Long-Term Clinical Outcomes After Angiographically Defined Very Late Stent Thrombosis of Drug-Eluting Stent

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ABSTRACT

Background: The advent of drug-eluting stent (DES) use has raised concerns regarding later occurring stent thrombosis, especially very late stent thrombosis (VLST), and little is known about long-term clinical outcomes after VLST occurrence.

Hypothesis: Long-term clinical outcomes after detection of VLST may be poor.

Method: We evaluated 3572 consecutive patients who received DES implantation from May 2004 to July 2007 at 3 hospitals. The primary outcomes were a composite of major adverse cardiac events (MACE) including cardiac death, myocardial infarction (MI), target-lesion revascularization (TLR), and target-vessel revascularization (TVR) after VLST occurrence.

Results: We identified 19 patients (0.53%) with angiographically documented stent thrombosis developing over 1 year after DES implantation. The mean time to VLST occurrence was 899 days (899 ± 353). Discontinuation of antiplatelet drugs was noted in 4 (21%) patients and the average duration of discontinuation was 4 days. Clinical presentations of VLST were mainly MI (17 patients, 89%). Balloon angioplasty was only performed in 12 patients (63%) and stent implantation in 7 patients (37%). Mean follow-up duration from VLST occurrence was 620 days (620 ± 256). During clinical follow-up after VLST occurrence, no cardiac deaths or MIs were detected. Target-vessel revascularization was done in 2 (11%) patients and TLR in 1 patient (6%). Major adverse cardiac events occurred in 3 (16%) patients during long-term clinical follow-up.

Conclusions: Clinical presentation of VLST after DES implantation is associated with serious adverse events, such as MI. Long-term follow-up outcomes after VLST occurrence appear unfavorable and more data from larger studies are warranted.

Introduction

Drug-eluting stents (DES) significantly reduce the rates of in-stent restenosis (ISR) and target-lesion revascularization (TLR) compared with bare-metal stents.[1,2] The advent of DES has also raised safety concerns regarding stent thrombosis (ST), which is a catastrophic, albeit infrequent, complication that results in myocardial infarction (MI) or sudden cardiac death.[3,4] However, little is known about the long-term clinical outcomes after very late stent thrombosis (VLST) detection and this study is aimed at assessing long-term clinical outcomes after angiographically documented VLST of DES.

Methods

Study Population and Protocol

From May 2004 to July 2007, a total of 3572 consecutive patients who underwent percutaneous coronary intervention (PCI) with DES at Inje University Busan Paik Hospital, Yeungnam University Medical Center, and Keimyung University Dongsan Hospital in South Korea and who subsequently suffered from angiographically documented VLST during follow-up were enrolled.

Procedures and Antiplatelet Therapy

All interventions were performed according to current standard guidelines; interventional strategy including periprocedural glycoprotein IIb/IIIa inhibitor and intravascular ultrasound (IVUS) use were left to the discretion of the operator. Patients were prescribed aspirin and clopidogrel. A loading dose of clopidogrel (300 mg or 600 mg) was given to patients without pretreatment. Patients were advised to maintain life-long aspirin therapy. Prior to October 2006, patients who received sirolimus-eluting stents (SES) were prescribed clopidogrel for 3 or 6 months depending on the complexity of the procedure, whereas patients treated with paclitaxel-eluting stents (PES) were given a 6-month

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prescription. After that time point, all patients were prescribed clopidogrel for 1 year. The use of glycoprotein IIb/IIIa inhibitors during PCI was left to the discretion of the interventional cardiologist.

Follow-Up

Coronary angiography follow-up was performed in all living patients at 6 to 8 months after occurrence of VLST and clinical follow-up was done from hospital records and telephone interviews with the patients or their relatives.

Study Outcomes and Definitions

Study outcomes were major adverse cardiac events (MACE) such as cardiac death, MI, target-lesion revascularization (TLR), target-vessel revascularization (TVR), and recurrent stent thrombosis (ST). Myocardial infarction was defined as elevation of creatine kinase (CK) levels to twice the upper limit of normal with a rise in CK-MB fraction, chest pain lasting $\geq$30 minutes, or appearance of new electrocardiographic changes. TLR was defined as either surgical or percutaneous re-intervention driven by significant (>50%) luminal diameter narrowing within the stent or the 5 mm borders proximal and distal to the stent and that was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. TVR was defined as revascularization within the target vessel encompassing the target lesion.

The ST, categorized as VLST includes any event beyond 1 year after DES implantation, was defined as the association of clinical symptoms with angiographic confirmation of thrombotic stent occlusion. Clinical signs and symptoms were considered to be present if at least 1 of the following criteria was met: (1) sudden onset of typical chest pain with duration >20 minutes; (2) ischemic ECG changes; (3) typical rise and fall of cardiac biomarkers.

Angiographic criteria for ST were met when the thrombolysis in myocardial infarction (TIMI) flow was: (1) Grade 0 with occlusion originating in the persistent region or (2) Grade 1, 2, or 3 in the presence of a thrombus originating in the persistent region according to Academic Research Consortium recommendations.[5,6]

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation (SD) for continuous variables and as frequencies for categorical variables. Major adverse cardiac event-free survival distributions were estimated according to the Kaplan-Meier method. A probability value <0.05 was considered significant. Data were analyzed with the SPSS 12.0 software for Windows (SPSS, Inc. Chicago, IL).

Results

Among a total of 3572 consecutive patients who underwent DES implantation, 3207 patients were treated with an SES (Cypher, Cordis, Warren, NJ) and 365 patients with a PES (Taxus, Boston Scientific, Natick, MA); during the index period, there were 19 patients (0.53%) with definite VLST. Baseline characteristics of patients with VLST are represented in Table 1. Very late stent thrombosis developed in 17 patients with SES and in 2 patients with PES. Left anterior descending (9/19, 47%) and right coronary artery (9/19, 47%) were the predominant sites for VLST (Table 2). Mean time to occurrence of VLST was 899 (899 ± 353) days and clinical presentation of VLST was mostly as MI (17/19, 89%), mainly ST-elevation MI (13/17, 76%). Among patients presenting with VLST, 4 had discontinued antiplatelet medication including aspirin. Glycoprotein IIb/IIIa inhibitors were given to 6 patients and a thrombolytic agent was added in 2 patients. Thrombosuction was performed in 13 patients, balloon angioplasty was done in 12 patients, and an additional stent was reimplanted in 7 patients. There was no in-hospital death or MI (Table 3). All patients underwent clinical follow-up (100%) with mean duration from VLST detection of 620 (620 ± 256) days. TVR was detected in 2 patients, TLR in 1 patient, and there was no cardiac death or MI. There was 1 noncardiac death secondary to hepatocellular carcinoma. Therefore, total MACE was 16% (3/19, in Table 4).

Table 1. Baseline Characteristics of the 19 Patients with VLST

Age, y	60 ± 13
Male	17 (89%)
Diabetes mellitus	6 (32%)
Hypertension	5 (26%)
Smoking	13 (68%)
Hyperlipidemia	6 (32%)
Previous history	
Myocardial infarction	0
Percutaneous coronary intervention	1 (5%)
Coronary artery bypass graft	0
Clinical diagnosis	
Stable angina	4 (21%)
Unstable angina	5 (26%)
Non-ST-elevation myocardial infarction	6 (32%)
ST-elevation myocardial infarction	4 (21%)
Left ventricular ejection fraction, %	54 ± 12

Abbreviations: VLST, very late stent thrombosis.

Table 2. Initial Angiographic and Procedural Outcomes of the 19 Patients with VLST

Angiographic Diagnosis	
≥2-vessel	7 (37%)
Involved vessel	
Left anterior descending artery	9 (47%)
Left circumflex artery	1 (6%)
Right coronary artery	9 (47%)
Bifurcation intervention	1 (6%)
Chronic total occlusion	1 (6%)
Multivessel intervention	4 (21%)
≤2.5 mm stent implantation	2 (11%)
Number of implanted stents	1.5 ± 0.8
Stent used	
Sirolimus-eluting stent	17 (89%)
Paclitaxel-eluting stent	2 (11%)
Stent diameter, mm	2.9 ± 0.3
Total stent length, mm	43 ± 21
Procedural success	19 (100%)

Abbreviations: VLST, very late stent thrombosis.

Table 3. Clinical and Procedural Characteristics at the Time of Detection of Stent Thrombosis

Detection duration to occurrence of VLST, d	899 ± 353
Discontinuation of antiplatelet agent	4 (21%)
Duration of antiplatelet agent discontinuation, d	2, 5, 4, 2
Antiplatelet agent used	
Aspirin only	8 (53%)
Aspirin + Clopidogrel	3 (20%)
Asprin + Clopidogrel + Cilostazol	4 (27%)
Very late stent thrombosis	19 (100%)
Diagnosis	
Unstable angina	2
Non-ST-elevation myocardial infarction	4
ST-elevation myocardial infarction	13
Left ventricular ejection fraction, %	48 ± 10
Glycoprotein IIb/IIIa inhibitor	6 (32%)
Thrombolytics	2 (10%)
Primary percutaneous coronary intervention	15 (79%)
Treatment methods	
Thrombosuction	14 (74%)
Balloon angioplasty only	7 (37%)
Balloon angioplasty with stent implantation	12 (63%)
In-hospital death	0

Abbreviation: VLST, very late stent thrombosis.

Follow-up coronary angiography was performed in 74% (14/19) of patients. In-stent restenosis was found in 50% (7/14) with restenosis type being mainly focal (72%, 5/7, Table 4). The cumulative MACE free survival rate is presented in Figure 1.

Discussion

The major findings of this study were that although VLST was uncommon (0.53%), its presentation is perilous, mainly as MI, and its associated long-term follow-up outcomes after VLST appear unfavorable.

Currently there are limited data on long-term outcomes of VLST. One study showed unfavorable long-term clinical outcomes after definite stent thrombosis, which were associated with diabetes mellitus, left ventricular ejection fraction <45%, long total stent length, complex coronary lesions, TIMI flow grade <3 after PCI, and implantation of an additional coronary stent during primary PCI.[7] Our study also dealt with long-term clinical results, but focused on angiographically-defined VLST and not acute or subacute thrombosis; the results were also unfavorable with a 16% MACE rate and a 50% restenosis rate. It might be interesting to compare acute and subacute ST patients with late ST patients; however, data are scarce because of the rare incidence of ST, and therefore a large study would be needed.

The optimal treatment strategy for VLST is not firmly settled. Our study showed that all MACE, TLR, and TVR were detected in patients with balloon angioplasty only. Although it is not yet conclusive from this study, placing another stent might be helpful for this particular subset of patients.

One study showed that the incidences of VLST with DES compared to bare-metal stent (BMS) have a steady annual rate of increase of 0.2% to 0.6% for up to 3 years and possibly an even longer period.[4] Another study showed that increased rates of VLST were found for both SES (0.6% vs 0%, $P = 0.025$) and PES (0.7% vs 0.2%, $P = 0.028$) compared with BMS.[8] Similarly, a meta-analysis of 14 trials, which enrolled 4958 patients randomized to SES or BMS, with 59 months of

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Table 4. Clinical Follow-Up Results of the 19 Patients after Detection of VLST

Mean follow-up duration, d	620 ± 256
MACE	
Cardiac death	0
Noncardiac death	1 (6%)
Myocardial infarction	0
Target-lesion revascularization	1 (6%)
Target-vessel revascularization	2 (11%)
Total cardiac MACE	3 (16%)
Angiographic follow-up	14 (74%)
Restenosis	7 (50%)
Types	
Focal	5 (72%)
Edge	0
Diffuse	1 (9%)
Total occlusion	1 (9%)

Abbreviations: MACE, major adverse cardiac events; VLST, very late stent thrombosis.

follow-up, showed an increased rate of VLST with SES (0.6% vs 0.05%, $P = 0.02$) without an increase in adverse events.[9] Our study also evidenced a similar incidence of VLST of 0.53% over 3 years; the clinical presentation of VLST was mostly catastrophic as acute MI (89%). From these results, we reconfirmed that VLST may be rare, but its consequences are dangerous.

Procedural and pathologic risk factors such as local hypersensitivity reaction of the stent; ostial and/or bifurcation stenting; malapposition/incomplete apposition of struts[6]; restenosis; and strut penetration into a necrotic core could affect occurrences of VLST and poor endothelialization has been proposed as the most important pathologic predictor of late stent thrombosis. The latter factors might affect long-term outcomes.[10]

The limitation of this study is that the population is too small to judge the effectiveness of treatment modalities because incidence of ST is quite low, a multicenter study would be needed. The second problem is lack of usage of an imaging tool such as IVUS or optical coherence tomography for the detection of endothelialization of stents during follow-up. The third problem is that we could not present exact incidences of VLST because many VLST cases were missed, either due to sudden MI death or lack of angiography, although we enrolled patients after development of angiographically visualized stent thrombosis.

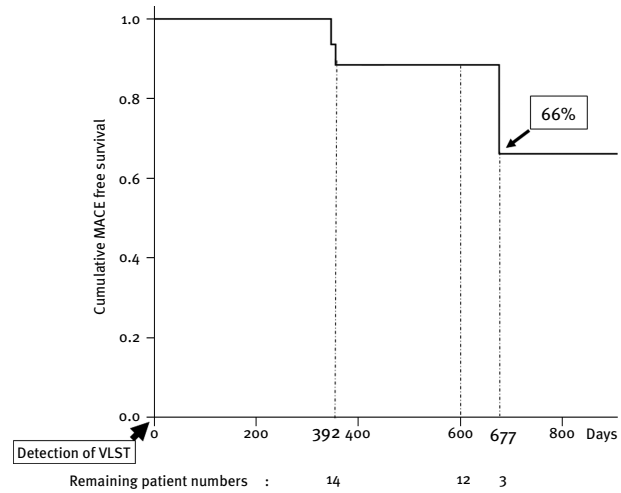

Figure 1. Cumulative MACE-free survival is represented. Clinical follow-up duration was 620 ± 256 days. Abbreviations: MACE, major adverse cardiac event; VLST, very late stent thrombosis.

Conclusions

The clinical presentation of VLST after DES implantation is associated with serious adverse events such as MI. Long-term follow-up outcomes after detection of VLST appear unfavorable and more data from larger studies are warranted.

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