Prolonging Dual Antiplatelet Therapy Improves Long-term Prognosis in Diabetic Patients Undergoing Complex Percutaneous Coronary Intervention with Drug-eluting Stents

Xu Jingjing

Fuwai Hospital

Jia Sida

Fuwai Hospital

Zhu Pei

Fuwai Hospital

Song Ying

Fuwai Hospital

Yuan Deshan

Fuwai Hospital

Zhao Xueyan

Fuwai Hospital

Yao Yi

Fuwai Hospital

Jiang Lin

Fuwai Hospital

Li Jianxin

National Clinical Research Center for Cardiovascular Diseases¹, Chinese Academy of Medical Sciences and Peking Union Medical College

Zhang Yin

Fuwai Hospital

Song Lei

Fuwai Hospital

Gao Lijian

Fuwai Hospital

Qiao Shubin

Fuwai Hospital

Yang Yuejin

Fuwai Hospital

Xu Bo

Fuwai Hospital

Gao Runlin

Fuwai Hospital

Han Yaling

The General Hospital of Northern Theater Command

Yuan Jinqing (✉ dr_jinqingyuan@sina.com)

Fuwai Hospital

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Abstract

Background The optimal dual antiplatelet therapy (DAPT) duration after percutaneous coronary intervention (PCI) remains controversial, especially for patients at high risk of ischemic events. Diabetes mellitus (DM) and complex coronary interventions have been considered as high risk factors for ischemic events. We aim to investigate if prolonging DAPT duration in diabetic patients after drug-eluting stent (DES) implantation can reduce long-term adverse events.

Methods This study is an observational cohort study carried out in the largest cardiovascular center in China. 10,724 patients who underwent PCI from January, 2013 to December, 2013 were consecutively enrolled. The inclusion criteria included: documented history of DM; underwent DES implantation; free of adverse events within 1 year after operation; and had at least one high thrombotic risk technical aspects. These patients were divided into three groups according to DAPT duration: Standard group ($11 \leq \text{DAPT} \leq 13$ months) and prolonged group ($13 < \text{DAPT} \leq 24$ months; $\text{DAPT} > 24$ months). Baseline characteristics and 5-year clinical outcomes were collected and analyzed.

Results A total of 2,403 diabetic patients with complex PCI were included in the current analysis (Standard DAPT $n=689$; Prolonged DAPT $n=1714$). Baseline and angiographic characteristics, and complexity of PCI were comparable among patients with different DAPT durations. Patients in $13 < \text{DAPT} \leq 24$ months group had lowest incidence of MACCE, all cause death and cardiac death. After adjustment of confounding factors, the 13-24 months DAPT duration was related with lower risk of MACCE (HR: 0.544, 95%CI: 0.373-0.795) and all cause death (HR: 0.605, 95%CI: 0.387-0.944). DAPT duration >24 months was related with lower risk of all-cause death (HR: 0.681, 95%CI: 0.493-0.942) and cardiac death (HR: 0.620, 95%CI: 0.403-0.952). Prolonging DAPT duration did not increase the risk of major bleeding ($13 < \text{DAPT} \leq 24$ months: HR: 1.356, 95%CI: 0.766-2.401; $\text{DAPT} > 24$ months: HR: 0.967, 95%CI: 0.682-1.371).

Conclusions For diabetic patients undergoing complex PCI, prolonging DAPT duration might improve long-term prognosis by reducing the risk of adverse ischemia events and without increasing the risk of bleeding.

Background

Although dual antiplatelet therapy (DAPT) is already routinely used as secondary prevention for patients undergoing percutaneous coronary intervention (PCI), the optimal duration of DAPT continues to be debated ^[1]. Diabetes mellitus (DM) has long been considered as a high-risk factor for ischemic events, patients of coronary artery disease complicated with DM showed poor prognosis ^[2]. Complex coronary artery disease, such as multi-vessel disease, chronic total occlusions and multi-stent implantation, are also deemed as high thrombotic risk factors. Since prolonging DAPT has been proved to reduce the incidence of ischemic events ^[3], it might benefit diabetic patients undergoing complex PCI even more.

However, the benefit is offset by a potential increase in risk of bleeding. Therefore, it suggested that DAPT duration should be tailored according to the risk of ischemia and bleeding in current guidelines^[4~6].

A previous study from our center reported that compared with standard DAPT duration (1 year), prolonged DAPT to more than 1 year could reduce the incidence of all-cause death, cardiac death and stent thrombosis after 2-year follow-up in patients who underwent PCI with drug-eluting stents (DES), without increasing the risk of bleeding^[7]. However, for patient complicated with DM undergoing complex PCI, it is not clear that whether prolonging DAPT will continue to be beneficial beyond 2 years. Therefore, we further investigated 5-year clinical outcomes to evaluate the exact impact of different DAPT durations on long-term prognosis.

Patients And Methods

Study population

A total of 10,724 patients underwent PCI at Fu Wai Hospital, National Center for Cardiovascular Diseases (Beijing, China) from January to December 2013. The exclusion criteria includes: patients received only bare metal stents (n=64), treated with balloon angioplasty alone (n=237), had adverse cardiovascular and cerebrovascular events or bleeding events within 1 year after PCI (n=612), DAPT duration < 1 year (n=157), and single antiplatelet therapy (n=120). Finally, 2,403 patients with confirmed diagnosis of diabetes mellitus and at least one high thrombotic risk technical aspects were enrolled. Patients were divided into three groups according to DAPT duration: standard group ($11 \leq \text{DAPT} \leq 13$ months, n=689) and prolonged group ($13 < \text{DAPT} \leq 24$ months, n=1133, $\text{DAPT} > 24$ months, n=581). (Fig.1).

Procedures and medications

PCI strategy and stent type were at the treating physician's discretion. Before the procedure, patients not taking long-term aspirin and clopidogrel received a loading dose of 300 mg aspirin and 300 mg or 600 mg clopidogrel orally. During the procedure, unfractionated heparin (100 U/kg) was administered to all patients, with glycoprotein IIb/IIIa inhibitors in accordance with the 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.

Patient follow-up

All patients were evaluated by clinic visits or by phone at 1, 3, 6 months and 1, 2, 5 years after the procedure. Patients were advised to return for coronary angiography if clinically indicated by symptoms or if showing signs of myocardial ischemia.

Definitions

The duration of DAPT was defined as the length between the date of PCI and DAPT cessation. Patients were divided into two groups according to different DAPT duration: standard DAPT

(11months $\leq$ DAPT $\leq$ 13months, n=689) and prolonged DAPT group (DAPT duration >13months, n=1714). Prolonged DAPT group was further divided into two subgroups: 13months< DAPT $\leq$ 24months, n=1133 and DAPT >24 months, n=581. (Fig.1). Myocardial Infarction (MI) was defined according to the third universal definition of myocardial infarction^[8]. Bleeding was defined according to the definition of the Bleeding Academic Research Consortium^[9]. New-generation DES was defined as second-generation DES and biodegradable polymer DES.

The definition of diagnostic criteria for diabetes mellitus refer to the guideline of the prevention and treatment of type 2 diabetes mellitus in China (2020 Edition): definite history of diabetes mellitus or symptoms of diabetes mellitus complicated with fasting blood glucose $\geq$ 7.0mmol/L or HbA1c $\geq$ 6.5%^[10]. The high thrombotic risk technical aspects refers to the risk criteria for extended treatment with a second antithrombotic agent from 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, including at least 3 stents implanted, at least 3 lesions treated, total stent length >60 mm, history of complex revascularization (left main, bifurcation stenting with $\geq$ 2 stents implanted, chronic total occlusion)^[11].

Endpoints

The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all-cause death, MI and stroke at 5-year follow up. The secondary endpoints were the individual components of MACCE and bleeding. All endpoint events were adjudicated by two independent cardiologists, and disagreement was resolved by consensus.

Statistical analysis

Continuous variables were compared by one-way ANOVA test, as appropriate. Categorical variables were compared by using Bonferroni method in Z-test between columns, and the overall p value was calculated by Pearson's χ^2 test. Continuous variables were presented as mean $\pm$ standard deviation and categorical variables as number with frequency. Survival curves were calculated using Kaplan–Meier estimates and compared with the log-rank test regarding endpoints. We took the standard DAPT as reference and justified variables of age, gender, BMI, hypertension, hyperlipidemia, previous PCI and SNYNTAX score before PCI for multivariable Cox regression models. Results of COX regression analysis were expressed as Hazard Ratio (HR) and 95% confidence interval (CI). Subgroup analyses were performed using factors of high ischemia and high bleeding risk (age, gender, history of smoking, previous PCI or previous MI, ACS, cardiac function and renal function) to analyze interactions between DAPT duration and the selected factors for the outcomes.

Two-tailed P values of <0.05 were considered to be statistically significant. All analyses were conducted with SPSS version 20.0 (IBM, Armonk, NY, USA).

Result

Baseline Characteristics

Standard DAPT accounted for 28.7% (689/2403) and prolonged DAPT for 71.3% (1714/2403) respectively. Patients’ baseline characteristics were shown in Table 1. The basic and angiographic characteristics were similar among the three groups of different DAPT durations, except for a lower incidence of previous CABG in $13 < \text{DAPT} \leq 24$ months group, a higher level of fasting blood glucose in DAPT > 24 months group, and a higher incidence of unstable angina in $11 \leq \text{DAPT} \leq 13$ months group.

Table 1 Baseline characteristics among three DAPT duration groups

	Standard DAPT	Prolonging DAPT			
	11-13 mos. n=689	13-24 mos. n=1133	>24 mos. n=581	F/ χ^2	P value
Age,y	58.40±10.28	57.82±10.07	58.67±10.13	1.567	0.209
Female, %	150 (21.8)	275 (24.3)	142 (24.4)	1.790	0.409
BMI,kg/m2	25.95±3.12	25.99±3.10	26.11±3.02	0.439	0.645
Risk factors					
Hypertension, %	446 (64.7)	754 (64.5)	370 (63.7)	1.548	0.461
Hyperlipidemia, %	446 (64.7)	784 (69.2)	397 (68.3)	4.043	0.132
Family history of CAD , %	150 (21.8)	259 (22.9)	145 (25.0)	1.850	0.397
Smokeing, %	386 (56.0)	623 (55.0)	323 (55.6)	0.647	0.958
Previous MI, %	120 (17.4)	208 (18.4)	108 (18.6)	0.358	0.836
Previous PCI, %	151 (21.9)	254 (22.4)	158 (27.2) _{ab}	6.116	0.047*
Previous CABG, %	44 (6.4)	26 (2.3) _{ac}	33 (5.7)	21.108	<0.001*
Previous stroke, %	82 (11.9)	123 (10.9)	67 (11.5)	0.501	0.778
Peripheral vascular disease, %	20 (2.9)	23 (2.0)	21 (3.6)	3.933	0.140
Examination					
Fasting blood glucose, mmol/L	6.77±2.49	6.62±2.36	6.96±2.57 _{ab}	3.385	0.022*
HbA1c, %	6.94±1.27	6.97±1.40	6.94±1.35	0.146	0.864
HGB before PCI, g/L	141.21±15.98	140.23±16.03	141.64±15.14	1.757	0.173
PLT before PCI, *10 ⁹ /L	205.50±56.60	208.54±53.66	204.52±52.83	1.279	0.279
WBC, *10 ⁹ /L	7.02±1.96	6.99±1.90	6.95±1.95	0.217	0.805
TC, mmol/L	4.30±1.14	4.26±1.13	4.20±1.04	1.253	0.286
TG, mmol/L	1.88±1.08	1.87±1.30	1.78±1.06	1.181	0.307
LDL-C, mmol/L	2.56±0.94	2.53±0.94	2.50±0.88	0.514	0.598
HDL-C, mmol/L	1.04±0.29	1.03±0.29	1.03±0.28	0.101	0.904
UA, μ mol/L	346.88±83.94	337.70±87.27	342.92±90.64	2.446	0.087

eGFR, ml/min	92.58±14.36 _{bc}	90.63±15.51	90.73±14.96	3.986	0.019*
LVEF, %	61.87±7.84	62.04±7.59	61.34±7.76	1.562	0.210
Clinical and Angiographic characteristics					
Pre-Syntax Score	15.27±8.49	15.29±8.17	15.34±8.12	0.010	0.990
No. of target lesion	1.78±0.81	1.78±0.82	1.84±0.83	1.278	0.279
No. of stents per patient	2.54±1.11	2.67±1.17	2.65±1.26	2.913	0.055
New generation DES, %	585 (84.9)	962 (84.9)	492 (84.7)	4.322	0.364
ACS, %	445 (64.6) _b	640 (56.5)	338 (58.2)	11.982	0.003*
AMI, %	109 (15.8)	196 (17.3)	93 (15.8)	0.941	0.625
UA, %	336 (48.8) _b	444 (39.2)	245 (42.2)	10.552	0.005*

Standard DAPT: 11months≤DAPT duration ≤13months, Prolonged DAPT: DAPT duration>13 months

BMI=body mass index, CABG=coronary artery bypass grafting, CAD=coronary artery disease, DAPT= dual antiplatelet therapy, GFR=glomerular filtration rate, HbA1c=glycosylated hemoglobin, HDL-C=High density lipoprotein cholesterol, LDL-C=Low density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MI=myocardial infarction, PCI=percutaneous coronary intervention, PLT=platelet, HGB=hemoglobin, AMI= Acute myocardial infarction, TC=total cholesterol, TG=triglyceride

*: p<0.05

a means significant difference with group 11months≤DAPT≤13months, b means significant difference with group 13months<DAPT≤24months, c means significant difference with group DAPT >24 months (in 0.05 level).

Five-year Outcomes

During 5-year follow-up, the incidences of MACCE, all cause death and cardiac death in prolonged DAPT groups were significantly lower than standard DAPT group, with the group of 13<DAPT≤24 months being the lowest (11≤ DAPT ≤13months vs. 13< DAPT ≤24months vs. DAPT >24 months: MACCE 8.1% vs. 4.6% vs. 6.0%, p=0.008, all cause death 4.6% vs. 1.9% vs. 2.2%, p=0.002, cardiac death: 3.0% vs. 1.0% vs. 1.2%, p=0.002, respectively). The incidence of stroke and bleeding had no differences among the three groups (Table 2). A Kaplan–Meier estimate showed similar trend (Fig. 3).

Table 2. 5-year outcomes among different DAPT duration

	Standard DAPT	Prolonged DAPT		χ^2	P value
	11-13 mos. n=689	13-24 mos. n=1133	>24 mos. n=581		
MACCE	56 (8.1) _b	52 (4.6)	35 (6.0)	9.591	0.008*
All cause death	32 (4.6) _b	22 (1.9)	13 (2.2)	12.404	0.002*
Cardiac death	21 (3.0) _b	11 (1.0)	7 (1.2)	12.416	0.002*
Myocardial infarction	30 (4.4)	33 (2.9)	30 (5.2)	5.838	0.054
Stroke	26 (3.8)	28 (2.5)	19 (3.3)	2.607	0.272
Major bleeding	17 (2.5)	39 (3.4)	15 (2.6)	1.792	0.408

Standard DAPT: 11months≤DAPT duration≤13months, Prolonged DAPT: DAPT duration>13 months

MACCE = major adverse cardiac and cerebrovascular events, Mos: months

*: p<0.05

a means significant difference with group 11months≤DAPT≤13months, b means significant difference with group 13months<DAPT≤24months, c means significant difference with group DAPT >24 months (in 0.05 level).

High thrombotic risk technical aspects

The high thrombotic risk technical aspects of patients with different DAPT duration are shown in figure 2. There was no significant difference of complex coronary intervention technique among three DAPT duration groups.

Multivariable analysis

COX multivariable regression analysis showed that compared with standard DAPT duration, prolonged DAPT to 13-24 months significantly reduced the risk of MACCE (HR: 0.544, 95%CI: 0.373-0.795) and all-cause death (HR: 0.605, 95%CI: 0.387-0.944). DAPT duration >24 months significantly reduced the risk of all cause death (HR: 0.681, 95%CI: 0.493-0.942) and cardiac death (HR: 0.620, 95%CI: 0.403-0.952). (Table 3).

Table 3. COX regression analysis of prolonging DAPT for long-term prognosis

	Standard DAPT	Prolonging DAPT	
	11-13 mos. n=689	13-24 mos. n=1133	>24 mos. n=581
		HR (95% CI)	HR (95% CI)
MACCE	Ref	 0.544(0.373-0.795)	 0.860(0.696-1.063)
All cause death	Ref	 0.605(0.387-0.944)	 0.681(0.493-0.942)
Cardiac death	Ref	 0.661(0.368-1.189)	 0.620(0.403-0.952)
MI	Ref	 0.624(0.380-1.025)	 1.091(0.846-1.407)
Stroke	Ref	 0.622(0.364-1.063)	 0.895(0.665-1.204)
Major bleeding	Ref	 1.356(0.766-2.401)	 0.967(0.682-1.371)

Adjusted Variables: age, gender, hypertension, hyperlipidemia, previous PCI, SNYTAX score before PCI

MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, Mos: months

Subgroup analysis

We performed subgroup analysis on all-cause death and MACCE between standard DAPT and 13-24 months DAPT to evaluate patients with risk enhancers of ischemia or bleeding. Variables for subgroup analysis included age, gender, smoking history, previous PCI or previous MI history, ACS, cardiac dysfunction (LVEF <40%) and renal dysfunction (eGFR<60ml/min/1.73m²). DAPT between 13-24 months could reduce the risk of all cause death and MACCE in the subgroups of age ≥ 65 years and <65 years old, male patients, patients with smoking history, patients with and without previous PCI or previous MI history, ACS patients, patients with and without cardiac dysfunction and patients without renal dysfunction. As shown in Table 4.

Table 4. Subgroup analyses on all-cause death and MACCE between standard DAPT and 13-24 months DAPT

*P value for interaction in each subgroup analysis

**Unable to calculate in this subgroup due to unreliable results of renal dysfunction subgroup

Adjusted Variables: age, gender, BMI, hypertension, hyperlipidemia, previous PCI, SNYTX score before PCI

LVEF = Left Ventricular Ejection Fraction

Discussion

The objective of this study is to investigate appropriate DAPT duration for patients at high risk of ischemic events such as diabetic patients and patients undergoing complex PCI. The major findings are as follows: (1) Compared with standard DAPT duration, prolonged DAPT duration in high ischemia risk patients undergoing PCI with DES is common in China. (2) For patients complicated with high ischemic risk, such as DM or complex coronary intervention, prolonged DAPT duration could reduce incidence of adverse cardiovascular events. (3) Prolonged DAPT does not increase the risk of bleeding. (4) Patients at high ischemic risk benefits even more when combined with risk enhancers of ischemic events.

DM and complex coronary intervention increase ischemic risk

DM is a major risk factor for coronary heart disease, which makes patients vulnerable to atherosclerosis due to the damage of vascular endothelium and vascular dysfunction caused by metabolic abnormalities of blood glucose. In addition, high platelet reactivity and hypercoagulability in patients with DM also increase the risk of thrombosis and ischemic events significantly^[12]. Complex coronary interventions could also increase the risk of thrombosis. Although advancement in interventional equipments and

techniques have largely enabled interventional cardiologists to revascularize extremely difficult coronary lesions^[13], the ischemic risk should be paid more attention.

Selection of DAPT duration and guidelines recommendation

DAPT benefits patients undergoing PCI by reducing the incidence of stent thrombosis and strengthening the secondary prevention of coronary heart disease^[14]. The American and European guidelines recommended a 12-month DAPT for patients after DES implantation and adjusting DAPT duration according to the risk of ischemic and bleeding^[15, 16]. Guidelines recommend appropriately extending of DAPT duration if patients had complex CAD combined with high-risk factors of ischemia^[4].

In the current study, standard DAPT accounted for 28.7% and prolonged DAPT for 71.3%, respectively. The high proportion of prolonging DAPT reflects cardiologists' preference to extend DAPT in patients with high ischemic risk .

Benefits of prolonging DAPT duration

The benefit of prolonging DAPT is still controversial. The TIMI 38 Coronary Stent Registry showed similar recurrent ischemic events between patients continued and discontinued DAPT ($p=0.74$ for cardiovascular death/myocardial infarction/stroke, $p=0.72$ for definite or probable stent thrombosis)^[18]. The DAPT Study indicated that continued treatment with thienopyridine could reduce the rates of stent thrombosis (0.4% vs. 1.4%, HR 0.29 [95% CI: 0.17 to 0.48], $P<0.001$) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%, hazard ratio, 0.71 [95% CI: 0.59 to 0.85], $P<0.001$)^[3]. However, these studies did not strictly distinguish the risk of ischemia.

In our study, prolonged DAPT was associated with a decrease of adverse cardiovascular events in 5-year follow-up in diabetic patients undergoing complex PCI. DAPT duration between 13 to 24 months group has the lowest incidences of MACCE, all cause death, and cardiac death. For patients with high ischemic risk, prolonged DAPT duration appropriately is beneficial by reducing adverse cardiovascular ischemic events. Therefore, risk stratification for patients after DES is essential in order to guide the decision-making of DAPT duration.

Prolonging DAPT does not increase bleeding risk

The biggest concern about prolonging DAPT is the increased risk of bleeding, especially for Chinese patients, who are considered at higher risk of bleeding^[19]. In our study, no significant difference in risk of bleeding was found among the three groups, which proves the safety of prolonging DAPT.

More benefits for patients combined with risk enhancers

Subgroup analysis with risk enhancers of ischemia or bleeding in the current study showed that, prolonging DAPT to 13-24 months reduced the risk of all-cause death and MACCE for the subgroups of age ≥ 65 years and <65 years old, male patients, patients with smoking history, patients with and without

previous PCI or previous MI history, ACS patients, patients with and without cardiac dysfunction and patients without renal dysfunction. These results indicated that, for patients with high ischemic risk, appropriately prolonging of DAPT duration would bring more benefits if combined with risk enhancers. The more risk factors of ischemia combined, the more definite benefits patients would gain from prolonging DAPT duration.

Limitations

Several limitations of this study should be considered. First, being an observational study, evaluation of medication efficacy is limited. In addition, the observational study was designed non-randomized with unmeasured confounders that may preclude definitive conclusions. Second, only patients who could tolerate prolonged DAPT were enrolled, which may introduce selection bias into this analysis. Third, information on how DAPT was discontinued was not available.

Conclusions

For diabetic patients undergoing complex PCI, appropriately prolonging DAPT duration could improve long-term prognosis by reducing the risk of adverse cardiovascular ischemia events without increasing the risk of bleeding.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Fuwai Hospital (Approval No. 2021-1501), and written informed consent was provided by patients before the intervention.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

Competing interests: Not applicable.

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Authors' contributions

XJJ, contributed to project design and article writing, JSD, ZP, SY, YDS, contributed to data collection and arrangement, ZXY, contributed to project design, YY, JL, LJX, contributed to data sorting, patients follow-up and statistics, ZY, SL, GLJ, QSB, YYJ, XB, contributed to project design and operation, GRL, HYL, YJQ, project design and overall plan.

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Figures

Figure 1

Flow Chart

Figure 2

High thrombotic risk in technical aspects of different DAPT duration

Figure 3

The Kaplan–Meier estimate curve of different DAPT duration