ONOMY Science

American Journal of Cardiology and Cardiovascular Diseases
ISSN 2641-2438

Research Article Open Access

Decide the Duration of Dual Antiplatelet Therapy (DDD)

Aisha Siraj[1*], Mojdeh Nasiri[2], Negin Nouri[3], Sabeeda Kadavath[1]and Negar Salehi[1]

[1] Department of Cardiology, University of Arkansas For Medical Sciences, Little Rock, Arkansas, USA
[2] Department of Epidemiology and Biostatistics, Michigan State University, Lansing , Michigan, USA.
[3] Clinical Research Coordinator, Dynamic Drug Advancement South Ajax, ON, Canada.

***Corresponding Author:** Aisha Siraj, University of Arkansas for Medical Sciences, Address: 4301 W Markham St, Little Rock, AR, 72205, Phone: 718-675-9271; Email: Aishasiraj@gmail.com

Citation: Decide the Duration of Dual Antiplatelet Therapy (DDD). Am J of Card and Cardiovas Disc. 2019; 2(2): 01-09.

Submitted: 23 August 2019; **Approved:** 28 August 2019; **Published:** 30 August 2019

Abstract

Dual antiplatelet therapy (DAPT) post percutaneous intervention has been studied extensively. However, the optimal duration of treatment remains a clinical challenge, particularly in high-risk patients. We reviewed 16 trials important to current date trials focus on the duration of DAPT, including studies on short-term and extended duration DAPT and 4 meta-analyses between 2008- 2019. The data was further explored for the proportion of high-risk patients, type of stent, bleeding risk-score used, and overall outcomes. We also evaluated the sub-group analysis in these trials that involve high-risk patients and their outcomes for the duration of DAPT. According to the 2016 ACC guidelines, indicators of high risk are presentation of acute coronary syndrome at the time of PCI, stent length, stent size, bifurcation lesion, type of lesion, generation of the stent, diabetes mellitus, chronic kidney disease, and low ejection fraction (EF<40%). Based on available evidence, short-term DAPT (i.e. 6 months) is safe in low-risk patients undergoing the second-generation Drug-Eluting Stent implant. However, in high risk patients, subgroup analysis suggests that, short term of DAPT to be non-inferior to more than 12 months of DAPT.

Keywords: Dual Antiplatelet Therapy; Acute Coronary Syndrome; Percutaneous Coronary Intervention

Introduction

The role of the dual antiplatelet therapy (DAPT) in the management of coronary artery disease (CAD) with percutaneous coronary intervention (PCI) for patients with acute coronary syndrome (ACS) is well established (1) (2). Landmark trials such as PCI-CURE, ISAR, STARS and CREDO defined the role of DAPT in the ACS patients with PCI (3) (4) (5) (6). It is known that the Drug-Eluting Stents (DES) are prone to late thrombosis due to antiproliferative agents, that prevent in-stent restenosis and result in better target vessel revascularization (TVR). However, paradoxically, DES create an environment of higher risk for thrombosis due to delayed or incomplete endothelialization of the stent (7). Thus, the duration of DAPT can be a vital predictor of stent thrombosis(8) Contemporary studies have confirmed the role of DAPT in remote ACS as well as in stable CAD. The subset analysis of CHARISMA and PEGASUS TIMI 54 trials, revealed the benefit of prolonged DAPT over 28-33 months (8) (9) (10). Meanwhile, with the advent of the second-generation DES, short-term DAPT (3-6 months) was found safe and effective. In 2016, Udell et al demonstrated in their meta-analysis that DAPT beyond one year among stable high-risk patients with prior myocardial infarction (MI) decreased ischemic events, while the risk of major bleeding increased. Nevertheless, risk/benefit ratio favored the continuation of therapy beyond one year (11). These findings challenged prevailing view regarding the optimal duration of the DAPT, particularly concerning the newer generations of DESs and patients with high-risk of adverse outcomes. Therefore, duration of DAPT has become a pertinent issue not only for patients presenting with ACS but also for those with stable CAD.

In 2016, ACC/AHA guidelines recommended

DAPT for 6 months in stable ischemic heart disease following DES and 12 months following ACS with either medical therapy, post PCI or Post coronary bypass surgery (CABG). (class 1 recommendation) (12). This was based on the available data especially from the PCI-CURE trial and some observational studies (13) (14) (10) (15) (16). In the updated ACC/AHA guidelines DAPT is recommended for 6-12 months for low-risk, stable patients following second generation DESs (Class I, IIb recommendation) (2) (3) (2-3) and at least 12 months for patients presenting with ACS (12). Similarly, the 2017 European guidelines proposed 6 month of DAPT with DESs in patients without high risk features for bleeding in chronic stable angina and 12 month in patients with ACS and without high risks features of bleeding (Class 1, level A recommendation) (17) (16).

In this review, we evaluate the evidence for short (<12 months) vs long term (>12 months) DAPT with emphasis on high risk patients. According to the ACC/AHA guidelines the risk factors for recurrent cardiovascular ischemic events are: ACS presentation at the time of PCI, stent length, stent size, bifurcation lesion, type of lesion, generation of the stent, diabetes mellitus (DM), chronic kidney disease (CKD) and low ejection fraction (EF<40%). Currently, DAPT includes typically a P2Y12 receptor inhibitor (i.e. clopidogrel, ticagrelor or prasugrel) along with aspirin 81 mg.).

Major Randomized Trials That Evaluated Short-Term Dual Antiplatelet Therapy (<1 Year)

Several trials have evaluated short term DAPT (Table 1 and Table 2). These include the following trials: The PRODIGY; EXCELLENT; REST; Optimize; Zeus; Italic; ISAR-SAFE; Security; SMART-CHOICE and STOPDAPT-2. In these trials, PRODIGY and ZEUS had the highest percent of patients with high risk while OPTIMIZE performed a subgroup analysis with high risk patients as defined by ACC/AHA guidelines.

The PRODIGY trial evaluated prolonged 24 months vs. short-term 6 months DAPT in patients with Bare Metal Stents (BMS) and DESs (18). In this trial, 23% of patients had NSTEMI and 33% presented with STEMI. The incidence of the primary endpoint (non-fatal MI, death from any cause, or stroke between 30 days and two years) was 6.0% and 6.8% for short-term and long-term DAPT, respectively (hazard ratio (HR)=0.87, 95% CI=0.58-1.31, P=0.51). The event rate was 10.0% and 10.1% among short-term and prolonged DAPT, respectively (HR=0.98, 95% CI=0.74- 1.29, P=0.91). There was no significant difference between the two treatment strategies; however, patients in the 24-month arm had an increased risk for bleeding (18)(17).

The EXCELLENT trial's primary endpoint was target vessel failure (i.e. thrombosis or restenosis) (19). Patients were excluded if presented with myocardial infarction within 72 hours prior to intervention. Target vessel failure at 6 and 12 months was 4.3% and 4.8%, respectively (p=0.001 for non-inferiority). Although stent thrombosis was higher at 6 months vs. 12 months, (0.9% vs. 0.1%, hazard ratio=6.02, 95% CI=0.72- 49.96, P=0.10) the risk of death and myocardial infarction did not differ. Among diabetic patients, target vessel failure occurred more frequently at 6 vs 12-month (HR=3.16, 95% CI=1.42- 7.03, P=0.005). The non-inferiority margin was wide, and the study was underpowered for the analysis on death or myocardial infarction.

The RESET trial evaluated the safety and efficacy of 3 vs 12 months of DAPT following DES. (20). The primary composite endpoint was cardiovascular death, MI, stent thrombosis (ST), TVR or bleeding. The primary endpoint was present in 4.7% of patients assigned to E-ZES 3-month DAPT compared to 4.7% of patients assigned to the 12 months DAPT (95% CI=-2.5 to 2.5, P=0.84, P<0.001 for non-inferiority). The occurrence of stent thrombosis was similar between the 2 groups (0.2% vs. 0.3%, 95% CI=0.5- 0.3, P=0.65). The study evaluated patients at 1-year follow up, but did not include high-risk patients. All the procedures were elective and 85.7% patients presented with stable or unstable angina.

The OPTIMIZE trial evaluated the clinical non-inferiority of 3 vs. 12 month of DAPT in patients undergoing PCI (21). The primary endpoint was net adverse clinical and cerebral events (NACCE), i.e., death from any cause, MI, stroke or major bleeding. They excluded all patients presenting with ACS. OPTIMIZE concluded that patients with stable CAD or low-risk ACS, 3 months of DAPT was non-inferior to 12 months for NACCE (6.0% vs. 5.8%, P =0.002) and without a significant increase in stent thrombosis. However, the study showed a trend towards the higher incidence of bleeding in patients with longer duration of DAPT. A review of subgroup analysis had a trend towards high relative risk for NACCE in patients with diabetes, complex lesions, multi-vessel intervention, longer stent, and small caliber vessels; however, none of these factors were statistically significant.

In ZEUS trial Zotarolimus-Eluting stents (ZES) were compared to the BMSs for safety and efficacy (22). This study selected patients with high risk for thrombosis or bleeding. This study included both diabetic and acute MI patients. Interestingly, the median duration of DAPT was 33 days (IQR= 30- 180 days) for BMS and 31 days (IQR=30- 180 days) for

ZES groups. Compared with BMS, ZES implantation with tailored DAPT regimen resulted in a lower risk of 1-year Major Adverse Cardiac Event (MACE). In the ZES group, 140 patients (17.5%) presented the primary endpoint, compared with 178 patients (22.1%) in the BMS group. This is because of the lower MI (2.9% vs. 8.1%, P < 0.001) and TVR rates (5.9% vs.10.7%, P=0.001) in the ZES group.

The ITALIC trial compared MI, urgent TVR, composite event of death, stroke and major bleeding following second generation Xience V stent deployment (23). The trial also evaluated aspirin resistance. Patients with aspirin resistance and patients who achieved primary endpoint within 6 months of DAPT were excluded. This included previous PCI and ACS patients. In more than half of the patients, two or more lesions were stented. Non-inferiority was demonstrated for 6 vs. 24month DAPT, with an absolute risk difference of 0.11% at the 95% CI. No significant difference for bleeding and stent thrombosis was found between the two groups (23). The trial was prematurely terminated due to limited recruitment.

The ISAR-SAFE was a randomized, double blind, placebo-controlled trial that evaluated the clinical non-inferiority of 6 vs. 12 month DAPT with clopidogrel (24). In order to reduce the selection bias this included patients on clopidogrel at 6 months after DES implantation. Overall 40% of the patients presented with an ACS and 8% with an STEMI. Patients were randomly assigned to either clopidogrel or placebo after 6-month of DES implantation. The primary endpoints included death, MI, stroke, and thrombolysis in myocardial infarction major bleeding. The trial showed no significant difference in primary endpoint between the two study groups (1.5% at 9 months vs. 1.6% at 12 months, limit of non-inferiority 2%, P for non-inferiority <0.001) (24).

The SECURITY trial evaluated the non-inferiority of 6 vs. 12 month DAPT in patients undergoing PCI with second-generation DES (25)(24). Overall patients had low-risk clinical profile, 61.6% of patients presented with stable angina and 38.4% with unstable angina in each group. The primary endpoint was cardiovascular death, MI, stent thrombosis, or bleeding base on Bleeding Academic Research Consortium (BARC) score at 12 months. The primary endpoint at 12 months DAPT was not significantly different (risk difference=0.8%, 95% CI=2.4- 1.7%, P= 0.469). They concluded that there is no additional benefit for prolonged DAPT beyond 6 months in diabetic patients treated by second-generation DES. However, his trial had very low event rates and was underpowered to demonstrate a difference in cardiac death, MI, stroke, or bleeding between the study arms and a relationship between stent type and outcome. (25)

The latest two trials, which tested dual-antiplatelet therapy (DAPT) regimens of 3 months and 1 month, are also noteworthy for giving a P2Y12 inhibitor after DAPT instead of aspirin monotherapy, which is a more common approach. Each randomized about 3,000 patients.

SMART- CHOICE(26) was a multicenter trial by Dr. Hahn and colleagues, conducted in South Korea, enrolled 2,993 patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents. Patients were randomized to receive either standard DAPT with aspirin and a P2Y12 inhibitor, or aspirin plus a P2Y12 inhibitor for 12 month versus 3 month respectively and the latter group received P2Y12 monotherapy 9 month followed first 3 month. Patients were classified by enrolling center, clinical presentation, type of stent, and type of P2Y12 therapy. Acceptable P2Y12 therapies were clopidogrel, ticagrelor, and prasugrel. The primary endpoint was a composite of major adverse cerebrovascular and cardiac events (MACE), including stroke, MI, or all-cause death, at 12 months after percutaneous coronary intervention.

Primary endpoint analysis showed that the cumulative rate of major adverse cerebrovascular and cardiac events was similar between both groups, at 2.9% in the P2Y12 group versus 2.5% in the DAPT group, which was statistically significant for noninferiority (P = .007). (26)

Similarly, the components of the primary endpoint – stroke, MI, or all-cause death – did not vary significantly between groups. No significant difference was detected for the risk of stent thrombosis. Although the major bleeding rate was comparable between groups, the overall bleeding rate was significantly lower in the P2Y12 inhibitor group than the DAPT group (2.0% vs. 3.4%; P = .02).(26)

The second trial, known as STOPDAPT-2, enrolled 3,009 patients who received a CoCr-EES drug-eluting stent at 89 medical centers in Japan.(27) Exclusion criteria including patients on oral anticoagulation, patients who could not tolerate clopidegrel, or history of the brain bleeding. Half of the patients were randomly assigned to receive standard DAPT. The other half took aspirin plus clopidogrel or prasugrel (another P2Y12 inhibitor) for the first month and took clopidogrel only after that, with patients who took prasugrel initially switching to clopidogrel after the first month.

In the one-month DAPT group, aspirin was stopped at one month in 96 percent of patients, while DAPT was continued up to one year in 88 percent of patients in the standard 12-month DAPT-

group. Overall, stopping aspirin after one month reduced the risk of adverse events by 36 percent. After one year, 2.4 percent of patients who stopped aspirin after one month experienced the composite primary endpoint compared to 3.7 percent among those following standard DAPT.

An analysis of secondary endpoints revealed stopping aspirin after one month significantly reduced the rate of bleeding. Overall, 0.4 percent of those stopping aspirin experienced major bleeding compared to 1.5 percent among those following standard DAPT. Furthermore, stopping aspirin after one month did not increase the events related to clotting, known as ischemic events, in a secondary endpoint that included a composite of death from cardiovascular causes, heart attack, clotting around the stent or stroke.(27)

Major Randomized Trials That Evaluated Prolonged Dual Antiplatelet Therapy (>1 Year)

Several trials have evaluated long term DAPT (Table 3 and Table 4). These include the following trials: The DES LATE; DAPT; ARCTIC; and OPTIDUALtrials. In these trials, DES LATE and DAPT had the highest proportion of the patients with high risk as defined by ACC/AHA guidelines

The DES LATE trial hypothesized that 12-month DAPT might provide better protection against cardiovascular events compared to >12 months DAPT. They randomized 5,045 Patients, who were receiving DAPT and were free of MACE and major bleeding for at least 12 months after DES implantation. Two cohorts included aspirin alone and aspirin + clopidogrel followed for 48 months (25). The study had about 60% patients with ACS, including 12% with STEMI at the time of DES implantation. The primary endpoint was composite of cardiac death, MI, or stroke within 24 months after randomization, and the rates of primary endpoint were 2.4% and 2.6% in monotherapy and DAPT, respectively (HR=0.94, 95% CI=0.66- 1.35, P=0.75). Interestingly, this study did extensive sub-group analysis of individual factors including age, gender, DM, low ejection fraction, bifurcation lesion, stent length and even type of DES. There was no statistical difference in the primary endpoint, and TIMI major bleed 48 months with aspirin monotherapy or DAPT (HR=0.67, 95% CI=0.47- 0.95, P=0.026). (28)

The DAPT trial was one of the largest trials concluded that evaluated the benefits of dual antiplatelet therapy beyond one year (13). At the end, the treatment group with aspirin with clopidogrel had lower stent thrombosis compare to the aspirin alone. (0.4% vs. 1.4%, HR=0.29, 95% CI=0.17- 0.48, P<0.001). Also, the treatment group had fewer major cardiovascular and cerebrovascular events (4.3% vs. 5.9%, HR=0.71, 95% CI=0.59- 0.85, P<0.001). The results of the DAPT trial with treatment beyond one year demonstrated a reduction in major cardiovascular events but had an increase in the risk of bleeding (2.5% vs. 1.6%, P=0.001). There was a borderline difference in all-cause mortality between the two groups (1.5% in patients with aspirin alone beyond 12 months vs. 2.0% in thienopyridine group, P=0.052). Nonetheless, the rate of death from cardiovascular causes were similar in both groups. It is important to note that there was a larger number of patients with the history of cancer assigned to extended DAPT group, and this might explain the difference in mortality (26).The Patient population in DAPT study had various types of DES implantation. They had about 42% of patients presenting with ACS, including 10% with STEMI.

The ARCTIC Interruption trial was a continuation of the ARTIC trial. This evaluated the superiority of DAPT at 18 versus 12 months for the primary endpoint of death, MI, stent thrombosis, stroke, and urgent revascularization (14). The study showed no benefit with the extension of DAPT beyond one year using first and second-generation DES. Primary endpoint occurred in 4% of the patients in both groups (HR=1.17, 95% CI=0.68_2.03, P=0.58) (14). The study also showed higher major and minor bleeding in patients with longer duration of DAPT (12 [2%] patients vs three [1%] patients; HR 0·26 [0·07–0·91]; p=0·04). (14).

The OPTIDUAL trial was designed to show the superiority of 48 months of DAPT over 12 months in reducing death, MI, and stroke (29). The study was terminated early due to not reaching the primary endpoint when 1385 out of 1966 enrolled (5.8% versus 7.5%, HR=0.75, 95% CI=0.50- 1.28) Multiple types of DES including first-generation DES (34.3%), and second-generation DES (65.7%) were used in this study. ACS was seen in 36.2% of cases. This trial had relatively low event rate, and, they selected patients after 12 months of DAPT therapy without major adverse events, accordingly patients had a low bleeding risk.

Meta-Analyses of Studies That Evaluated Dual Antiplatelet Therapy Duration

With a large number of trials and large patient population, several meta-analyses attempted to evaluate the risk-benefit ratio of long- vs. Short-term DAPT. Some of the most extensive meta-analysis were comprised 10 RCT, 14 RCTs, 10 RCTs, and 7 RCTs, performed by Palmerini et al., Elmariah et al., Giustino et al. and Ziada et al. respectively (30) (31) (32) (33)(29-32).

Palmerini et al. evaluated ten trials with 31,666

patients and demonstrated that shorter DAPT was associated with significantly lower rates of bleeding but increased rate of MI and stent thrombosis (30). Shorter DAPT was also associated with significantly lower rates of all-cause mortality due to decreased non-cardiac mortality. Therefore, long duration of DAPT needs to be carefully considered against the risk of bleeding vs the risk of stent thrombosis (30) (29).

Elmariah et al. demonstrated that prolonged DAPT was not associated with increased all-cause mortality compared to short-term DAPT (≤ 6 months) (30). They analyzed 14 trials that had 69,644 patients, of which 10 trials had subjects with CAD post PCI and/or ACS. There was no all-cause and cardiovascular mortality difference in prolonged- versus short- duration DAPT. However, they did not consider cardiovascular events, instead they focused only on the mortality outcomes.

Giustino et al. included the same trials as Palmerini et al. but with 32,135 patients. They concluded that stent thrombosis and MI was higher in the short-term DAPT groups, but the effect was attenuated by the second- vs. first- generation DESs. All-cause mortality was higher in the long-term DAPT; however, the difference was not statistically significant. It is noteworthy that the impact of short-term DAPT on stent thrombosis was attenuated with the use of second-generation DES (32).

Ziada et al. evaluated 7 trials with 15,874 randomized patients. They demonstrated that abbreviated DAPT was not associated with an increase in mortality, MI, or stent thrombosis, while the bleeding complications were significantly less in the short term DAPT (29). Therefore, short-duration DAPT can be reasonable for patients with high risk of bleeding who underwent PCI with second-generation DESs. (19) (30) (33).

Summary

The duration of DAPT is a dynamic area to evaluate with studies that vary in their structure and patient cohorts. Various studies and meta-analysis have suggested that short-term DAPT can be used safely without significantly affecting the incidence of stent thrombosis and mortality particularly in patients with the newer generation DESs. The trials included in this review were conducted between the periods of 2008-2019. The overall focus was to summarize the findings of the trials while specifically focusing on the incidence of high-risk subjects. Most of the trials evaluated the non-inferiority of short-term (6 months or less) vs. long-term (1 year or more) therapy. Many studies had limitations of low recruitment, early termination, and lower than expected adverse event rates, thus had limited statistical power. The complexity of arterial lesions and multiple stents were not reported uniformly, and in majority of trials, there was no attempt to risk stratify patients concerning duration of the DAPT. In addition, trials often used different bleeding scores and often enrolled low-risk patients (Table1). These facts have often led the clinical practice to continue DAPT for a longer duration than recommended by the guidelines. Most importantly, not only have different trials used different types of stents, but also, within the same trial multiple types of stents have been used (Table1, 2).

The PRODIGY and ZEUS had the highest proportion of patients presenting with acute MI (Table 2) and DES LATE had the highest proportion of complex lesions. Interestingly, even trials with highest proportion of high risk- patient (i.e. ZEUS, PRODIGY and RESET) have demonstrated the safety of short duration DAPT compared to 12 months. While most studies have not performed risk stratification for patients undergoing PCI, the ZEUS and DES LATE trials evaluated the benefit, or non-inferiority, of the duration of DAPT in patients with high risk for recurrent events and stent thrombosis. Interestingly DES LATE study also did extensive sub-group analysis of individual factors such as age, gender, DM, low ejection fraction, bifurcation lesion, stent length, and even type of DES with no statistically significant difference in the primary endpoints. The longest mean length of the stents among the studies was 38mm in ITALIC trial (Table 2), while in common practice, we often exceed this in patients with complex and multiple lesions. The PEGASUS TIMI-54 trial demonstrated that the use of DAPT for more than 1 year following MI reduced the composite risk of cardiovascular death, MI, or stroke (hazard ratio: 0.84; 95% CI: 0.74 to 0.95) but increased major bleeding (hazard ratio: 2.32; 95% CI: 1.68 to 3.21) (10).

The latest 2 Trials SMART- CHOICE and STOP DAPT2 showed that the very short DAPT duration of 1 month would be a potential option even in patients without high bleeding risk. Given the very low rates of stent thrombosis in studies using contemporary drug-eluting stents, avoiding bleeding with de-escalation of antiplatelet therapy may be more important than attempting further reduction of stent thrombosis with intensive antiplatelet therapy.

Although the data support non-inferiority of short-term vs. long-term DAPT, the optimal duration of DAPT in high-risk patients and those with recurrent events remains challenging. One clear trend is higher bleeding incidence with longer duration DAPT ((7),(18), and (33)). Some studies have also

demonstrated an increased incidence of mortality, MI, and strokes with longer duration of the DAPT ((7), (34)). These results suggest the need for conducting further studies in cohorts with higher risk of poor cardiovascular outcomes, including patients with diabetes mellitus, peripheral vascular disease, chronic renal dysfunction, multi-vessel CAD, heart failure, complex lesions, low- and high- risk ACS, MI, and high bleeding risk. Moreover, it should be considered that the optimal duration of DAPT is somewhat of a moving target given continued improvements in stent technology and clinical experience. Finally based on available evidence it would be reasonable to state that short-term DAPT (i.e. 6 months) is perhaps safe and can be recommended in low-risk patients or patients with high risk of bleeding who receive second-generation DES implant.

However, until there is better risk stratification and classification of high-risk patients, we still have to consider using extended DAPT (i.e., 12 months or beyond). Possibly, high-risk patient may benefit in certain cases from the extended DAPT, not through the prevention of stent thrombosis, but likely through the prevention of cardiovascular events, as shown in the DAPT and DES LATE trial (thus far the trials with the most number of patients) ((28), (13), and (15)). Until further studies are conducted, the duration of DAPT is depends on the judgement of the treating physician while taking into account an individual patient's risks profile. Additional studies are anticipated especially given continued progress in stent and device technology while the risk of bleeding complications secondary to DAPT persists.

Table 1: Summarizing stent types, outcomes, limitations of the short term DAPT trials.

Trial	Study Arms and Duration of DAPT	Stent Type	Results	Bleeding Classification	Advantages and Limitations
PRODIGY	n = 983 for 6 mo vs. 987 for 24 mo	Third generation thin-strut BMS, E-ZES, Taxus, or Xience V	Death from any cause, MI, or stroke was significantly less with 24 vs. 6 mo DAPT. Long-term DAPT was associated with higher bleeding events	TIMI and BARC scoring classification	First and second generation DES and BMS were included
EXCELLENT	n = 722 for 6 mo vs. 721 for 12 mo	EES or SES in 3:1 ratio	Target vessel failure was non-inferior at 6 compare to 12 mo of DAPT	TIMI classification	Low event rate than expected, thrombosis and/or restenosis were combined and no report of Revascularization, MI or death
RESET	n = 1058 for 3 mo vs. 1059 for 24 mo	EES, E-ZES, R-ZES, SES	DAPT with E-ZES stent for 3 vs.12 mo with other stents was non-inferior for cardiovascular death, MI, stent thrombosis, Revascularization or bleeding	TIMI classification	Study was underpowered, limited to 1 year, and did not include high risk patients
OPTIMIZE	n = 1560 for 3 mo vs. 1560 for 12 mo	E-ZES	ZES only in stable coronary arterEmerald Isley disease and low risk ACS, 3 vs.12 mo DAPT is not inferior for all-cause death, MI, stroke or major bleeding.	GUSTO criteria and BARC	Well powered study compared to other trials
Z-EUS	n=803 BMS vs 801 ZES	ZES, BMS	When compared to BMS E-ZES stent with abbreviated DAPT had less thrombosis, MI, revascularization	BARC TIMI GUSTO	DAPT was based on the patient's risk profile not on the type of stent used DES vs BMS
ITALIC	n = 953 for 6 mo vs. 941 for 24 mo	Xience V	Bleeding rates and thrombosis for 6 vs. 24 mo was ns	TIMI Classification	Low enrollment
ISAR-SAFE	n=1998 for 6 mo vs. 2007 for 12 mo	BMX, ZES, EES, BES, SES, PES	6 vs 12 mo DAPT was noninferior for cardiac death, MI, stroke, TIMI bleeding	TIMI	trial used only clopidogrel low reported events early termination of trial
SECURITY	n=682 for 6 mo vs. 717 for 12 mo	Endeavor Resolute stent, Nobori stent, Biomatrix, Promus, Xience stent	6 vs 12 mo DAPT was noninferior for cardiac death, MI, stroke, definite or probable ST	BARC	Low event rate than expected, underpowered included only patients with low-risk profile
STOPDAPT -2	N=1500 in the 1-month DAPT group and N=1509 in the12-month-DAPTgroup	CoCr-EES	compare 1 month of DAPT with 12 months of DAPT after CoCr-EES implantation	CREDO-Kyotobleeding	Both cardiovascular and bleeding events was used as the primary end point, Second, the present study was not powered for noninferiority for the major secondary cardiovascular composite end poin
SMART-CHOICE	1495 P2Y12 inhibitor alone vs 1498 DAPT for 12 months	Xience, Promus, Orsiro	P2Y12inhibitor monotherapy after3 months of DAPT compared with prolonged DAPT was noninferior for MACE	BARC	Non-inferiority margin was relatively wide, Open-label trial not placebo control, Trial was on low risk-population.

Table 2: Summarizing the high-risk factors and stent type for short term DAPT

Name	No. of patients	Age (mean)	Acute MI (%)	Mean or Median Stent Length (mm)	Mean or Median Stent size (mm)	Lesion B 2 / C (%)	Previous MI (%)	DM (%)	Prior PCI or CABG (%)	EF <50 (%)
PRODIGY	1970	67.9	55.7	30	3	66.4	26.8	24.2	29.1	
EXCELENT	1443	62.7	0	28		53	5.1	38.1	10.2	
RESET	2117	62.4	14.3	22.8	3.18	68.6	1.7	29.3	4.5	
OPTIMIZE	3119	61.6	0	32.74		37.2	34.7	35.4	27.7	35.8
ZEUS	1606	71.8	46.5	28	3	73.1	23.9	26.2	26	
ITALIC	1953	61.9	7.4	36.5	3.1		16	36.7	29.5	19.7
ISAR-SAFE	4000	67.2	18.4	28		43.9	25.2	24.5	7.6	
SECURITY	1399	65.2	0	19.1	3	21	20.7	30.7	23.2	
STOPDAPT -2	3045	68.1	37.7	30.3	2.98	28.8	13.8	39.0	34.6	4.3
SMART-CHOICE	2993	64.6	11.0	38.0		36.4	11.0	38.2	11.5	

Table 3: Summarizing stent types, outcomes, limitations of the long term DAPT trials

Trial	Study Arms and Duration of DAPT	Stent Type	Results	Bleeding Classification	Avantages and Limitaions
DES-LATE	All patients additional 24 months; n=2514 aspirin alone, n=2531 DAPT	Sirolimus Paclitaxel Zotarolimus Everolimus Others	DAPT beyond 12 mo significantly reduced major cardiovascular and cerebrovascular events but increased risk of bleeding	TIMI	The study was based on all generations of DES. They had 2 separate cohorts over period. Adherence rate in DAPT was relatively low.
DAPT	After 12 mo of DAPT: n = 5020 ASA + clopidegrel vs.n = 4941 ASA+ placebo for 12 mo	Cypher, E-ZES, Taxus, and EES	18mo vs 12 mo DAPT was nonsuperior for cardiac death, MI, stroke, ST, urgent revascularization	GUSTO and BARC criteria	The study was based on all generations of DES
ARCTIC Interruption	After 12 mo of DAPT: n = 5020 ASA + clopidegrel vs.n = 4941 ASA+ placebo for 12 mo	1st and 2nd generation DES	48mo vs 12 mo DAPT was nonsuperior for cardiac death, MI, stroke	STEEPLE	
OPTIDUAL	n=697 for 12 mo vs. n=701 for 48 mo	DES(Sirolimus, Paclitaxel, zotarolimus, Everolimus, Biodegradable polymer, Biolimus Eluting stent	48mo vs 12 mo DAPT was nonsuperior for cardiac death, MI, stroke	ISTH	Underpowered study due to low enrollment

Table 4: Summarizing the high-risk factors and stent type for long term DAPT trials.

Name	No. of patients	Age (mean)	Acute MI (%)	Mean or Median Stent Length (mm)	Mean or Median Stent size (mm)	Lesion B2/C (%)	Previous MI (%)	DM (%)	Prior PCI or CABG (%)	EF <50 (%)
DES LATE	5045	62.4	23	30.4		78.5	3.9	28	11.7	
DAPT	9961	61.7	26	27.6		43.3	21.6	30.6	42.1	
ARCTIC INTERRUPTION	1259	64	0				30.4	33.4	48	
OPTIDUAL	1385	64.1	26.9	18.7			17.4	31.4	31.6	

Cite this article: Decide the Duration of Dual Antiplatelet Therapy (DDD). Am J of Card and Cardiovas Disc. 2019; 2(2): 01-09.

REFERENCES

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet Lond Engl. 1996; 348: 1329-1339.
2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345: 494-502.
3. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet Lond Engl. 2001; 358: 527-33.
4. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334: 1084-1089.
5. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998; 339: 1665-1671.
6. Steinhubl SR, Berger PB, Mann JT, Fry ETA, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002; 288: 2411-2420.
7. Habib A, Finn AV. Endothelialization of drug eluting stents and its impact on dual anti-platelet therapy duration. Pharmacol Res. 2015; 93: 22-27.
8. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007; 297: 159-168.
9. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006; 354: 1706-1717.
10. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015; 372: 1791-800.
11. Udell JA, Bonaca MP, Collet J-P, Lincoff AM, Kereiakes DJ, Costa F, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016; 37: 390-399.
12. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. J Am Coll Cardiol. 2016; 68: 1082-1115.
13. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. N Engl J Med. 2014 ; 371: 2155-2166.
14. Collet J-P, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet Lond Engl. 2014; 384: 1577–1585.
15. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016; 68: 1116-1139.
16. Spencer FA, Prasad M, Vandvik PO, Chetan D, Zhou Q, Guyatt G. Longer- Versus Shorter-Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis. Ann Intern Med. 2015; 163: 118-126.
17. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTSThe Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018; 39: 213-260.
18. Valgimigli M, Campo G, Percoco G, Monti M, Ferrari F, Tumscitz C, et al. Randomized comparison of 6- versus 24-month clopidogrel therapy after balancing anti-intimal hyperplasia stent potency in all-comer patients undergoing percutaneous coronary intervention Design and rationale for the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). Am Heart J. 2010; 160: 804-811.
19. Gwon H-C, Hahn J-Y, Park KW, Song YB, Chae I-H, Lim D-S, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012; 125: 505-513.
20. Kim B-K, Hong M-K, Shin D-H, Nam C-M, Kim J-S, Ko Y-G, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012; 60: 1340-1348.
21. Feres F, Costa RA, Bhatt DL, Leon MB, Botelho RV, King SB, et al. Optimized duration of clopidogrel therapy following treatment with the Endeavor zotarolimus-eluting stent in real-world clinical practice (OPTIMIZE) trial: rationale and design of a large-scale, randomized, multicenter study. Am Heart J. 2012; 164: 810-816.
22. Valgimigli M, Patialiakas A, Thury A, McFadden E, Colangelo S, Campo G, et al. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. J Am Coll Cardiol. 2015; 65: 805-815.
23. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015; 65: 777-786.
24. Schulz-Schüpke S, Byrne RA, Ten Berg JM, Neumann F-J, Han Y, Adriaenssens T, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015; 36: 1252-1263.
25. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014; 64: 2086-2097.
26. Hahn J-Y, Song YB, Oh J-H, Chun WJ, Park YH, Jang WJ, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA. 2019; 321: 2428–2437.
27. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA. 2019; 321: 2414-2427.

Cite this article: Decide the Duration of Dual Antiplatelet Therapy (DDD). Am J of Card and Cardiovas Disc. 2019; 2(2): 01-09.

28. Lee CW, Ahn J-M, Park D-W, Kang S-J, Lee S-W, Kim Y-H, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. Circulation. 2014; 129: 304-312.

29. Helft G, Steg PG, Le Feuvre C, Georges J-L, Carrie D, Dreyfus X, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J. 2016; 37: 365-374.

30. Palmerini T, Sangiorgi D, Valgimigli M, Biondi-Zoccai G, Feres F, Abizaid A, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. J Am Coll Cardiol. 2015; 65: 1092-1102.

31. Elmariah S, Mauri L, Doros G, Galper BZ, O'Neill KE, Steg PG, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet Lond Engl. 2015; 385: 792–798.

32. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015; 65: 1298-1310.

33. Ziada KM, Abdel-Latif AK, Charnigo R, Moliterno DJ. Safety of an abbreviated duration of dual antiplatelet therapy (≤6 months) following second-generation drug-eluting stents for coronary artery disease: A systematic review and meta-analysis of randomized trials. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv. 2016; 87: 722-732.

34. Park S-J, Park D-W, Kim Y-H, Kang S-J, Lee S-W, Lee CW, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010; 362: 1374-1382.

Cite this article: Decide the Duration of Dual Antiplatelet Therapy (DDD). Am J of Card and Cardiovas Disc. 2019; 2(2): 01-09.