Dual Antiplatelet Therapy after Coronary Drug-eluting Stent Implantation in China: A Large Single Center Data

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Abstract

We investigated the real dual antiplatelet therapy (DAPT) duration after the drug-eluting stent (DES) treatment in China. 9,919 consecutive patients with DES implantation were enrolled. The follow-up DAPT cessation and associated factors with different DAPT durations were analyzed. The proportion of patients with DAPT coverage at 1-year follow-up was 97.3%, and decreased to 30.1% for 2-years. The distribution of DAPT duration (<1 year, =1 year and >1 year) was not significantly different among patients presented with AMI versus non-AMI (p=0.41), and new-generation DES versus first-generation DES (p=0.54). The multivariable analysis indicated some independent predictors of prolonging DAPT duration, including TVR (OR 2.50, 95% CI 2.04-3.06, p<0.001), stent numbers (OR 1.10, 95% CI 1.05-1.15, p<0.001), and previous coronary artery bypass grafting (OR 0.76, 95% CI 0.61-0.96, p=0.02). Other clinical factors such as the increased risks of bleeding and high ischemic risks were not associated with DAPT duration. 1-year DAPT after DES was applied to 97.3% in China. However, the DAPT duration after 1 year was not adjusted according to the patients' bleeding situation and ischemic risks.

Introduction

Dual antiplatelet therapy (DAPT), i.e., aspirin in combination with a P2Y12 antagonist, is an essential component of the treatment of patients undergoing percutaneous coronary intervention (PCI) especially with the drug-eluting stent (DES) [1]. Therefore, a minimum DAPT duration of 12 months after DES implantation had been recommended by guidelines, irrespective of reported clinical research results [1,2]. However, with the advent of new generation DESs, which are associated with a consistent reduction in stent thrombosis (ST) as compared with first-generation DES [3], the optimal duration of DAPT is being debated again. Although a reduced DAPT duration has been considered safe and with the reduced risk of bleeding complications [4-7], the ST longer than 12 months after the DES implantation was still observed [8]. Thus, updated guidelines with adjusted DAPT duration after DES implantation has been recommended according to the patients' bleeding and ischemic risks [9-11].

For real clinical cases, the DAPT duration after the DES implantation is more complicated, determined by both physicians' comprehension of the complex guidelines and the patients' compliance [12]. The data coming from the PARIS (patterns of non-adherence to anti-platelet regimens in stented patients) registry suggested that the proportions of patients with DAPT coverage after the DES implantation at 1-year and 2-year follow-up were 76.7% and 42.7%, respectively in 15 clinical sites in US and Europe [13]. However, less

has been reported about the situations in China. In this study, we analyzed a large amount of cases in the biggest cardiovascular center in China to investigate the DAPT duration and identify associated factors after the DES implantation.
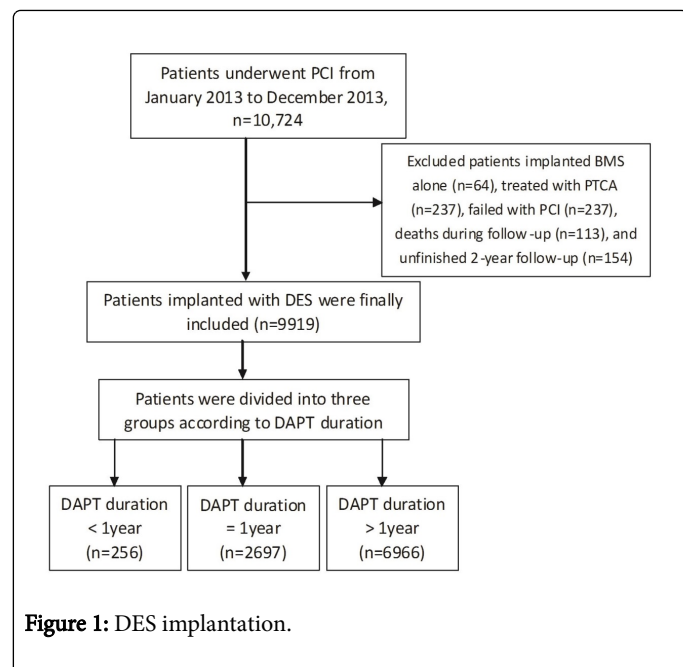
Patients and Methods

Study population

There were 10,724 patients undergoing the PCI treatment at Fu Wai Hospital, National Center for Cardiovascular Diseases (Beijing, China) from January to December in 2013. After excluding patients being implanted bare metal stent alone (n=64), treated with balloon angioplasty alone (n=237), failed with PCI (n=237), died during follow-up (n=113), and unfinished 2-year follow-up (n=154), 9,919 patients with the DES implantation were analyzed in this study (Figure 1). The study protocol has been approved by Institutional Review Board, and the written informed consent was provided to patients before the intervention.

Procedural and medications

The PCI strategy and stent type were left to treating physician's discretion. Before the procedure, if not taking long-term aspirin and clopidogrel, selective PCI patients received oral 300mg aspirin and clopidogrel (loading-dose 300 mg). Acute coronary syndrome (ACS) patients scheduled for PCI were given the same dose of aspirin and clopidogrel (loading-dose 300 mg or 600 mg) as soon as possible. During the procedure, unfractionated heparin (100 U/kg) was

administered to all patients, with glycoprotein IIb/IIIa inhibitors for operator's judgment. In 2013, other P2Y12 inhibitors such as prasugrel and ticagrelor were not routinely used in our center, only 16 patients (0.16%) received ticagrelor (loading-dose 180 mg) during that time.

Figure 1: DES implantation.

Patient follow-up

All patients were evaluated by clinic visits or by phone at 1, 3, 6, and 12 months after the procedure, and annually thereafter. Patients were advised to return for coronary angiography if clinically indicated by symptoms or shown myocardial ischemia.

Definitions

Duration of DAPT was defined as the length between the date of index PCI procedure and the DAPT cessation. The patients were divided into 3 groups according to DAPT duration: <1 year (0-11 months), =1 year (11-13 months), and >1 year (>13 months). New generation DES was defined as the second generation and biodegradable polymer DES. Myocardial Infarction (MI) was defined according to the third universal definition of myocardial infarction [14]. Target vessel revascularization (TVR) was defined as the repeated revascularization by PCI or surgery of the target vessel. Bleeding was defined by Bleeding Academic Research Consortium (BARC) [15]. All endpoints were adjudicated centrally by two independent cardiologists, and the disagreement was resolved by consensus.
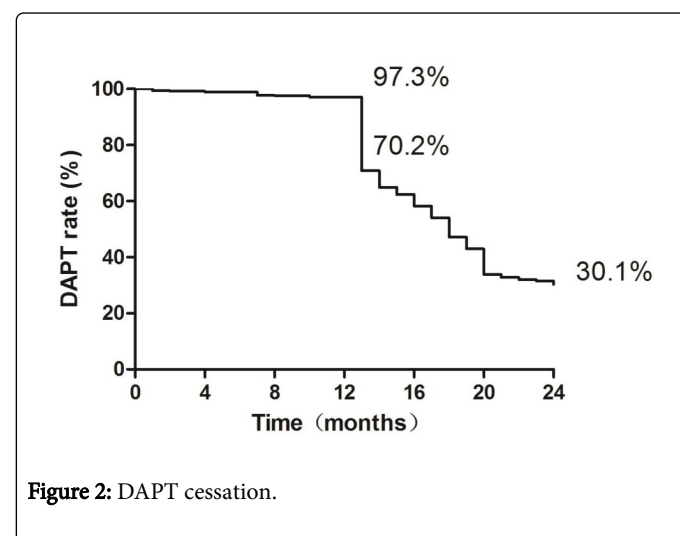
Statistical analysis

Continuous variables were presented as mean ± standard deviation, and Student's t tests or the Mann-Whitney rank sum test were performed for cross-group comparisons. Categorical variables were presented as frequency or ratio. The normally distributed continuous variables were compared using the 1-way ANOVA test, and categorical variables were compared by Pearson chi-square test among the three groups. The multivariate logistic regressions were used to evaluate the independent factors associated with shortening or prolonging DAPT duration over the study period, and the results were expressed by odds ratios (OR) with corresponding 95% confidence intervals. Both clinical and statistical significant covariates were considered in this model. All statistical analyses were performed at a significance level of two-sided 0.05 with the software of SAS® 9.2 (SAS Institute Inc, Chicago, IL).

Results

DAPT cessation during follow-up

The median follow-up time was 882 days (730-1101 days). The proportion of patients with the DAPT coverage at 1-year follow-up was 97.3%, and significantly dropped to 70.2% after 1 year, then decreased gradually thereafter till 30.1% at 2-year follow-up (Figure 2).

Figure 2: DAPT cessation.

Comparison among patients with different DAPT durations

The proportions of patients (9,919 in total) with the DAPT duration <1 year, =1 year, and >1 year were 2.6%, 27.2% and 70.2%, respectively. Patients' basic characteristics and clinical outcomes during the follow-up were shown in Table 1.

Basic characteristics were almost the same across three groups, except for the slightly older age, lower rate of hyperlipidemia and a higher rate of previous stroke in the group of DAPT duration <1 year. More stents / patient were found for the group of DAPT duration >1 year. During follow-up, patients in the >1 year group experienced more revascularization, and patients in the <1 year group had more stroke and bleeding events.

	DAPT duration <1 year (n=256)	DAPT duration=1 year (n=2697)	DAPT duration >1 year (n=6966)	p
Demographics				

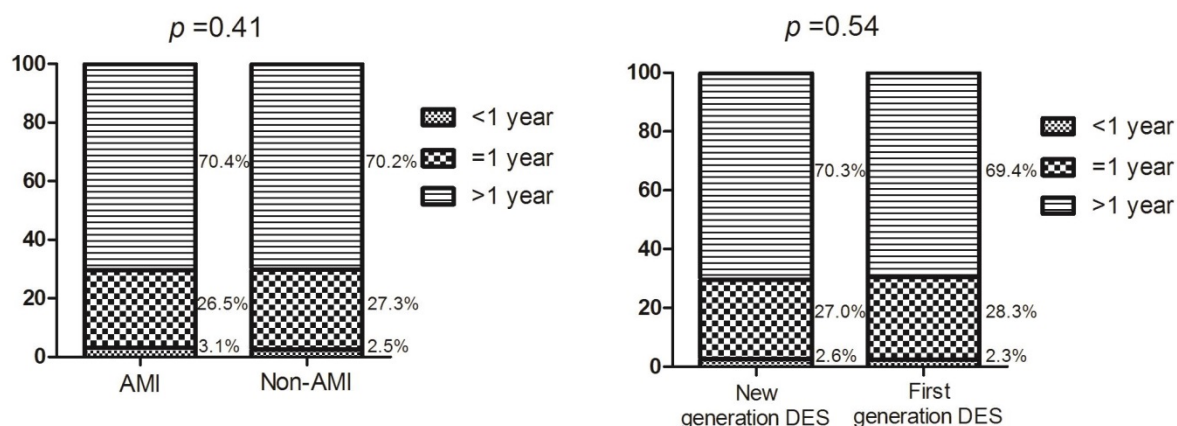|				
Age, y	60.07 ± 10.37	58.14 ± 10.28a	58.17 ± 10.18a	0.013
Age≥75 y, %	25 (9.8)	165 (6.1)a	402 (5.8)a	0.028
Female, %	65 (25.4)	627 (23.2)	1592 (22.9)	0.607
BMI, kg/m^2	25.98 ± 3.06	25.89 ± 3.17	25.96 ± 3.20	0.618
Weight ≤ 60 kg, %	37 (14.5)	388 (14.4)	958 (13.8)	0.702
Risk factors and medical history				
Hypertension, %	159 (62.1)	1732 (64.2)	4493 (64.5)	0.724
Diabetes mellitus, %	84 (32.8)	800 (29.7)	2124 (30.5)	0.496
Hyperlipidemia, %	149 (58.2)	1793 (66.5)a	4706 (67.6)a	0.006
Family history of CAD , %	67 (26.3)	698 (25.9)	1696 (24.4)	0.257
Smoke , %	140 (54.7)	1517 (56.2)	3988 (57.2)	0.376
Previous MI, %	46 (18.0)	489 (18.1)	1355 (19.5)	0.301
Previous PCI, %	54 (21.1)	647 (24.0)	1673 (24.0)	0.558
Previous CABG, %	11 (4.3)	130 (4.8)	259 (3.7)a,b	0.046
Previous stroke, %	42 (16.4)	262 (9.7)a	740 (10.6)a	0.003
Peripheral vascular disease, %	4 (1.6)	58 (2.2)	200 (2.9)	0.078
Clinical presentation				
AMI,%	53 (20.7)	469 (17.4)	1244 (17.9)	0.406
STEMI, %	33 (12.9)[b]	394 (14.6)	875 (12.6)[b]	0.028
Examination				
HGB before PCI, g/L	143.17 ± 15.98	141.28 ± 15.82a	140.83 ± 15.96[a]	0.042
PLT before PCI, *109/L	201.94 ± 54.27	204.14 ± 56.91	203.49 ± 53.93	0.771
HbAlc, %	6.49 ± 1.05	6.60 ± 1.20	6.64 ± 1.27	0.088
TC, mmol/L	4.08 ± 1.04	4.24 ± 1.11a	4.19 ± 1.07a	0.025
LDL-C, mmol/L	2.41 ± 0.90	2.52 ± 0.93	2.50 ± 0.91	0.158
eGFR, ml/min/1.73 m^2	83.93 ± 27.86	84.88 ± 27.60	83.94 ± 28.36	0.351
LVEF, %	63.24 ± 6.57	62.86 ± 7.27	62.86 ± 7.25	0.713
Angiographic and procedural characteristics				
LM or 3-vessel disease, %	13 (5.1)	117 (4.3)	297 (4.3)	0.816
LAD, %	232 (90.6)	2442 (90.5)	6275 (90.1)	0.769
Bifurcation disease, %	50 (19.5)	557 (20.7)	1394 (20.0)	0.754
Syntax Score	10.76 ± 7.81	11.56 ± 8.00	11.66 ± 8.00	0.189
No. of target lesion	1.38 ± 0.59	1.41 ± 0.67	1.43 ± 0.68	0.408
No. of stent per patient	1.80 ± 1.04	1.83 ± 1.03	1.92 ± 1.08a,b	<0.001
New generation DES, %	225 (87.9)	2321 (86.1)	6045 (86.8)	0.538
Clinical outcomes (no including death)				

Myocardial infarction, %	3 (1.2)	48 (1.8)	137 (2.0)	0.575
Target vessel revascularization, %	12 (4.7)	121 (4.5)	742 (10.7)a,b	<0.001
Stroke, %	10 (3.9)	40 (1.5)a	104 (1.5)a	0.009
Total bleeding, %	47 (18.4)	171 (6.3)a	464 (6.7)a	<0.001
Bleeding ≥ BARC 2, %	37 (14.5)	65 (2.4)a	165 (2.4)a	<0.001
a means significant difference compare with the group of DAPT duration <1 year;				
b means significant difference compare with the group of DAPT duration=1 year				
AMI=acute myocardial infarction; BMI=body mass index; CAD=coronary heart disease; CABG=coronary artery bypass grafting; eGFR=estimated Glomerular Filtration Rate; HGB=hemoglobin; HBA1c=hemoglobin A1c; LAD=left anterior descending artery; LDL-C=low density lipoprotein cholesterol; LM=left main; LVEF=left ventricular ejection fraction; MI=myocardial infarction; PCI=percutaneous coronary intervention; PLT=Platelet; STEMI=ST segment myocardial infarction; SYNTAX score=Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery score; TC=total cholesterol.				
Data are expressed as mean ± standard deviation; or counts (percentage).				

Table 1: Patients' baseline characteristics and clinical outcomes during follow-up.

DAPT in patients presented with AMI and implanted with new generation DES

Patients presented with AMI and implanted with the new generation DES accounted for 17.8% and 86.6% of the entire population, respectively. The proportions of patients with three different DAPT durations were shown in Figure 3 for these two particular subgroups of patients. The distribution of DAPT duration was not significantly different between patients with and without AMI (p=0.41), and implanted with the new generation and the first generation DES (p=0.54).
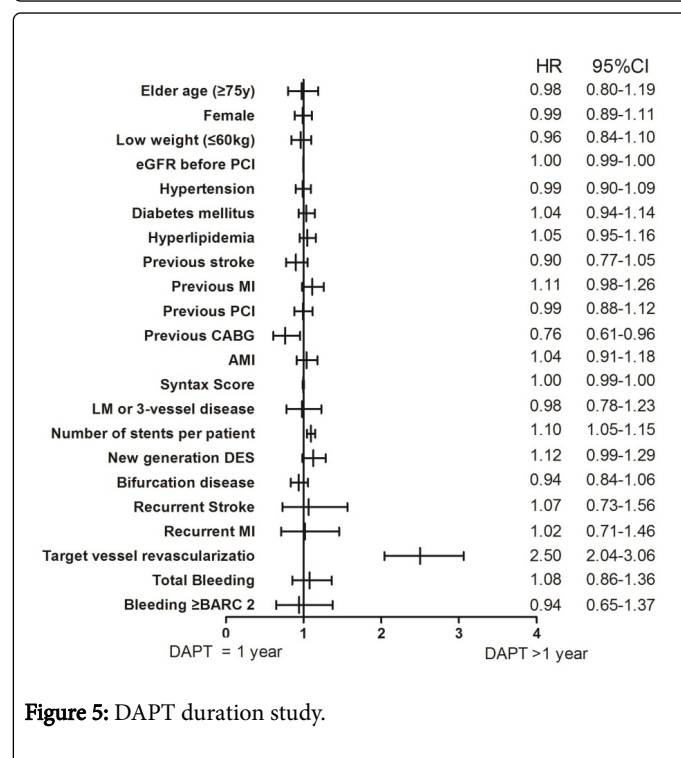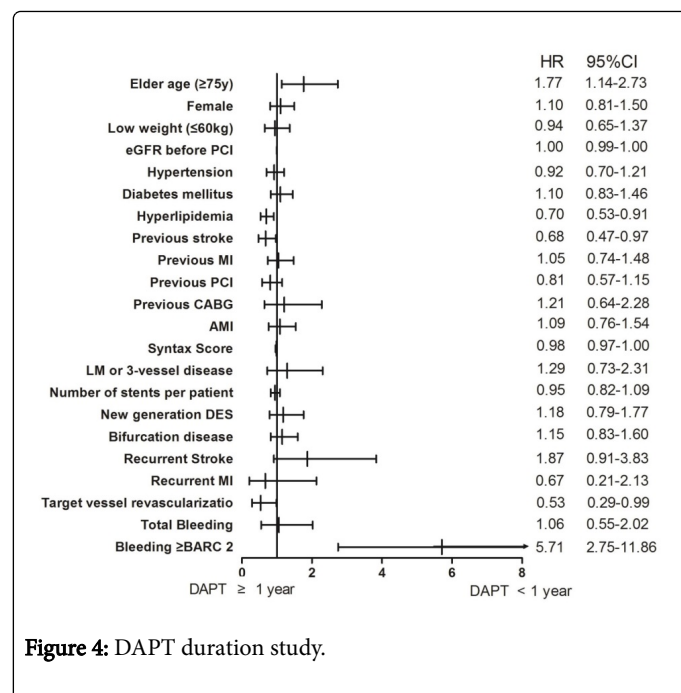

Figure 3: Patients presented with AMI.

Associated factors with different DAPT duration

The multivariable analysis results for all patients indicated that independent associated factors for shortening DAPT duration (<1 year versus ≥ 1 year) were age and bleeding condition (≥ BARC 2) during the follow-up, whereas patients with hyperlipidemia, previous stroke and experienced TVR during follow-up were prone to prolonging DAPT duration (Figure 4). If only the patients with DAPT duration ≥ 1 year were considered, the independent predictors of prolonging DAPT duration (>1 year versus =1 year) included the TVR during follow-up (OR 2.50, 95% CI 2.04-3.06, p<0.001), the stent number / patient (OR 1.10, 95% CI 1.05-1.15, p<0.001) and previous coronary artery bypass grafting (CABG) (OR 0.76, 95% CI 0.61-0.96, p=0.02). Other clinical factors such as increased risk of bleeding (e.g. age >75 years, prior stroke, low body weight <60 kg, renal dysfunction) and high ischemic risk (e.g. AMI, diabetes mellitus, peripheral artery disease, prior cardiovascular event, left main stenting, bifurcation stenting) were not associated with the DAPT duration (Figure 5).

Figure 4: DAPT duration study.

Figure 5: DAPT duration study.

Discussion

In this study, the DAPT duration after the DES implantation was investigated in a large amount of patients in a large Chinese cardiovascular center. The major findings of this study were as follows: (1) the proportion of patients with the DAPT duration ≥ 1-year was as high as 97.4 % after the DES implantation; (2) the distribution of DAPT duration (<1 year, =1 year, and >1 year) was not significantly different for patients with or without AMI, and implanted with either

the new generation or the first generation DES; (3) patients' clinical bleeding and ischemic risks had little impact on DAPT duration after DES implantation.

It is noted that 97.4% of patients were ≥ 1-year DAPT after the DES in this study, which was significantly higher than those observed in other studies. PARIS registry showed that the proportion of patients with DAPT coverage after DES implantation at 1 year was 76.7% in USA and Europe between 2009 and 2010 [13]. A newly reported meta-analysis demonstrated that the 1-year DAPT use after DES was 83% in 2007-2009 [12]. In 2012, Chinese guideline recommended at least 1-year of DAPT after the DES implantation [2], and it was not until 2016 that the renewed guideline recommended the individualized DAPT duration being determined based on the balance of bleeding and ischemic risks for each particular patient [11]. The patients in this study were followed up in 2013-2015. Thus, at least 1-year of DAPT was appropriate treatment duration at that time. These findings indicated the awareness of physicians and patients against adverse cardiac ischemic events and higher patients' adherence to the recommended treatment regime of DAPT in China.

The clinical presentation of AMI is believed as an important factor to the DAPT duration. 1-year DAPT after AMI had been recommended by previous guidelines [1,2] based on the duration of treatment in the pivotal P2Y12 receptor inhibitor studies [16-18]. However, the DAPT duration longer than 1 year after AMI [19-24] are recommended for patients who were not at high risk for bleeding. In addition, the second generation of DES is another important factor that clinicians would consider for adjusting the DAPT duration. Recently, numerous studies had demonstrated that patients with 3 to 6 months of DAPT compared with ≥ 12 months after implantation of the second generation DES had lower rates of bleeding, with similar rates of mortality, MI, and ST [4-7]. Therefore, current guidelines recommended DAPT for 6 months after the implantation of a second generation DES for a non-AMI indication [9-11]. However, this study found that patients with AMI did not have extended DAPT duration and patients implanted with the new generation DES did not have the shortening DAPT duration either. These findings indicated that AMI and the new generation DES were not factors to the DAPT duration. Furthermore, other clinical factors such as increased risk of bleeding (e.g. age >75 years, prior stroke, low body weight <60 kg, renal dysfunction) and high ischemic risk (e.g. diabetes mellitus, peripheral artery disease, prior cardiovascular event, prior coronary revascularization, left main stenting, bifurcation stenting) should also be considered for the recommended DAPT duration [25]. However, this study found that there was no association between these clinical factors with DAPT duration.

There is an ongoing controversy on the optimal duration of DAPT after DES implantation with shorter or longer durations than recommended by guidelines [26]. The findings of this study suggest that, clinicians preferred to prolong DAPT duration may because of the concerns about ischemic events in real-world clinical practice, but prolonging DAPT did not increase the patient's benefit. It prompted the need for more adequate evidence of DAPT duration, and more precise rules about the DAPT duration after DES implantation in order to guide clinicians to regulate the use of drugs.

Study Limitations

Several limitations have to be taken into consideration. First, the data of this study came from the same clinical center, not representing

the entire China. Second, the specified modes of DAPT cessation, included discontinuation, interruption, and disruption (with prognostic impacts) [13] could not be detected in this study. Third, factors influencing the DAPT adherence such as patients' economic status and the educational level were not considered in this study. Fourth, nonrandomized design of this study with unmeasured confounders may preclude the definitive conclusion, but observational study may be the only selection in order to detect the DAPT cessation in reality.

Conclusion

One year DAPT after DES was 97.4% in this large Chinese cohort of real-world patients. However, the DAPT duration was not adjusted due to different clinical scenarios. These findings demonstrated good adherence of DAPT after the DES in China, but there were still gaps in evidence-based practice.

Acknowledgments

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