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Original article

Long-term outcomes following very late stent thrombosis of drug-eluting stent

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ABSTRACT

Background: Long-term outcomes of very late stent thrombosis (VLST) after implantation of drug-eluting stents (DES) are still unclear. The aim was to evaluate the long-term outcomes after VLST of DES, and to analyze the related factors of long-term outcomes in these patients.

Methods: From January 2006 to February 2013, patients with angiographically defined VLST were studied. The clinical characteristics, angiography and interventional data, and anti-platelet therapy protocols were analyzed. The patients were divided into two groups according to the occurrence of major adverse cardiac events (MACE) during follow-up. The clinical and interventional data between the two groups were compared.

Results: Sixty-two patients were enrolled consisting of 55 males and 7 females with an average age of 58.6 ± 10.2 (41–82) years. The mean time from first implantation of DES to occurrence of VLST was 38.7 ± 18.1 (12.5–84) months. One patient died in hospital. Sixty-one patients survived to discharge, and MACE occurred in 17 patients after a median follow-up of 32.1 ± 19.1 (median: 44, range 5–88) months. The total MACE rate was 29.0% (18/62), and Kaplan–Meier survival analysis showed the estimated MACE-free survival was 45.1%. The rate of implantation of an additional first-generation DES during the first VLST in the group with events was higher (44.4% vs.11.4%, respectively, $p = 0.007$). The percentage of continuous dual antiplatelet therapy (DAPT) at the longest available follow-up was higher in the event-free group (27.8% vs. 75.0%, respectively, $p = 0.001$). Multivariable Cox regression analysis revealed that the only independent predictors for freedom of MACE during long-term follow-up was continuous DAPT at the longest available follow-up [hazard ratio (HR) = 0.30, 95% CI: 0.09–0.97, $p = 0.04$].

Conclusions: Long-term outcomes after VLST were unfavorable. Implantation of an additional first-generation DES might be avoided, and DAPT should be continued.

Introduction

Compared with bare metal stents (BMS), drug-eluting stents (DES) can significantly reduce the rates of in-stent restenosis (ISR) and target vessel revascularization (TVR) [1,2]. DES are used widely during clinical practice [3]. However, safety concerns regarding stent thrombosis (ST), especially late thrombosis, have arisen [4–6]. Although the rate of very late stent thrombosis (VLST) increased during clinical practice, there were few studies conducted regarding the long-term follow-up of VLST. Long-term outcomes of VLST after implantation of DES are still unclear and optimal strategies of revascularization and anti-platelet therapy are uncertain. Therefore, it is necessary to focus on long-term outcomes following VLST.

Materials and methods

Study population

From January 2006 to February 2013, 3945 patients who received emergency coronary angiographies were evaluated. The patients with angiographically defined VLST were enrolled.

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Angiographically confirmed ST was defined according to the Academic Research Consortium (ARC) definition [7]. VLST was defined according to the timing of the ST event occurring more than one year after the index procedure. The clinical characteristics, angiography and interventional data, and anti-platelet therapy protocols were analyzed.

Definition

Major adverse cardiac events (MACE) included myocardial infarction (MI), recurrence of ST, TVR, and death in all causes. The diagnosis of MI required detection of a rise and/or fall of cardiac biomarker values (cardiac troponin) with symptoms of ischemia and electrocardiographic changes [8]. Recurrent ST was defined according to the ARC definition [7]. TVR was defined as ischemia-driven percutaneous coronary intervention (PCI) performed in the same vessel as the index PCI with or without implantation of a stent or coronary artery bypass grafting (CABG). Deaths were classified as cardiac or non-cardiac. Dual antiplatelet therapy (DAPT) was defined as antiplatelet therapy with 100 mg/day aspirin and 75 mg/day clopidogrel. First-generation DES included sirolimus-eluting (SES) or paclitaxel-eluting stents (PES) with durable polymers. New-generation DES included bioabsorbable polymer-based DES, polymer-free DES, zotarolimus-eluting stents (ZES), and everolimus-eluting stents (EES) [9–11].

Clinical follow-up and grouping

Clinical follow-up was done from hospital records and telephone interviews with the patients or their relatives. According to occurrence of MACE during follow-up, the patients were divided into groups: with events or event free. The clinical and interventional data between the two groups were compared.

Statistical analysis

SPSS Statistics 17.0 software (Chicago, IL, USA) was used. Measurement data are expressed as mean ± standard deviation; enumeration data are expressed as percentages, and analyzed by *t*-test and χ^2 test (exact test if necessary), respectively. A Kaplan–Meier survival analysis was used to estimate MACE-free survival. Predictors of MACE were assessed with Cox regression analysis. A two-sided *p*-value of less than 0.05 indicated statistical significance.

Results

Sixty-two patients met the definition of definite VLST. There were 55 males, and the average age was 58.6 ± 10.2 (41–82) years. The mean time from first implantation of DES to occurrence of VLST was 38.7 ± 18.1 (12.5–84) months. Clinical presentation of VLST was acute MI in all patients, mostly with ST segment elevation in the anterior wall (46/62, 74.2%), nine in the inferior wall, two in the lateral wall, and five with non-ST-elevation MI. There were 41 patients, 17 patients, and 2 patients with Killip class 1, 2, and 3, respectively. There were two patients with cardiogenic shock (Killip class 4). When VLST occurred, aspirin was taken in 41 patients, clopidogrel in 1 patient, and DAPT in 5 patients. No antiplatelet agents were taken in the rest of the 15 patients (Table 1).

During the initial PCI procedure, first-generation DES was implanted in 54 patients, including SESs with durable polymer in 52 patients, PES in 1 patient, and combined SES and PES in 1 patient. New-generation DES were implanted in six patients, including bioabsorbable polymer-based SESs in three patients, ZESs in two patients, and EES in one patient. The type of DES was unclear in two patients who received the first PCI in other hospitals. According to the year of stent implantation and description by the family, DES in these two patients could be confirmed as first generation.

VLST occurred most frequently in the left anterior descending artery (LAD, 47/62, 75.8%), 1 in the left main artery, 3 in the circumflex, and 11 in the right coronary artery. Intra-aortic balloon pumps were implanted in seven patients. Due to health insurance issues, only three patients received intra-vascular ultrasound (IVUS) and two patients received optical coherence tomography (OCT) examination. Sixty patients received emergency PCI after angiography. Forty-three patients received additional stents re-implanted, had balloon angioplasty and/or thrombosis aspiration without stent implantation was performed in 14 patients, 2 patients received selective CABG after balloon angioplasty, and recanalization failed in 1 patient. Following intravenous thrombolytic therapy in another hospital, one patient received medication therapy after emergency angiography which showed there was flow of thrombolysis in myocardial infarction (TIMI) class 3. In the rest of the population, one patient received medication therapy and emergency angiography showed there was flow of TIMI class 3 with thrombosis which disappeared in selective repeat angiography. In the 43 patients that received additional stent

Table 1
Clinical characteristics of patients.

	Over all (*n* = 62)	With events (*n* = 18)	Event free (*n* = 44)	*p*
Male sex, *n* (%)	55 (88.7)	16 (88.9)	39 (88.6)	1.0
Age, years (mean ± SD)	58.6 ± 10.2	61.2 ± 10.3	57.5 ± 10.1	0.20
Detection duration to occurrence of VLST, m	38.7 ± 18.1	34.8 ± 15.1	40.3 ± 19.1	0.28
Region of MI (ST segment elevation in anterior wall), *n* (%)	46 (74.2)	14 (77.8)	32 (72.7)	0.76
Killip class of 1–2, *n* (%)	58 (93.5)	17 (94.4)	41 (93.2)	1.0
Risk factors				
Hypertension, *n* (%)	33 (53.2)	11 (61.1)	22 (50.0)	0.58
Diabetes mellitus, *n* (%)	17 (27.4)	4 (22.2)	13 (29.5)	0.76
Hyperlipidemia, *n* (%)	30 (48.4)	6 (33.3)	24 (54.5)	0.17
Smoking, *n* (%)	45 (72.6)	11 (61.1)	34 (77.3)	0.22
Medical treatment				
Statins, *n* (%)	56 (90.3)	15 (83.3)	41 (93.2)	0.34
ACEI/ARB, *n* (%)	23 (37.1)	6 (33.3)	17 (38.6)	0.78
B-blocker, *n* (%)	45 (72.6)	12 (66.7)	33 (75.0)	0.54
Insulin, *n* (%)	5 (8.1)	2 (11.1)	3 (6.8)	0.62
LVEF, %	55.8 ± 12.0	56.4 ± 11.1	55.5 ± 12.5	0.80
Peak value of cardiac troponin I, ng/ml	74.8 ± 72.8	72.0 ± 70.5	76.0 ± 74.6	0.84

VLST, very late stent thrombosis; MI, myocardial infarction; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVEF, left ventricular ejection fraction.