TOPIC HIGHLIGHT

WJC 6ᵗʰ Anniversary Special Issues (5): Myocardial infarction

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

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Abstract

Current percutaneous coronary intervention guidelines recommend 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 tried to shorten the dual antiplatelet therapy to 3-6 mo, especially following next-generation DES implantation, for cost-effectiveness. However, the clinical results are inconsistent and the data regarding next-generation DESs limited. In this report, recently published important pivotal reports regarding the optimal duration of dual antiplatelets following DES implantation are summarized.

Core tip: Recently published important pivotal reports regarding the optimal duration of dual antiplatelets following drug-eluting stent implantation are summarized.

INTRODUCTION

Multiple randomized clinical trials have shown the efficacy of drug-eluting stents (DES) in reducing restenosis and the need for target lesion revascularization (TLR) compared with bare-metal stents (BMS)[1,2]. Despite the reduced incidence of recurrence, safety issues related to DESs, such as stent thrombosis, late stent malapposition, aneurysm, stent fracture, endothelial dysfunction and restenosis, have been reported elsewhere, particularly with first-generation DESs. Furthermore, some observational studies have shown that the risk of death or myocardial infarction was even higher with DESs than BMSs, possibly due to a 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 recommend 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 tried to address this issue but the results are inconsistent and the data regarding second-generation DESs limited. In this report, the important pivotal reports regarding the optimal duration of dual antiplatelets following DES implantation, particularly in patients who underwent PCI with next generation DESs, are summarized.

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 +

Table 1 Clinical outcomes at 12 mo and 24 mo[1]

Clinical outcomes	At 12 mo		At 24 mo		HR (95%CI)[2]	P
	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

[1]For the total number of events for each type of end point, only the first event is 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; [2]Hazard 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]).

clopidogrel *vs* aspirin alone after 1 year). A randomized trial from South Korea showed that dual antiplatelets 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), a total of 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 were randomly assigned to receive clopidogrel plus aspirin or aspirin alone.

In this trial, more than half of the patients received a sirolimus-eluting stent (SES, Cypher, Cordis) and the other half received a paclitaxel-eluting stent (PES, Taxus, Boston Scientific) or a 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 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 the 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 antiplatelets 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, the DES-LATE trial reported that in 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 antiplatelets for 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 antiplatelets for longer than 6 mo[9-11]. Data comparing a shorter duration of dual antiplatelets compared with 12 mo of dual antiplatelets are very limited. The EXCELLENT (Efficacy of Xience/Promus *vs* Cypher to Reduce Late Loss After Stenting) trial from South Korea compared 6 mo *vs* 12 mo dual antiplatelet therapy following DES implantation[12].

Following DES implantation, 1443 patients were randomly assigned 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 was 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 more 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) in diabetic patients (Table 2).

This study population predominantly received an everolimus-eluting stent (EES, Xience or Promus, 74.8%)

Valgimigli M *et al*. Circulation 2012; 125: 2015-2026
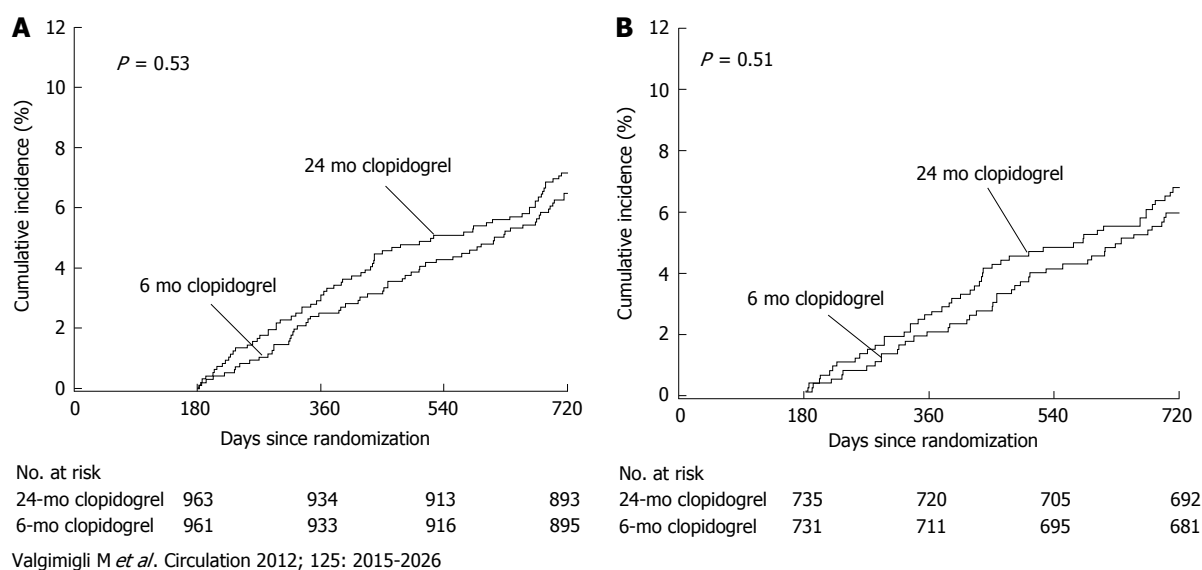
Figure 1 Landmark analyses of PRODIGY Trial[13]. Cumulative rates of composite of death, myocardial infarction or cerebrovascular accident in all recruited patients (A) or in patients randomly allocated to the drug-eluting stent groups (B) using the 6 mo landmark analysis.

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]	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]	56 (8.0)	60 (8.5)	0.94 (0.65-1.35)	0.72
Safety end point[4]	24 (3.3)	21 (3.0)	1.15 (0.64-2.06)	0.64

The percentages shown are Kaplan-Meier estimates from the intention-to-treat analysis. [1]HRs are for the 6 mo *vs* 12 mo DAPT group; [2]Target vessel failure was a composite of cardiac death, myocardial infarction or target vessel revascularization; [3]MACCE was a composite of death, myocardial infarction, stroke or any revascularization; [4]Safety end point was a composite of death, myocardial infarction, stroke, stent thrombosis or TIMI major bleeding. (Modified from Ref. [12]). DAPT: Dual antiplatelet therapy; TIMI: Thrombolysis in myocardial infarction; MACCE: Major cardiocerebral event.

and rest of the patients received SES (25.2%). The study population was heterogeneous in terms of different DESs, particularly first *vs* second generation DESs.

They concluded that 6 mo of dual antiplatelets did not increase the risk of target vessel failure at 12 mo after DES implantation compared with 12 mo of dual antiplatelets.

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

PRODIGY trial: (Dual antiplatelets 6 mo *vs* 24 mo). The purpose of the 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% in the 24 mo dual antiplatelet group compared with 10.0% in the 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 of clopidogrel therapy in patients who had received a balanced mixture of DES or BMS was not significantly more effective than a 6 mo regimen in reducing the composite of death from any cause, myocardial infarction or cerebrovascular accident.

Table 3 Two year clinical outcomes of TWENTE trial n (%)			
	Resolute ZES (n = 695)	Xience V EES (n = 692)	Difference (95%CI)	P
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]	90 (12.9)	82 (11.8)	1.1 (-2.4 to 4.6)	0.53
Patient-oriented composite endpoint[2]	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 (%). [1]Major 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]Patient-oriented composite endpoint is a composite endpoint of all-cause death, any myocardial infarction and any revascularization. (Modified from Ref. [17]). ZES: Zotarolimus-eluting stent; EES: Everolimus-eluting stent.

TWENTE Trial: (Discontinuation of dual antiplatelets after 12 mo in ZES and EES). Second-generation DESs, 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 overcoming the limitations 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 antiplatelets 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 TLRs 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 only occurred 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 of 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%), TLR (4.5% vs 11.5%) and stent thrombosis (0.8% vs 0.8%) were similar between the two groups. However, with regards 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 an increased frequency of bleeding complications and does not prevent the incidence of MACE, including stent thrombosis, during 5 years follow-up after SES implantation.

A recently published meta-analysis also supports a shorter duration of dual antiplatelets for both safety and efficacy following DES implantation[19]. They searched for randomized controlled trials that compared longer vs shorter dual antiplatelet duration after DES implantation from the database inception to December 2011. 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 = 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; and 1.93 (95%CI: 1.01-3.69; fixed-effects) for stroked and 2.51 (95%CI: 1.10-5.71, fixed-effects) for thrombolysis in myocardial infarction major bleeding. The number needed to treat for an additional harmful outcome was 217.6 for stroke and 243 for thrombolysis in myocardial infarction major bleeding. This meta-analysis provides no evidence of benefits with longer dual antiplatelet duration compared with a shorter

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

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