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Duration of dual antiplatelet treatment in the era of next generation drug-eluting stents

**Rha SW**. Dual antiplatelet duration following drug-eluting stenting

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**Abstract**

Current percutaneous coronary intervention guidelines recommended that dual antiplatelets (aspirin 100 mg + clopidogrel 75 mg daily) for at least 12 mo following drug-eluting stent (DES) implantation if patients are not at high risk of bleeding. Several reports have been tried to shorten the dual antiplatelet therapy up to 3-6 mo, especially following next-generation DES implantation for cost-effectiveness. However, the clinical results have been inconsistent and the data regarding next-generation DESs are limited. In this report, we summarized recently published important pivotal reports regarding the optimal duration of dual antiplatelets following DES implantation.

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**Key words:** Drug-eluting stent; Dual antiplatelet treatment; Percutaneous coronary intervention

**Core tip:** We summarized recently published important pivotal reports regarding the optimal duration of dual antiplatelets following drug-eluting sten implantation.

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**INTRODUCTION**

Multiple randomized clinical trials have shown the efficacy of drug-eluting stents (DES) in reducing restenosis and need for target lesion revascularization (TLR) as compared with bare-metal stents (BMS)[1,2]. Despite of reduced incidence of recurrence, safety issues related DESs such as stent thrombosis, late stent malapposition, aneurysm, stent fracture, endothelial dysfunction and restenosis were reported elsewhere, particularly with first-generation DESs. Further, some observational studies have shown that the risk of death or myocardial infarction was even higher with DESs than BMSs, possibly due to higher incidence of late or very late stent thrombosis[3].

Early or premature discontinuation of dual antiplatelet therapy has been reported as an important risk factor for late stent thrombosis following DES implantation[4,5]. Thus, current percutaneous coronary intervention (PCI) guidelines recommended that dual antiplatelets (aspirin + clopidogrel 75 mg daily) for at least 12 mo following DES implantation if patients are not at high risk of bleeding[6]. Several reports have been tried to address this issue but the results have been inconsistent and the data regarding second-generation DESs are limited. In this report, I would like to summarize important pivotal reports regarding the optimal duration of dual antiplatelets following DES implantation, particularly in patients underwent PCI with next generation DESs.

**OPTIMAL DURATION OF DUAL ANTIPLATELET THERAPY WITH DESS**

***Major clinical trials for duration of dual antiplatelets after DES implantation***

**REAL-LATE and ZEST-LATE trial:** (Aspirin+ Clopidogrel *vs* Aspirin alone after 1 year). A randomized trial from Korea have shown that the dual antiplatelet for longer than 12 mo following DES implantation was not significantly more effective than aspirin monotherapy[7]. In two trials (REAL-LATE and ZEST-LATE trials were merged), they randomly assigned a total 2701 patients who had received DESs and had been free of major adverse cardiac or cerebrovascular events and major bleeding for a period of at least 12 mo to receive clopidogrel plus aspirin or aspirin alone.

In this trial, more than half of the patients were received Sirolimus-eluting stent (SES, Cypher, Cordis) and rest of the patients received Paclitaxel-eluting stent (PES, Taxus, Boston Scientific) or Zotarolimus-eluting stent (ZES, Endeavor, Medtronic). Thus, the study population underwent PCI with predominantly first-generation DESs.

The median duration of follow-up was 19.2 mo. The cumulative incidence of primary outcomes (composite of myocardial infarction or death from cardiac causes) at 2 years was 1.8% with dual antiplatelet therapy, as compared with 1.2% with aspirin monotherapy (HR = 1.65; 95%CI: 0.80-3.36; *P =* 0.17). The individual risks of myocardial infarction, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death from any cause did not differ between the two groups. However, in dual therapy group, there was a non-significant increase in the composite risk of myocardial infarction, stroke, or death from any cause (HR = 1.73, *P =* 0.051) and in the composite risk of myocardial infarction, stroke, or death from cardiac causes (HR = 1.84, *P =* 0.06, Table 1). This trial concluded that the use of dual antiplatelet for longer than 12 mo following DES implantation was not more effective than aspirin monotherapy in reducing the rate of myocardial infarction or death from cardiac causes.

Recently, DES-LATE trial was reported that the patients who were on 12-mo dual antiplatelet therapy without complications, an additional 24 mo of dual antiplatelet therapy *vs* aspirin alone did not reduce the risk of major composite hard endpoints (cardiac deaths, myocardial infarction or stroke)[8].

**The EXCELLENT trial:** (Dual antiplatelet 6 mo *vs* 12 mo). Some previous registry data suggested that dual antiplatelet less than 12 mo after DES implantation does not increase major adverse cardiac events (MACE) and that there was no apparent clinical benefit from dual antiplatelet for longer than 6 mo[9-11]. Data comparing shorter duration of dual antiplatelets compared with 12-mo dual antiplatelets are very limited and the EXCELLENT (Efficacy of Xience/Promus *vs* Cypher to Reduce Late Loss After Stenting) trial from South Korea, they compared 6-mo *vs* 12-mo dual antiplatelet therapy following DES implantation[12].

They randomly assigned 1443 patients following DES implantation to receive 6-mo or 12-mo dual antiplatelets. The primary endpoint was a target vessel failure (composite of cardiac death, myocardial infarction, or ischemia-driven target vessel revascularization) at 12 mo.

The rate of target vessel failure at 12 mo were 4.8% in the 6-mo dual antiplatelet group and 4.3% in the 12-mo group (the upper limit of 1-sided 95%CI: 2.4%; *P =* 0.001 for non-inferiority with a predefined non-inferiority margin of 4.0%). Although stent thrombosis tended to occur frequently in the 6-mo dual antiplatelets group than 12-mo group (0.9% *vs* 0.1%, HR = 6.02; 95%CI: 0.72-49.96; *P =* 0.10), the risk of death or myocardial infarction did not differ in the two groups. In the pre-specified subgroup analysis, target vessel failure occurred more frequently in the 6-mo dual antiplatelet group (HR = 3.16; 95%CI: 1.42-7.03; *P =* 0.005) among diabetic patients (Table 2).

This study population predominantly received Everolimus-eluting stent (EES, Xience or Promus, 74.8%) and rest of patients received SES (25.2%). So the study population was heterogeneous in terms of different DESs, and particularly first *vs* second generation DESs.

They concluded that six-month dual antiplatelets did not increase the risk of target vessel failure at 12 mo after DES implantation compared with 12-mo dual antiplatelets.

Although 6-month dual antiplatelets cannot be recommended in the general population on the basis of this trial and this may be helpful for physicians to decide the duration of dual antiplatelets case by case in real-world clinical practice.

**PRODIGY trial:** (Dual antiplatelet 6 mo *vs* 24 mo). The purpose of PRODIGY trial (Prolonging Dual Antiplatelets Treatment After Grading Stent-Induced Intimal Hyperplasia) was to assess the effect of dual antiplatelets for 6 mo *vs* 24 mo on long-term clinical outcomes after PCI in a broad all-comers patient population receiving a balanced DES or base-metal stent (BMS)[13].

They randomly assigned 2013 patients to receive BMS, ZES, PES or EES. At 30 d, each stent group was randomly allocated to receive up to 6 mo or 24 mo of clopidogrel therapy in addition to aspirin.

The cumulative risk of the primary outcome (composite of death of any cause, myocardial infarction, or cerebrovascular accident) at 2 years was 10.1% with 24-month dual antiplatelet group compared with 10.0% with 6-mo group (HR = 0.98; 95%CI: 0.74-1.29; *P =* 0.91 Figure 1). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between the two groups; however, there was a consistently greater risk of hemorrhage in the 24-mo group. They concluded that a regimen of 24-mo clopidogrel therapy in patients who had received a balanced mixture of DES or BMS was not significantly more effective than 6-mo regimen in reducing the composite of death from any cause, myocardial infarction or cerebrovascular accident.

**TWENTE Trial:** (Discontinuation of dual antiplatelets after 12 mo in ZES and EES). Second-generation DES such as EES (Xience V, Abbott Vascular, Santa Clara, California) and ZES (Resolute ZES, Medtronic Inc, Santa Rosa, California) were developed to improve clinical outcomes by the overcoming the limitation of first-generation DESs[14,15]. The randomized TWENTE (The Real-World Endeavor Resolute *vs* Xience V DES Study in Twente) trial is an investigator-initiated study performed in a population with many complex patients and lesions and only limited exclusion criteria[16]. Patients were randomly assigned 1:1 to ZES (*n =* 697) or EES (*n =* 694).

Two year follow up information was available on all patients. A strict policy of discontinuation of dual antiplatelets after 12 mo was followed, which is of interest for the present pre-specified 2-year analysis of clinical outcomes[17]. The rate of continuation of dual antiplatelet beyond 12 mo was very low (5.4%). The primary endpoint of target vessel failure, a composite of cardiac death, target vessel-related myocardial infarction, and target vessel revascularization, did not differ between ZES and EES (10.8% *vs* 11.6%, *P =* 0.65), despite fewer target lesion revascularizations in patients with EES (2.6% *vs* 4.9%, *P =* 0.03). The patient-oriented composite endpoint was similar (16.4% *vs* 17.1%, *P =* 0.75). Two-year rates of definite or probable stent thrombosis were 1.2% and 1.4%, respectively (*P =* 0.63). Very late definite or probable stent thrombosis occurred only in 2 patients in each study arm (0.3% *vs* 0.3%, *P =* 1.00, Table 3).

They concluded that after 2 years of follow-up and stringent discontinuation of dual antiplatelets beyond 12 mo, Resolute ZES and Xience V EES showed similar results in terms of safety and efficacy for treating patients with a majority of complex lesions and off-label indications for DESs.

***Other recent clinical reports***

Kotani *et al*[18] recently reported 5-year follow up results after SES implantation. They analyzed a prospective registry of 2050 patients with SES during a 5-year follow-up. A total 1691 patients were divided into two groups; dual antiplatelets ≤ 12 mo, *n =* 749 and dual antiplatelets > 12 mo, *n =* 942 and compared the clinical outcomes using a landmark analysis. The frequencies of MACE (15.6% *vs* 18.2%), death (10.0% *vs* 11.5%), myocardial infarction (2.3% *vs* 2.1%), target lesion revascularization (4.5% *vs* 11.5%) and stent thrombosis (0.8% *vs* 0.8%) were similar between the two groups. However, with regard to bleeding, an increase in the frequency of hemorrhage events was observed after 4 years from the index procedure in the dual antiplatelets > 12 mo group. They concluded that dual antiplatelets beyond 12 mo was associated with increased frequency of bleeding complications and does not prevent the incidence of MACE, including stent thrombosis, during 5 years follow-up after SES implantation.

Recently published meta-analysis also support shorter duration of dual antiplatelets for both safety and efficacy following DES implantation[19]. They searched from database inception to December 2011 for randomized controlled trials that compared longer *vs* shorter dual antiplatelet duration after DES implantation. Three randomized controlled trials comparing 5622 patients were included. Compared with short-term therapy, longer dual antiplatelet duration had a pooled OR of 1.26 (95%CI: 0.88-1.80; *P =* 0.21, random-effects) for the primary outcomes of cardiac death, myocardial infarction or stroke, OR of 1.29 (95%CI: 0.85-1.93; fixed-effects) for all-cause death, 1.23 (95%CI: 0.78-1.93; fixed-effects) for cardiac death, 0.91 (95%CI: 0.58-1.42; random-effects) for myocardial infarction, 1.93 (95%CI: 1.01-3.69; fixed-effects) for stroked and 2.51 (95%CI: 1.10-5.71, fixed-effects) for TUMI major bleeding. The number needed to treat for an additional harmful outcome was 217.6 for stroke and 243 for TIMI major bleeding. This meta-analysis provides no evidence of benefits with longer dual antiplatelet duration as compared with a shorter course of therapy. It also reports significant harms with respect to major bleeding and stroke associated with prolonged dual antiplatelet use.

Another new clinical trial (OPTIDUAL; OPTImal DUAL antiplatelet therapy trial) is ongoing to assess the efficacy and safety of 12 *vs* 48 mo of dual antiplatelet therapy after DES implantation[20].

Lastly, regarding the clinical events associated with stent thrombosis, P2Y12 and thromboxane receptor is not the sole therapeutic measure to prevent the thrombotic risk. There must be different pathways leading to thrombotic events including hypersensitivity reactions[21, 22].

**CONCLUSION**

Despite of latest PCI guidelines of recommended at least 1-year of dual antiplatelet therapy, recent randomized clinical trials, registries and meta-analysis data showed that shorter duration of dual antiplatelet therapy is as effective as longer duration of dual antiplatelets regardless of DES type (whether first-generation or next generation DESs). Further, shorter duration of dual antiplatelets was associated with less bleeding complications without increasing incidence of stent thrombosis. Currently, at least 6 mo dual antiplatelets following next-generation DES implantation appears to be safe and effective even with expanded indication in contemporary PCI setting. However, caution should be exercised until get the enough clinical data in particular subset of higher risk patients including diabetes, aspirin and clopidogrel resistance or very complex lesion subset expecting vulnerability to stent thrombosis. In this review, we focused on only classical dual antiplatelets aspirin and clopidogrel. However, we have to get more data to define the role of newer generation P2Y12 inhibitors including Ticagrelor and Prasugrel, especially in acute coronary syndrome setting in the future.

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**Figure 1 Landmark analyses of PRODIGY Trial**[13]. Cumulative rates of composite of death, myocardial infarction, or cerebrovascular accident in all recruited patients (A) or in patients were randomly allocated to the drug-eluting stent groups (B) using the 6-month landmark analysis.

**Table 1 Clinical outcomes at 12 mo and 24 mo1**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Clinical Outcomes** | **At 12 mo** | | **At 24 mo** | | **HR**  **(95%CI)2** | ***P* Value** |
|  | Clopidogrel  +Aspirin | Aspirin  Alone | Clopidogrel  +Aspirin | Aspirin  Alone | Clopidogrel  +Aspirin | Aspirin  Alone |
| Primary end point: MI or death from cardiac causes | 0.7 | 0.5 | 1.8 | 1.2 | 1.65 (0.80-3.36) | 0.17 |
| Secondary end points |  |  |  |  |  |  |
| Death from any cause | 0.5 | 0.5 | 1.6 | 1.4 | 1.52 (0.75-3.50) | 0.24 |
| MI | 0.4 | 0.3 | 0.8 | 0.7 | 1.41 (0.54-3.71) | 0.49 |
| Stroke | 0.3 | 0.3 | 1.0 | 0.3 | 2.22 (0.68-7.20) | 0.19 |
| Stent thrombosis,definite | 0.2 | 0.1 | 0.4 | 0.4 | 1.23 (0.33-4.58) | 0.76 |
| Repeat revascularization | 1.7 | 1.1 | 3.1 | 2.4 | 1.37 (0.83-2.27) | 0.22 |
| MI or death from any cause | 0.8 | 0.8 | 2.3 | 1.7 | 1.57 (0.85-2.88) | 0.15 |
| MI, stroke, or death from  any cause | 1.1 | 1.1 | 3.2 | 1.8 | 1.73 (0.99-3.00) | 0.05 |
| MI, stroke, or death from  cardiac causes | 1.0 | 0.8 | 2.7 | 1.3 | 1.84 (0.99-3.45) | 0.06 |
| Major bleeding, according  to TIMI criteria | 0.2 | 0.1 | 0.2 | 0.1 | 2.96 (0.31-28.46\_ | 0.35 |

1For the total number of events for each type of end point, first events only are counted. Cumulative rates of events are based on Kaplan–Meier estimates. All deaths were considered to be from cardiac causes unless an unequivocal noncardiac cause could be established; 2Hazard ratios are for the dual-therapy group as compared with the aspirin-alone group. MI: Myocardial infarction. TIMI: Thrombolysis in myocardial infarction. (Modified from Ref [7]).

**Table 2 Clinical outcomes of EXCELLENT trial *n* (%)**

| **Clinical outcomes** | **6-mo DAPT**  **(*n =* 722)** | **12-mo DAPT**  **(*n =* 721)** | **HR**1 **(95%CI)** | ***P*** |
| --- | --- | --- | --- | --- |
| Target vessel failure[2](http://circ.ahajournals.org/content/125/3/505/T3.expansion.html#fn-7) | 34 (4.8) | 30 (4.3) | 1.14 (0.70–1.86) | 0.60 |
| Total death | 4 (0.6) | 7 (1.0) | 0.57 (0.17–1.95) | 0.37 |
| Cardiac death | 2 (0.3) | 3 (0.4) | 0.67 (0.11–3.99) | 0.66 |
| Myocardial infarction | 13 (1.8) | 7 (1.0) | 1.86 (0.74–4.67) | 0.19 |
| Death/myocardial infarction | 17 (2.4) | 14 (1.9) | 1.21 (0.60–2.47) | 0.58 |
| Target vessel myocardial infarction | 12 (1.7) | 6 (0.8) | 2.00 (0.75–5.34) | 0.16 |
| Cerebrovascular accident | 3 (0.4) | 5 (0.7) | 0.60 (0.14–2.51) | 0.48 |
| Target lesion revascularization | 17 (2.4) | 18 (2.6) | 0.94 (0.49–1.83) | 0.86 |
| Target vessel revascularization | 22 (3.1) | 22 (3.2) | 1.00 (0.56–1.81) | 0.99 |
| Any revascularization | 43 (6.2) | 43 (6.2) | 1.00 (0.66–1.53) | 0.99 |
| Stent thrombosis | 6 (0.9) | 1 (0.1) | 6.02 (0.72–49.96) | 0.10 |
| Any bleeding | 4 (0.6) | 10 (1.4) | 0.40 (0.13–1.27) | 0.12 |
| TIMI major bleeding | 2 (0.3) | 4 (0.6) | 0.50 (0.09–2.73) | 0.42 |
| MACCE[3](http://circ.ahajournals.org/content/125/3/505/T3.expansion.html#fn-9) | 56 (8.0) | 60 (8.5) | 0.94 (0.65–1.35) | 0.72 |
| Safety end point4 | 24 (3.3) | 21 (3.0) | 1.15 (0.64–2.06) | 0.64 |

DAPT indicates dual antiplatelet therapy; TIMI: Thrombolysis in myocardial infarction; MACCE: Major cardiocerebral event. The percentages shown are Kaplan-Meier estimates from the intention-to-treat analysis. 1HRs are for the 6-month *vs* 12-month DAPT group; 2Target vessel failure was a composite of cardiac death, myocardial infarction, or target vessel revascularization; [3](http://circ.ahajournals.org/content/125/3/505/T3.expansion.html#fn-9)MACCE was a composite of death, myocardial infarction, stroke, or any revascularization; 4Safety end point was a composite of death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding. (Modified from Ref. [12])

**Table 3 Two-year clinical outcomes of TWENTE Trial *n* (%)**

|  | **Resolute ZES (*n* = 695)** | **Xience V EES (*n* = 692)** | **Difference (95%CI)** | ***P* Value** |
| --- | --- | --- | --- | --- |
| Target vessel failure | 75 (10.8) | 80 (11.6) | -0.8 (-4.1 to 2.6) | 0.65 |
| Death |  |  |  |  |
| Any cause | 29 (4.2) | 33 (4.8) | -0.6 (-2.8 to 1.6) | 0.59 |
| Cardiac cause | 11 (1.6) | 19 (2.7) | -1.2 (-2.7 to 0.4) | 0.14 |
| Target vessel–related myocardial infarction |  |  |  |  |
| Any | 37 (5.3) | 39 (5.6) | -0.3 (-2.7 to 2.1) | 0.80 |
| Q-wave | 8 (1.2) | 9 (1.3) | -0.2 (-1.3 to 1.0) | 0.80 |
| Non–Q-wave | 29 (4.2) | 30 (4.3) | -0.2 (-2.3 to 2.0) | 0.88 |
| Clinically indicated target vessel revascularization |  |  |  |  |
| Any | 39 (5.6) | 35 (5.1) | 0.6 (−1.8 to 2.9) | 0.65 |
| Target lesion failure | 73 (10.5) | 68 (9.8) | 0.7 (−2.5 to 3.9) | 0.68 |
| Clinically indicated target lesion revascularization |  |  |  |  |
| Any | 34 (4.9) | 18 (2.6) | 2.3 (0.3 to 4.3) | 0.03 |
| Death from cardiac causes or target vessel myocardial infarction | 46 (6.6) | 53 (7.7) | -1.0 (-3.8 to 1.7) | 0.45 |
| Major adverse cardiac events[1](http://www.sciencedirect.com/science/article/pii/S073510971301485X#tbl2fnlowast) | 90 (12.9) | 82 (11.8) | 1.1 (-2.4 to 4.6) | 0.53 |
| Patient-oriented composite endpoint[2](http://www.sciencedirect.com/science/article/pii/S073510971301485X#tbl2fndagger) | 114 (16.4) | 118 (17.1) | -0.7 (-4.6 to 3.3) | 0.75 |
| Stent thrombosis |  |  |  |  |
| Definite (0-720 d) | 6 (0.9) | 1 (0.1) | 0.7 (-0.0 to 1.5) | 0.12 |
| Definite or probable (0-720 d) | 8 (1.2) | 10 (1.4) | -0.3 (-1.5 to 0.9) | 0.63 |
| Definite, probable, or possible (0-720 d) | 14 (2.0) | 20 (2.9) | -0.9 (-2.5 to 0.8) | 0.29 |
| Very late definite or probable (361-720 d) | 2 (0.3) | 2 (0.3) | 0 (-0.6 to 0.6) | 1.00 |

Values are n (%).1Major adverse cardiac events is a composite of all-cause death, any myocardial infarction, emergent coronary artery bypass surgery, and clinically indicated target lesion revascularization; [2](http://www.sciencedirect.com/science/article/pii/S073510971301485X#tbl2fndagger)Patient-oriented composite endpoint is a composite endpoint of all-cause death, any myocardial infarction, and any revascularization. (Modified from Ref. [17]).