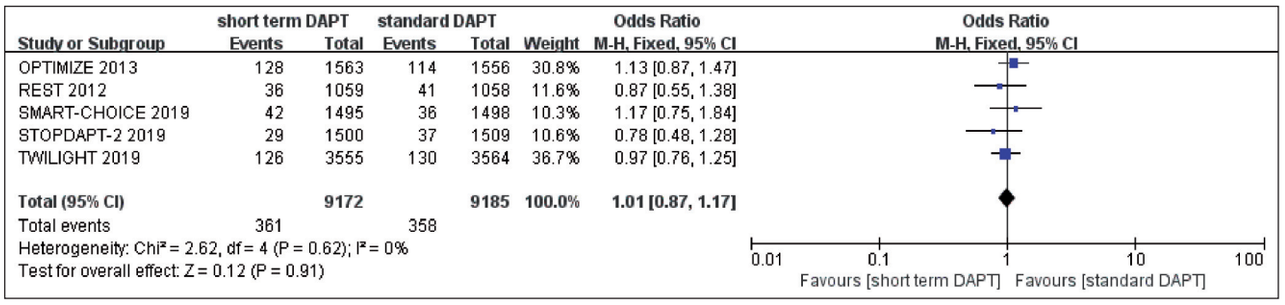

Fig. 3: Forest plots of MACCE

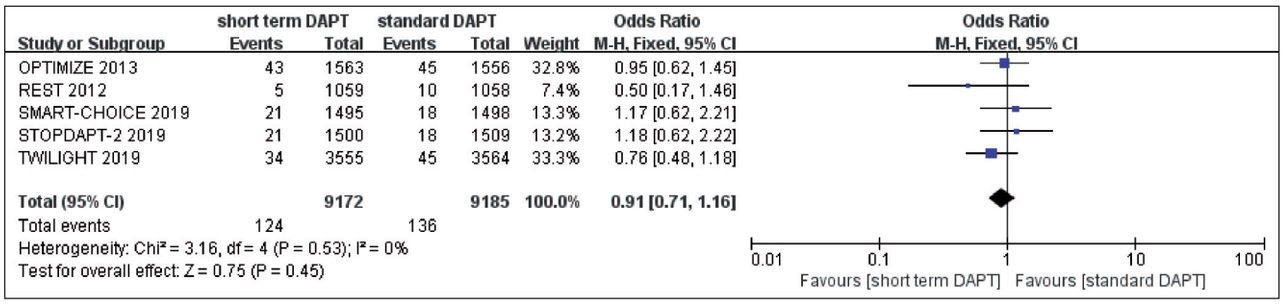

Fig. 4: Forest plots of all-cause death

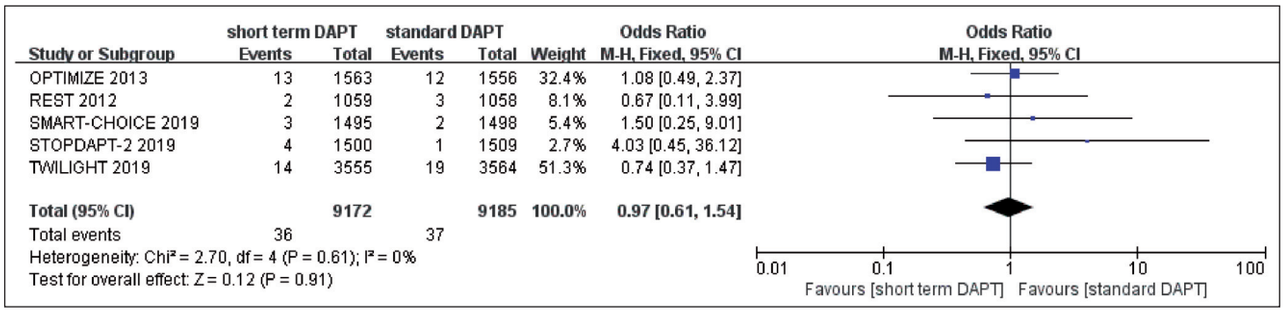

Fig. 5: Forest plots of stent thrombosis

any-cause death, and stent thrombosis were similar to short term DAPT. The results suggested that short term DAPT was noninferior to 12 months for ischemic events, with significantly reduce the risk of bleeding.

It has been 18 years since the benefits of DAPT have been discovered in the CURE trial, the optimal duration of DAPT after PCI remains an important debate (Yusuf et al. 2001). Mehran et al. (2013) suggested an independent association between discontinuing DAPT and stent thrombosis, particularly after implantation of first-generation DES. However, the development of second-generation DES with improved vascular healing and reendothelialization could significantly reduce the incidence of stent thrombosis (Dangas et al. 2013; De Luca et al. 2017). Moreover, statins were used widely that could lower the risk of recurrence of major cardiac events in patients with ACS. So in the STOPDAPT-2 trial, 90% of patients recieved a statin (Leone et al. 2018). Thus, short term DAPT followed by P2Y12 monotherapy is a considerable strategy as it has been shown to reduce the risk of bleeding (Palmerini et al. 2017). A systematic review found that shorter DAPT (3-6 months) led to higher rates of stent thrombosis than longer DAPT (12-24 months), but the latter effect was significantly attenuated by the use of second-generation DES (Giustino et al. 2015). In the present meta-analysis, we reported that the incident of stent thrombosis was 0.39% (36 of 9172) in the short term DAPT group and 0.4% (37 of 9185) in the standard DAPT group, respectively, and there was no significant difference between the two groups. The main reason may be related to the total use of second-generation DES. Moreover, MACCE and all-cause mortality in the short term DAPT group were the same as in the standard DAPT group. These results demonstrated that the effect on anti-ischemic risk of short term DAPT was noninferior to standard DAPT.

Large studies have shown that major bleeding is associated with increased mortality that may offset the benefits of DAPT in anti-ischemic risk (Rao et al. 2006; Budaj et al. 2009). Previous studies have attempted to switch from DAPT to ASA monotherapy to reduce bleeding risk. Such as the DAPT trial was designed to compare the safety and efficacy of 12 months DAPT followed by 18 months of ASA monotherapy *versus* 30 months DAPT (Mauri et al. 2014). However, the risk of bleeding was reduced yet the increasing risk of rebound stent thrombosis and myocardial infarction occurred within 3 months of switching from DAPT to ASA monotherapy. P2Y12 inhibitors have been shown to possess more potent platelet inhibitory effects. Thus, the DAPT or P2Y12 monotherapy in patients after PCI was designed to compare the efficacy and safety of short term DAPT and standard DAPT. In the present meta-analysis, we included recent studies on the efficacy and safety of short term DAPT (≤ 3 months) *versus* 12 months DAPT. The part results of safety showed that short term DAPT could significantly reduce the risk of bleeding compared with the standard DAPT group, including any bleeding and major bleeding. Thus, for security reasons, switching from DAPT to P2Y12 monotherapy may be a viable strategy for patients after PCI.

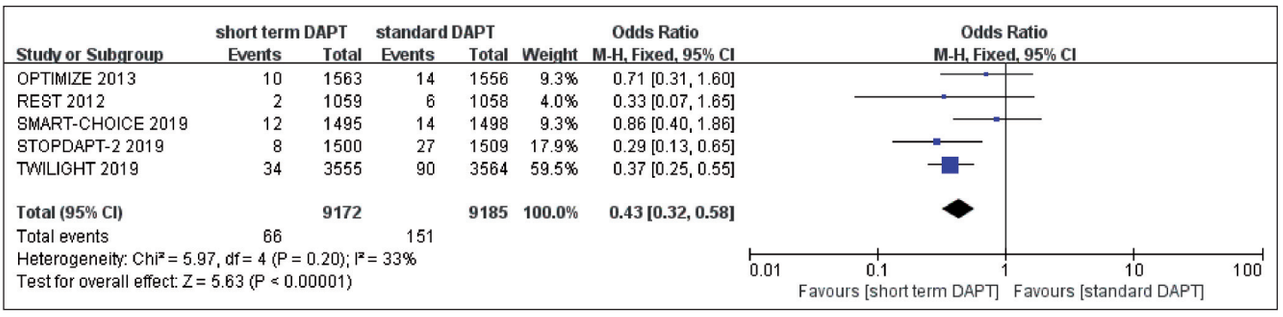

Fig. 6: Forest plots of major bleeding

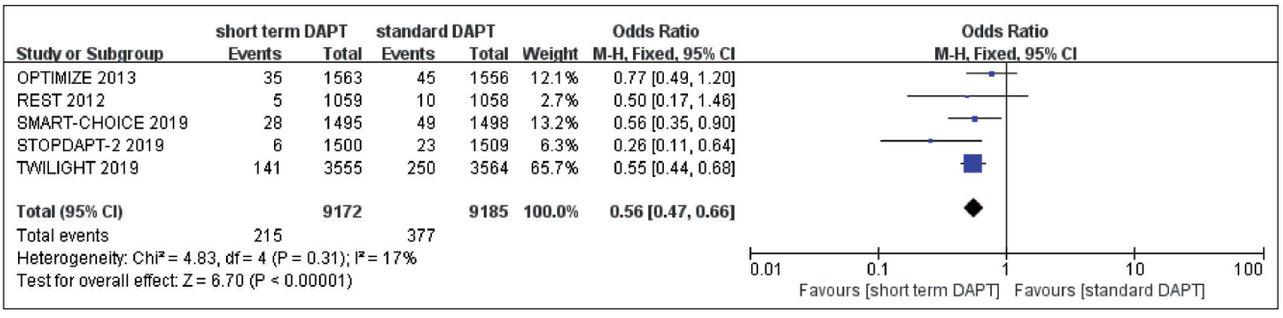

Fig. 7: Forest plots of any bleeding

The main limitation of this meta-analysis is that the number of patients who are at high risk for ischemic or hemorrhagic complications in some studies is still insufficient. Such as the ratio of patients with ACS were 37.4% and 38.2% in the OPTIMIZE and STOPDAPT-2 trials, respectively. But in the BIONYX trial with few exclusion criteria, in which recruited 60-70% of ACS patients (von Giustino et al. 2018). It may affect us to evaluate the risks of ischemic and bleeding. Second, more evidence needs to be acquired for diverse races. It was suggested that P2Y12 inhibitors have marked interethnic differences in the pharmacokinetics and pharmacodynamics (Jeong 2014). Third, only low incident of stent thrombosis occurs with second-generation DES. It may be related to the short-term follow-up (usually 12 months), but the occurrence of stent thrombosis will continue to 2 or 3 years after PCI, or even longer. Finally, although no significant heterogeneity was shown in this meta-analysis, subgroup analysis for the main endpoint is till lacking. Thus, it is hard to explore specific subgroups earning the best benefit from short term DAPT. Therefore, to clarify the effect of shortend DAPT on ischemic and bleeding complications, more relevant studies evaluating shorter duration of DAPT in contemporary clinical practice are needed.

In conclusion, our findings support the assumption that short term DAPT followed by P2Y12 monotherapy could reduce the risk of bleeding without increasing the incidence of ischemic events in patients after PCI with implantation of second-generation DES compared with standard DAPT. Therefore, short term DAPT may be a promising strategy to balance ischemic events and bleeding complications in patients after PCI.

4. Experimental

4.1. Study selection

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Moher et al. 2009). We conducted a systematic search for the relevant studies published in Medline, Embase, CoChrane Library for RCTs until November 2019. The search terms included the following: duration of dual antiplatelet therapy, aspirin, acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel, P2Y12 inhibitor monotherapy, percutaneous coronary intervention, drug-eluting stents.

4.2. Inclusion criteria

Studies that met the following criteria were included: the study was a RCT; participants who received DAPT after PCI with EDS; the duration of DAPT consisted of a shorter group (≤ 3 months) and a longer group (≥ 12 months); discontinuation of aspirin and continuation of P2Y12 inhibitor monotherapy.

4.3. Exclusion criteria

The studies that met the following criteria were excluded: the study was not a RCT; the study had no data available; one-arm study; case reports or reviews.

4.4. Data extraction and quality assessment

Two reviewers (Liu and Li) independently assessed the RCTs being included. The discrepancies were resolved through discussion or by a third reviewer (Wu) participating in the evaluation. The quality assessment was assessed according to the Cochrane Collaboration's tool for assessing the risk of bias with the following factors: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; other bias. In each factor, studies were labeled as low, high or unclear risk of bias due to the presence or absence of sufficient information.

4.5. Statistical analysis

Data analysis was performed using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). The risk ratio (OR) with 95% confidence interval (CI) was used to count the dichotomous variables, and the Mantel-Haenszel method was used to calculate. Heterogeneity analysis was performed on the included studies by I^2 statistic. When I^2>50% and P<0.10, the heterogeneity was considered statistically significant then the random effects model was used, whereas the fixed effects model was used when I^2<50% and P>0.10. P<0.05 were considered significant.

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Conflict of interests: All authors had access to the data and played a role in writing this manuscript. The authors declare that they have no conflict of interests.

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