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Original Article

Clinical outcome in patients with stent thrombosis at different times after drug eluting stent implantation

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Abstract: Objective: To compare the clinical outcome of patients with stent thrombosis (ST) occurred at different time after drug-eluting stent (DES) implantation. Methods: Patients with angiographically defined ST after DES implantation were divided into 2 groups based on the time of ST occurrence: ST during early phase (≤30 days) and ST during late phase (>30 days). Clinical characteristics, interventional data, and outcomes during hospitalization and long-term follow-up between two groups were compared. Results: Forty-two patients in the group of ST during the early phase and 89 patients in the group of ST during the late phase were enrolled. The incidence of major adverse cardiac events (MACE) during hospitalization was higher in the group of ST during the early phase than that in the group of ST during the late phase (16.7% *vs.* 4.5%, respectively, *P*=0.037). During a median follow-up of 38.0 (15.0-62.0) months, there was no difference in the estimate event-free survival between the two groups (41.9% in the group of ST during early phase and 36.3% in the group of ST during late phase, Log Rank, *P*=0.43). Only age ≥60 years (hazard ratio [HR]: 2.32, *P*=0.012) and left ventricular ejection fraction <50% (HR: 2.71, *P*=0.004) were the independent predictors of total MACE. Conclusions: The patients with ST during the early phase had a higher incidence of MACE in hospital. However, there is no difference in the long-term outcome between the two groups.

Keywords: Drug eluting stent, stent thrombosis, follow-up

Introduction

Although DES can significantly reduce the rate of in-stent restenosis (ISR) and revascularization compared to bare-metal stent (BMS) [1-3], concerns about the risk of ST have arisen since the introduction of DES [4, 5]. The mechanisms of ST occurring during the early phase (≤30 days) and late phase (>30 days) after DES implantation were different [6], which might translate into differential clinical outcome. However, the clinical prognosis, particularly the long-term prognosis is unclear in patients with ST of different time after DES implantation. Previous studies comparing clinical outcome between patients with ST at different time points also enrolled numerous patients after BMS implantation [7-9]. The mechanism for ST after DES implantation was different from that after BMS implantation [6, 10]. Therefore, the results of the abovementioned studies may not truly reflect the long-term prognosis of patients after DES implantation. The aim of this study was to evaluate the clinical prognosis in patients with different occurrence time of ST after DES implantation.

Materials and methods

Study population and group

From January 2005 to April 2015, patients with angiographically defined ST after DES implantation were enrolled. Patients were divided into 2 groups according to the time of ST occurrence [11]. The group of ST in early phase (30≤ days) included acute ST and sub-acute ST according to ARC criteria [12]. The group of ST during the late phase (>30 days) included late ST and very late ST (VLST) according to ARC criteria [12]. Clinical, angiographic, and interventional data of the 2 groups were collected and compared. The follow-up was performed by phone conversation with patients and their family, outpatient visits, and review of inpatient medical records. The outcomes of hospitalization and long-term follow-up were analyzed.

Table 1. Clinical demographic of patients

	Group of ST in early phase (n=42)	Group of ST in late phase (n=89)	*P*
Sex (Male), n (%)	28 (66.7)	73 (82.0)	0.07
Age (mean ± SD)	62.69±11.89	59.02±11.13	0.09
DAPT discontinued at ST, n (%)	4 (9.5)	81 (91.0)	<0.001
ST-elevation myocardial infarction in anterior wall, n (%)	23(54.8)	61 (68.5)	0.17
Cardiogenic shock, n (%)	8 (19.0)	5 (5.6%)	0.03
Risk factors, n (%)			
Hypertension	28 (66.7)	48 (53.9)	0.19
Diabetes Mellitus	10 (23.8)	26 (29.2)	0.68
Hyperlipidemia	30 (71.4)	53 (59.6)	0.24
Smoker	24 (57.1)	63 (70.8)	0.16
Onset of ST in hospital	20 (47.6)	0 (0)	<0.001
O-B time (n=126), min[median (Q1, Q3)]	158 (124, 317)	279 (204, 429)	<0.001
Glycoprotein IIB/IIIA inhibitors, n (%)	38 (90.5)	73 (82.0)	0.30
Adjusted antiplatelet therapy, n (%)	21 (50.0)	6 (6.7)	<0.001
LVEF (n=129), % (mean ± SD)	52.00±11.49	55.98±11.79	0.07
Peak cTnI, ng/ml (mean ± SD)	73.15±65.13	69.32±68.66	0.76

DAPT, dual antiplatelet therapy; ST, stent thrombosis; O-B time, onset- balloon time; LVEF, left ventricular ejection fraction; cTnI, cardiac troponin I.

Revascularization and antiplatelet therapy

The choice of treatment strategy, including thrombus aspiration, re-implantation of additional stent, type of stent, implantation of intra-aortic balloon pump (IABP), and examination of intravascular ultrasound (IVUS) or optical coherence tomography (OCT) was decided by the operators.

Loading doses of 300 mg aspirin and 600 mg clopidogrel were used preoperatively unless dual antiplatelet therapy (DAPT) was given for more than 72 hours. Administer of tirofiban was decided by the operators. DAPT was recommended for at least 1 year. The operators decided whether to adjust the strategy of antiplatelet therapy.

Definitions

ST was defined according to ARC criteria [12]. According to the timing of ST occurrence, ST was categorized into acute stent thrombosis (within 24 hours), sub-acute stent thrombosis (from 24 hours to 30 days), late ST (between 30 days and 1 year), and VLST (more than 1 year).

Major adverse clinical cardiac events (MACE) included non-fatal myocardial infarction (MI), recurrent ST, target vessel revascularization (TVR), and death. The diagnosis of MI required detection of a rise and/or fall of cardiac biomarker values (cardiac troponin) with symptoms of ischemia and ECG changes [13]. Recurrent ST was defined as definite ST confirmed by angiography [12]. TVR was defined as the ischemia-driven percutaneous coronary intervention (PCI) performed in the same vessel with or without implantation of stent or coronary artery bypass grafting (CABG). Death was defined as all-cause mortality, including cardiac death and non-cardiac death.

DAPT was defined as antiplatelet therapy with 100 mg/day aspirin and 75 mg/day clopidogrel (or ticagrelor 90 mg twice/day after 2013). The first generation DESs included the sirolimus-eluting stent and the paclitaxel-eluting stent with durable polymers. The new generation DESs included the biodegradable polymer-based DES, polymer free DES, zotarolimus-eluting stent, and everolimus eluting stents [14, 15].

Statistics

Statistical analysis was performed with the SPSS 17.0 statistical software package (Chicago, IL, USA). Normally distributed mea-

Table 2. Angiographic and intervention therapeutic characteristics

	Group of ST in early phase (n=42)	Group of ST in late phase (n=89)	*P*
Initial lesion and procedure characteristics			
1st generation DES implanted, n (%)	25 (59.5)	75 (84.3)	0.004
Emergency procedure, n (%)	16 (38.1)	33 (37.1)	1.00
Two-stent technique for bifurcation, n (%)	2 (4.8)	3 (3.4)	0.66
ISR, n (%)	0	1 (1.1)	1.0
CTO, n (%)	4 (9.5)	3 (3.4)	0.21
Number of stents, n (mean ± SD)	1.86±0.93	1.39±0.63	0.001
Stent diameter, mm (mean ± SD)	2.97±0.40	3.04±0.36	0.24
Stent length, mm (mean ± SD)	44.93±25.86	33.77±17.09	0.01
Peak pressure, atm (mean ± SD)	16.60±3.02	15.75±2.53	0.97
Lesion and procedure characteristics at occurrence of ST			
Multiple thrombosis, n (%)	3 (7.1)	0 (0)	0.03
Target vessel of LM/LAD, n (%)	30 (71.4)	65 (73.0)	1.0
Non infarct related artery with stenosis >50%, n (%)	35 (83.3)	75 (84.3)	1.0
With lesion of LM, n (%)	5 (11.9)	7 (8.0)	0.52
Self-recanalization of IRA (TIMI grade 2 or 3), n (%)	4 (9.5)	12 (13.5)	0.58
Collateral circulation of Rentrop 2 or 3, n (%)	9 (21.4)	20 (22.5)	1.0
Thrombosis aspiration, n (%)	18 (42.9)	35 (39.3)	0.71
Additional stent implantation, n (%)	8 (19.0)	59 (66.3)	<0.001
Re-implantation of 1st generation DES, n (%)	4 (9.5)	14 (15.7)	0.42
Stent number (n=67), n (mean ± SD)	1.13±0.35	1.41±0.65	0.08
Stent diameter (n=67), mm (mean ± SD)	3.06±0.51	3.15±.37	0.55
Stent length (n=67), mm (mean ± SD)	22.75±16.25	36.47±16.74	0.03
Peak pressure, atm (mean ± SD)	16.75±1.49	18.14±2.67	0.16
Final flow of TIMI grade 3, n (%)	36 (85.7)	80 (89.9)	0.60
IABP, n (%)	20 (47.6)	12 (13.5)	<0.001

DES, drug eluting stent; ISR: intra-stent restenosis; CTO, chronic total occlusion; LM, left main artery; LAD, left anterior descending artery; IRA, infarct related artery; TIMI, thrombolysis in myocardial infarction; IABP, intra-aortic balloon pump.

surement data are expressed as mean ± SD, and non-normally distributed continuous data were expressed as medians (Q1, Q3). Categorical data are expressed as percentages. The Student's *t*-test, rank sum test, and chi-square test were used (Fisher's exact test was used when appropriate). The estimated cumulative survival was assessed by the Kaplan-Meier method. Cox regression analysis was used to calculate the HR for factors of MACE. Univariate analysis was initially conducted, and variables (if $P<0.05$) were included in the multivariate analysis. Statistical significance was defined as 2-tailed $P<0.05$.

Results

Clinical data

A total of 131 patients were enrolled, including 101 males and 30 females, with the average age of 60.2±11.5 (32-90) years. There were 42 patients in the group of ST during the early phase (45 lesions), including 6 patients with acute ST [2.92±2.06 (1.5-7) hours after stent implantation] and 36 patients with sub-acute ST [6.28±4.55 (1-20) days after stent implantation]. There were 89 patients in the group of ST during the late phase, including 3 patients with late ST [4.0±1.0 (3-5) months after stent implantation] and 86 patients with VLST [38.0 months (25.0, 54.5) after stent implantation].

When ST occurred, the incidence of discontinued DAPT was significantly lower in the group of ST during the early phase than in the group of ST during the late phase ($P<0.001$, **Table 1**). In the group of ST in early phase, 38 patients received DAPT, 3 patients used only clopidogrel, and 1 patient took no antiplatelet agent. In the group of ST during the late phase, 8 patients

Table 3. MACE during Follow-up

	Group of ST in early phase (n=37)	Group of ST in late phase (n=86)	*P*
ST, n (%)	2 (5.4)	7 (8.1)	0.72
MI, n (%)	3 (8.1)	11 (12.8)	0.55
TVR, n (%)	6 (16.2)	11 (12.8)	0.58
Mortality, n (%)	3 (8.1)	6 (7.0)	1.00
MACE, n (%)	10 (27.0)	22 (25.6)	1.00

ST, stent thrombosis; MI, myocardial infarction; TVR, target vessel revascularization; MACE, Major adverse clinical cardiac events.

received DAPT, 60 patients used only aspirin, 3 patients used only clopidogrel, and 18 patients took no antiplatelet agent.

Clinical presentation of ST was acute MI in all patients, mostly with ST segment elevation in the anterior wall (81/131, 61.8%), 3 (2.3%) in both anterior and inferior wall; 26 (19.8%) in the inferior wall, 5 (3.8%) in the lateral wall, and 16 (12.2%) with non-ST-elevation MI. There were 65 patients (49.6%), 37 patients (28.2%) and 16 patients (12.1%) with Killip class 1, 2, and 3, respectively. There were 13 patients (9.9%) with cardiogenic shock (Killip class 4). The incidence of cardiogenic shock was significantly higher in the group of ST during the early phase than in the group of ST during the late phase (*P*=0.03, **Table 1**).

Antiplatelet therapy was adjusted in 27 patients. Among them, the dose of aspirin and/or clopidogrel was doubled in 6 patients, cilostazol was added in 13 patients, and clopidogrel was replaced by ticagrelor in 8 patients. The rate of adjusting antiplatelet therapy was significantly higher in the group of ST in early phase than in the group of ST in late phase (*P*<0.001, **Table 1**).

Angiographic and interventional data

During the initial PCI, the first generation DESs was implanted into 100 patients. The percentage of the first generation DESs implanted was lower in the group of ST during the early phase than in the group of ST during the late phase (*P*=0.004, **Table 2**). The number of stents and the total length of the stents implanted in the initial PCI were significantly higher in the group of ST in early phase than in the group of ST in late phase (*P*=0.001 and *P*=0.01, respectively, **Table 2**).

The target vessel was the left main artery in 3 cases (2.3%), left anterior descending artery (LAD) in 89 cases (67.9%), both LAD and left circumflex artery in 2 cases (1.5%), both LAD and right coronary artery in 1 case (0.8%), left circumflex artery in 8 cases (6.1%), and right coronary artery in 28 cases (21.4%). The incidence of multiple ST in the group of ST in early phase was higher than in the group of ST in late phase (*P*=0.03, **Table 2**).

After angiography, 126 patients received emergency PCI. Additional stents were implanted in 67 patients. Only balloon angioplasty and/or thrombosis aspiration were performed in 58 patients, of whom 2 patients received elective CABG, and recanalization failed in 1 patient. Five patients underwent only coronary angiography. Among them, TIMI (thrombolysis in myocardial infarction) flow grade 3 was observed in 3 patients who received conservative medication therapy, 1 patient underwent CABG, another patient died just after angiography due to cardiac rupture. The rate of additional stent implantation was significantly lower in the group of ST in early phase than in the group of ST in late phase (*P*<0.001, **Table 2**). IABP was inserted in 32 (24.4%) patients. IVUS and OCT were performed in only 3 patients respectively.

Follow-up

Eight patients died in the hospital within 10.5 days after the onset of ST. In the early ST group, 5 patients died of severe heart failure or cardiogenic shock. In the group of ST during the late phase, 3 patients died of cerebral hemorrhage, cardiac rupture, and cardiogenic shock. Subacute ST occurred in 2 patients in the group of ST during the early phase, while 1 patient in the group of ST during the late phase. The incidence of MACE was higher in the group of ST during the early phase than in the group of ST during the late phase (16.7% and 4.5%, respectively, *P*=0.037).

One hundred and twenty-three patients survived to discharge. MACE occurred in 32 patients during follow-up for a median of 38.0 (15.0, 62.0) months. There was no difference between the two groups in MACE during follow-up (27.0% in the group of ST in early phase and 25.6% in the group of ST in late phase, respectively; *P*=1.00. **Table 3**). In the group of ST during the late phase, it was noticed that there were 7 cases of recurrent VLST at a median of

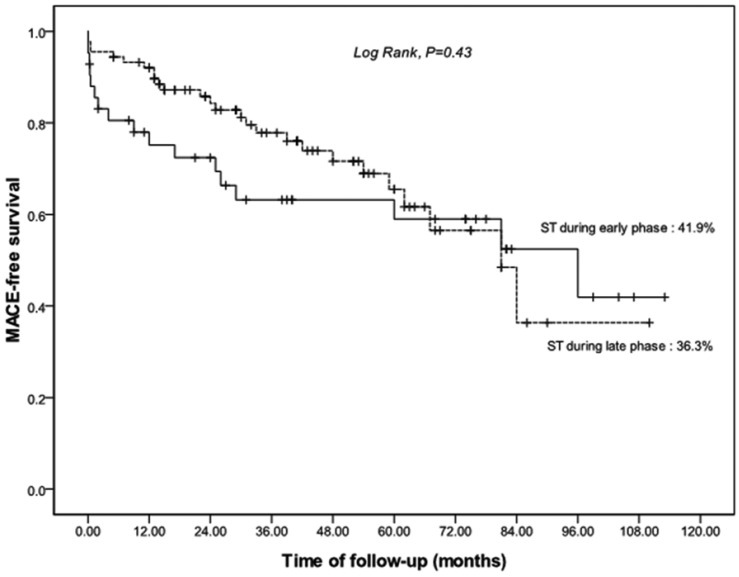

Figure 1. Cumulative MACE-free survival rates between the 2 groups during follow-up.

Table 4. Cox regression analysis for total MACE-related factors

	HR	95% CI	*P*
Cox univariate regression analysis			
Age ≥60 years	2.01	1.07-3.78	0.029
LVEF <50%	2.68	1.45-4.96	0.002
Cardiogenic shock	3.72	1.70-8.13	0.001
IABP	1.89	1.00-3.54	0.049
Cox multivariate regression analysis			
Age ≥60 years	2.32	1.21-4.46	0.012
LVEF <50%	2.71	1.37-5.35	0.004
Cardiogenic shock	1.63	0.57-4.67	0.367
IABP	1.17	0.56-2.47	0.679

LVEF, left ventricular ejection fraction; IABP, intra-aortic balloon pump.

42 (24-59) months after the initial ST. Of these 7 patients, 6 had 1 VLST event and the other had 2 VLST events.

The Kaplan-Meier analysis revealed that the estimated overall MACE-free survival rate in all patients was only 38.4%. The MACE-free survival rates were 41.9% in the group of ST during the early phase and 36.3% in the group of ST during the late phase (Log Rank, *P*=0.43; **Figure 1**).

Cox univariate regression analysis revealed that age ≥60 years, LVEF ≤50%, cardiogenic shock, and IABP implantation were risk factors (*P*<0.05) for total MACE. Age (≥60 year) and LVEF (<50%) were confirmed as the independent predictive factors in the Cox multivariate regression analysis (**Table 4**).

At the longest available follow up, 33.3% of patients in the early ST group continued to receive DAPT, which was lower than in the group of ST during the late phase (55.1%, *P*= 0.025). There was no significant difference in estimated MACE-free survival between patients that received continuous DAPT and patients that did not (57.3% in patients received continuous DAPT and 32.2% in patients stopped continuous DAPT, respectively, Log Rank, *P*=0.24; **Figure 2A**). Secondly, in the early ST group, there was either no significant difference in estimated MACE-free survival between patients that received continuous DAPT and those that did not (57.1% in patients received continuous DAPT and 42.3% in the patients stopped continuous DAPT, respectively, Log Rank, *P*=0.17; **Figure 2B**). However, in the group of ST during the late phase, the estimated MACE-free survival was higher in patients that received continuous DAPT than in patients that stopped continuous DAPT (56.7% in patients received continuous DAPT and 21.4% in the patients stopped continuous DAPT, respectively, Log Rank, *P*=0.03; **Figure 2C**). Cox multivariate analysis also revealed that continuous DAPT at the longest available follow up was one of the independent predictive factors for freedom of MACE events in the group of ST in late phase (HR: 0.42, 95% CI: 0.18-0.96, *P*=0.04).

Discussion

The mechanisms of ST at different times after DES implantation were different. During the early phase (≤30 days), procedural factors are most likely responsible for ST and include underexpansion of stent, dissection at the stent edge, plaque rupture in the residual atherosclerotic lesion [6]. Whereas during the late phase (>30 days), most ST occurs because of

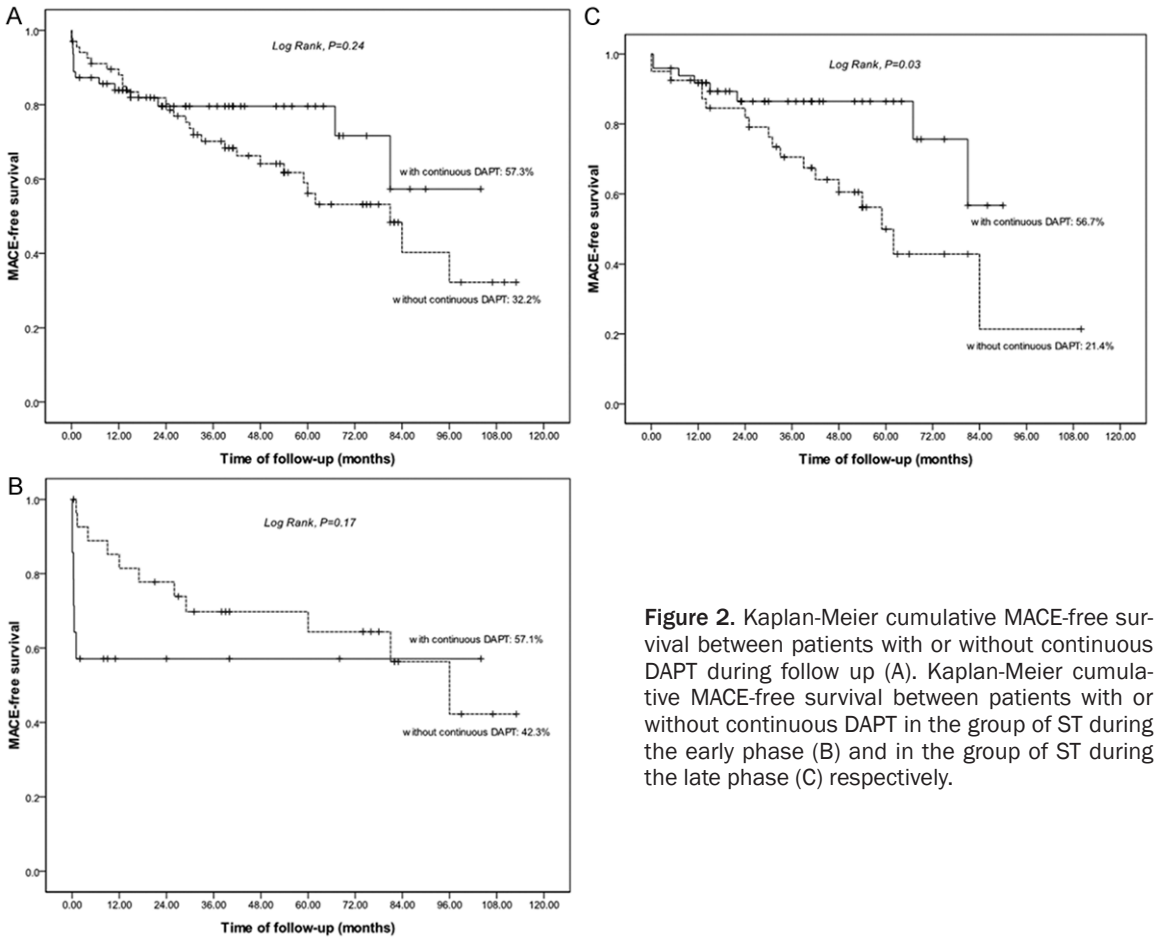

Figure 2. Kaplan-Meier cumulative MACE-free survival between patients with or without continuous DAPT during follow up (A). Kaplan-Meier cumulative MACE-free survival between patients with or without continuous DAPT in the group of ST during the early phase (B) and in the group of ST during the late phase (C) respectively.

delayed arterial healing, incomplete endothelial coverage, local inflammation, and local hypersensitivity [6, 16, 17]. Recent studies have demonstrated that advanced neoatherosclerosis with neointimal rupture was the most common mechanism of ST during the late phase [18, 19]. The varied mechanism of ST at different time points may result in the differences in clinical prognosis.

However, the clinical prognosis, particularly long-term prognosis remains unclear in patients with ST at different time points after DES implantation. Numerous patients after BMS implantation have been included in previous studies. Kubo et al. enrolled 152 patients with angiography-confirmed ST and divided them into early ST, late ST, and VLST groups. In the study by Kubo *et al.*, 57.2% of patients received BMS implantation, and the results indicated that there was no difference in in-hospital events and that the long-term outcome was better in the VLST group [7]. Armstrong et al. enrolled 152 patients with angiography-confirmed ST. It is not clear which type of stent was implanted during the initial procedure, and a short-term follow-up indicated that the 30-day mortality was significantly lower in the VLST group than that in the early ST group [8]. In another observational study by Armstrong et al., 43.3% of patients received BMS or stent with unknown type. The early follow-up showed that the in-hospital mortality was significantly higher in the early ST group [9].

Compared with BMS, incomplete intimal coverage and late stent malapposition were more common in DES [6, 17, 18]. The neo-arterial atherosclerosis after DES implantation was more common and presented earlier [10]. In another study by Kubo *et al.*, angiographic stent fracture was seen in 36.7% of VLST lesions after DES implantation, while none was seen in lesions after BMS implantation [20]. These different pathological changes after implantation of stents with different types may contribute to

the long-term prognosis. Therefore, the above-mentioned studies enrolled patients after BMS might not accurately reflect the prognosis of patients with ST after DES.

However, the time of follow-up was short in the few studies focusing on the clinical outcomes of ST according to time after DES. Patients with ST after DES implantation were enrolled in the study by Daemen *et al.* and were divided into early ST group (0-30 days) and late ST group (>30 days) [11]. There was no significant difference in incidence of events in both hospital and six months follow up between the two groups [11]. VLST (>1 year) may occur again because the factors for late ST may remain active. Furthermore, these patients may discontinue DAPT 1 year after the 2nd revascularization according to the current guideline. Therefore, follow-up less than 1 year might be unable to reflect the true long-term prognosis in these patients.

In this study, the incidence of in-hospital MACE was significantly higher in the group of ST during the early phase compared with the group of ST during the late phase. The incidence of cardiogenic shock was higher in the early ST group than in the group of ST during the late phase. Moreover, the incidence of multiple ST in the early ST group was higher. The pathological changes of ST may not be limited to a single site. Furthermore, ST in one site might result in unstable hemodynamics, activating platelets, activating coagulation, and the autonomic nervous system. It may subsequently trigger the formation of ST in another site. In addition, only patients with definite ST confirmed by angiography were enrolled in this study, and the patients with probable or possible ST based on the ARC definition were not included. In the early ST group, 47.6% of patients had ST during their hospital stay, whereas all ST occurred outside of the hospital in the group of ST during the late phase. There might be patients with ST resulting in sudden death outside of the hospital before they had chance to receive repeat angiography. Therefore, the "survivor bias" was bigger in the group of ST during the late phase.

During a median of 38.0 (15.0-62.0) months of follow-up, the overall incidence of MACE was not different in the 2 groups. This result was different from the above-mentioned studies that included patients with BMS. Compared with the early ST group, K-M survival analysis showed that MACE-free survival was higher in the group of ST during the late phase in early follow-up. However, with prolonged follow-up, the cumulative survival in the group of ST during the late phase gradually declined. In the group of ST during the late phase, VLST reoccurred in 7 patients within a median time of 42 months after their initial VLST. Among them, 1 patient had 2 repeated episodes of VLST. This observation suggests that the factors of occurrence of VLST may remain active.

Some patients received an adjusted antiplatelet therapy in this study, and the rate of adjusted antiplatelet therapy was significantly higher in the early ST group. Low response to antiplatelet agents may be an important risk factor for ST after DES [21, 22]. It has been previously reported that early but not late ST is influenced by residual platelet aggregation in patients undergoing coronary interventions [23]. However, the real role of antiplatelet therapy guided by platelet function monitoring is uncertain [24, 25]. The latest guideline does not recommend the routine monitoring of the platelet function in patients after PCI (III) [26]. Even in patients with ST, there is no evidence to suggest that platelet function testing is effective in guiding antiplatelet therapy (IIb) [26]. Hence, platelet function testing was not applied routinely to all patients in this study.

The optimal duration of DAPT after DES is still controversial [27, 28], and there are no recommendations regarding DAPT duration for patients with ST. In this study, continuous DAPT at the longest available follow up was not the risk factor of the total MACE. However, the further subgroup analysis showed that continuous DAPT was an independent predictive risk factor for MACE-free events in the late group but not in the early group. This result suggests that a prolonged DAPT may be considered for patients who had ST during the late phase.

Currently, the optimal revascularization strategy for ST remains unclear. Kim et al. studied patients with VLST after DES and found that all MACE occurred in patients that had received only balloon angioplasty, and the author suggested additional stent should be implanted in these patients [29]. Nevertheless, the study by Werkun et al. reached a different conclusion that additional stent implantation should be

avoided because the rate of MACE was higher in the patients received additional stent implantation [30]. Because 73.5% patients with early ST were included in the study by Werkun *et al*. [30], this conclusion might be only suitable for patients with early ST. Similarly with the previous studies [7, 9], this study showed that the rate of additional stent implantation was significantly lower in the early group than in the late group. This result suggests that varied PCI strategies should be used for ST occurring at different time points. Additional stent implantation is not recommended for patients with early ST unless they are definite dissection and incomplete coverage of the lesion. However, additional stent implantation may be considered in patients with ST in late phase if they have residual stenosis and plaque rupture because neo-atherosclerosis is a major cause of ST during late phase [18, 19].

There were also some study limitations: First of all, this is a retrospective observational study. Although there might be difficult because of the low incidence and the critical clinical conditions, a prospective randomized study is necessary to explore the optimal strategy of revascularization and anti-platelets therapy in these patients. Secondly, the power to identify predictors was reduced due to the fact that this is a single-center study with a small sample size. Therefore, it is necessary to design a multi-center cohort study. Thirdly, only a few patients received IVUS and OCT examination due to the issue of health insurance. IVUS and OCT are useful to study morphological changes of thrombosis, endothelial coverage, neoatherosclerosis, and vascular remodeling. Fourthly, there might be some differences in the mechanism of ARC defined late ST and VLST. However, the patients with late ST and VLST were grouped together in this study due to the low number of patients.

Compared with the patients with ST during the late phase, patients with ST during the early phase had a higher incidence of MACE in hospital. However, there is no difference in the long-term outcome between the two groups.

Disclosure of conflict of interest

None.

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