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EXPRESS PUBLICATION

Late Angiographic Stent Thrombosis (LAST) Events With Drug-Eluting Stents

Andrew T. L. Ong, MBBS, FRACP, Eugène P. McFadden, MD, FRCPI, FACC, Evelyn Regar, MD, PHD, Peter P. T. de Jaegere, MD, PHD, Ron T. van Domburg, PHD, Patrick W. Serruys, MD, PHD, FACC

Rotterdam, the Netherlands

OBJECTIVES We sought to describe the incidence of late angiographic stent thrombosis (LAST) events in an unselected drug-eluting stent (DES) population.

BACKGROUND Concerns have been raised that LAST may be a potential limitation of DES.

METHODS We have previously reported the angiographic incidence of early stent thrombosis (1.0%) in this prospective cohort of 2,006 patients treated with either sirolimus-eluting stents (SES) (n = 1,017) or paclitaxel-eluting stents (PES) (n = 989). We continued long-term follow-up to determine the incidence of LAST events, defined as angiographically proven stent thrombosis associated with acute symptoms more than 30 days after DES implantation. All patients had at least 1 year of follow-up, mean duration 1.5 years.

RESULTS There were eight angiographically confirmed LAST events in seven patients: three with SES (at 2, 25, and 26 months) and five with PES (at 6, 7, 8, 11, and 14.5 months). Three cases were related to complete cessation of antiplatelet therapy, two cases occurred while patients were on aspirin therapy within one month of cessation of clopidogrel, and three cases occurred at a time when patients were apparently clinically stable on aspirin monotherapy. We observed no cases of LAST in patients who were on dual antiplatelet therapy. Two deaths occurred directly as a result of LAST.

CONCLUSIONS Angiographically proven late stent thrombosis occurs with an incidence of at least 0.35% (95% confidence limits 0.17% to 0.72%) in patients treated with DES. Importantly, it may also occur when patients are stable on antiplatelet monotherapy. (J Am Coll Cardiol 2005; 45:2088–92) © 2005 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have revolutionized the practice of interventional cardiology with their proven efficacy in reducing restenosis rates. In the U.S., up to 80% of stent implantations currently are with DES. A meta-analysis of 11 randomized trials confirmed the efficacy and safety profile of these stents, but these trials were not powered to detect or exclude an effect of DES on rare events such as stent thrombosis (1). Since April 2002, we have adopted a policy of universal DES implantation for all patients irrespective of clinical presentation or angiographic features, the "all-comers" approach. Based on this approach, we were able to define the incidence of early stent thrombosis (<30 days) in a DES population of 2,006 patients (2).

Our institution has been confronted with patients presenting with late angiographic stent thrombosis (LAST) events, an unexpected occurrence given the long period of dual antiplatelet therapy prescribed in comparison to bare stents (3). Late angiographic stent thrombosis events were uncommon with bare stents except after brachytherapy (4), and subsequent to that report, dual antiplatelet therapy was prolonged for that population. Furthermore, in animal models, DES may delay or cause incomplete healing to a greater degree than with bare-metal stents (5). Therefore, we sought to investigate the incidence of LAST events in the DES population.

METHODS

Study design and patient population. Briefly, since April 2002, we have adopted a policy of universal DES implantation for all patients irrespective of clinical presentation or angiographic characteristics, known as an "all-comers population." We have previously reported on the incidence of early stent thrombosis (defined as stent thrombosis occurring within the first 30 days following stent implantation) in 2,006 consecutive patients after DES implantation (2). This study population thus comprises 1,017 patients treated with sirolimus-eluting stents (SES) from April 2002 to February 2003, and 989 patients treated with paclitaxel-eluting stents (PES) from February 2003 to December 2003. We continued a long-term (minimum one year) follow-up on this cohort of patients to determine the incidence of LAST.

Follow-up. Post-discharge survival status was obtained from the Municipal Civil Registries. A health questionnaire was sent to all living patients with specific questions on re-hospitalization and adverse events. As the principal referral center within the region, repeat procedures are normally performed at our institution and recorded prospec-

From the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. This study was supported by the Erasmus Medical Center, Rotterdam, and by unrestricted institutional grants from Boston Scientific Corporation and Cordis, a Johnson & Johnson company.

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Abbreviations and Acronyms

DES = drug-eluting stents
IVUS = intravascular ultrasound
LAST = late angiographic stent thrombosis
MI = myocardial infarction
PES = paclitaxel-eluting stents
SES = sirolimus-eluting stents
TIMI = Thrombolysis In Myocardial Infarction

tively in our database. For patients who suffered an adverse event at another center, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information.

Procedure and antiplatelet management. All interventions were performed according to current standard guidelines, with the interventional strategy including periprocedural glycoprotein IIb/IIIa inhibitor and intravascular ultrasound (IVUS) use left to the discretion of the operator. Patients were pretreated with aspirin and a loading dose of 300 mg clopidogrel.

Duration of clopidogrel therapy. Upon completion of the index procedure, patients are advised to maintain lifelong aspirin therapy. Patients who received SES were prescribed clopidogrel for three or six months depending on the complexity of the procedure, whereas patients treated with PES were given a six-month prescription. In the Netherlands, clopidogrel after stenting is not reimbursed by medical insurance companies and our department has covered the cost for patients treated here. As a tertiary referral center, most of our patients are referred from other institutions and after discharge from our institution, are managed by referring physicians at peripheral centers. Late decisions regarding antiplatelet therapy are at their discretion.

Definition of LAST. Late angiographic stent thrombosis is defined as late—occurring at least one month after DES implantation with acute symptoms; angiographic—stent thrombosis confirmed angiographically; stent thrombosis—defined as Thrombolysis In Myocardial Infarction (TIMI) flow 0 or 1 or the presence of flow-limiting thrombus (TIMI flow 1 or 2).

RESULTS

Baseline and procedural characteristics. The average age of our patients was 62 years, with 72% being male (Table 1). Over half had multivessel disease on angiography, one-third presented with unstable angina, and 22% with an acute myocardial infarction (MI) as the indication for treatment. Stent type was approximately equally distributed as was the enrolment period. On average, 1.9 lesions in 1.4 vessels were treated with 2.3 stents implanted, totaling 43 mm/patient.

Findings. Follow-up was complete for 98% of the population. Mean follow-up was 1.5 ± 0.5 years. There were eight LAST events in seven patients, three with SES and five with PES (Tables 2 and 3), with an overall incidence of 0.35% (95% confidence limits 0.17% to 0.72%). All patients were male, and all presented at the time of LAST with an acute ST-segment elevation MI. Figure 1 is a representative example of LAST. No differences in patient characteristics (Table 1) were noted between patients with and without LAST. None of the 20 patients described in the previous report with early stent thrombosis (2) developed LAST.

There were two deaths in the seven patients with LAST. One death (Patient #6) occurred in a patient who received a SES to the left anterior descending coronary artery (LAD). Late angiographic stent thrombosis 25 months later resulted in a large anterior MI with cardiogenic shock and the patient died from refractory left ventricular failure two days later. The second death occurred in a patient (Patient #7) who had a pre-existing occlusion of the right coronary artery that received collaterals from the LAD. A single SES was implanted at a proximal LAD lesion. Late angiographic stent thrombosis 26 months later resulted in a large acute anterior MI with cardiogenic shock and the patient died on the catheterization table. Of note, in both these patients, initial attempts to pass a wire through the previous stent were unsuccessful because the wires, on each occasion, appeared to pass between the outside of the stent and the

Table 1. Baseline and Procedural Characteristics of Drug-Eluting Population

	Drug-Eluting Stents (n = 2,006)
Baseline characteristics	
Age, yrs, mean ± SD	61.9 ± 11.3
Male, %	72
Diabetes, %	17
Hypercholesterolemia, %	58
Current smoker, %	28
Hypertension, %	41
Previous myocardial infarction, %	33
Previous PCI, %	25
Previous CABG, %	9
Multivessel disease, %	57
Indication for index procedure	
Stable angina, %	42
Unstable angina, %	33
Acute myocardial infarction, %	22
Silent ischemia, %	3
Procedural characteristics	
Number of lesions treated, mean ± SD	1.9 ± 1.0
Number of vessels treated, mean ± SD	1.4 ± 0.6
LAD, n	1,135
LCx, n	665
RCA, n	784
Others, n	163
Patients treated with SES, n	1,017
Patients treated with PES, n	989
Total stented length, mm (mean ± SD)	43 ± 31
Number of stents implanted, n (mean ± SD)	2.3 ± 1.5
At least one ≤2.50 mm stent implanted (%)	38
Bifurcations stented, %	18
Glycoprotein IIb/IIIa use (%)	25

CABG = coronary artery bypass grafting; LAD = left anterior descending; LCx = left circumflex; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; RCA = right coronary artery; SES = sirolimus-eluting stent.

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Table 2. Characteristics of Patients With LAST

Pt. No.	Age, Gender	Months to Event	DES Type	Treated Vessel	Nominal Stent Diameter, mm	Total Stented Length, mm	Antiplatelet Therapy at Time of LAST	Notes	Clinical Presentation	Clinical Outcome at Hospital Discharge
1	74, Male	2	SES	Mid LAD	2.5	23	Nil	Aspirin and clopidogrel stopped 5 days prior	STEMI	Alive
2	57, Male	7	PES	RCA	3.0	68	Aspirin	Clopidogrel stopped 28 days prior	STEMI	Alive
3a	64, Male*	6	PES	Prox LAD†	3	32	Aspirin	Clopidogrel stopped 21 days prior	STEMI	Alive
3b‡	64, Male*	11	PES	Prox LAD	3	16	Nil	Aspirin stopped 5 days prior for surgery	STEMI	Alive
4‡	74, Male	14.5	PES	Prox LAD	3.5	20	Nil	Aspirin stopped 7 days prior for surgery	STEMI	Alive
5	39, Male	8	PES	Mid RCA†	3	20	Aspirin	Clopidogrel stopped 2 months prior	STEMI	Alive
6	63, Male	25	SES	Prox LAD	3	46	Aspirin	Clopidogrel stopped 19 months prior	STEMI with shock	Dead
7	71, Male	26	SES	Prox LAD	3	36	Aspirin	Clopidogrel stopped 23 months prior	STEMI with shock	Dead

*This patient had two separate episodes of late stent thrombosis. †Late stent thrombosis occurred within a stent-in-stent segment. ‡These two patients were included in a previous report (3).
LAST = late angiographic stent thrombosis; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

vessel wall. This is highly suggestive of acquired aneurysm formation at the stented site because on review, the initial procedural result was optimal. Due to hemodynamic instability, IVUS was not attempted. Autopsy was refused in both cases.

One patient (Patient #3) treated with a PES to the LAD developed two LAST events. The first occurred 11 months after the index procedure and re-presented with an anterior ST-segment elevation MI. He was treated with a new PES inside the original PES stent and lifelong clopidogrel was recommended; before discharge he was given his first prescription of six months worth of clopidogrel. He completed the prescribed six-month course of dual antiplatelet therapy and did not renew the prescription of clopidogrel. Twenty-one days later, he re-presented with lateral ST-segment elevation. Three new PES were used to re-canalize a diagonal branch occluded with thrombus. Intravascular ultrasound study did not reveal a specific contributory factor, in particular, there was no evidence of incomplete stent apposition.

With regard to antiplatelet therapy, three events occurred when patients had stopped all antiplatelet therapy (two were for non-cardiac surgery, and one due to non-compliance). Five events occurred in patients on aspirin monotherapy who had completed their prescribed course of clopidogrel. Two of these events occurred soon after (21 and 28 days) clopidogrel was stopped.

Treatment. Balloon angioplasty was performed in all patients, followed by new DES implantation in seven of eight (Table 3). Glycoprotein IIb/IIIa inhibitors were used in five cases. Intravascular ultrasound was performed in two patients with no evidence of incomplete stent apposition noted. A thrombectomy device was used in two cases. After an episode of late stent thrombosis, prolonged clopidogrel therapy was empirically recommended.

DISCUSSION

The purpose of this report is to highlight that LAST occurs with an incidence of at least 0.35% and possibly up to 0.72% after DES implantation. Furthermore, we have now observed that LAST may also occur not only in temporal relation to complete cessation of antiplatelet therapy (3), but may also occur shortly after clopidogrel is stopped but aspirin continued, and unexpectedly remote from clopidogrel cessation when patients were clinically stable on long-term aspirin therapy. We observed no episodes of LAST while patients were on dual antiplatelet therapy.

In the randomized trials of DES, late stent thrombosis has been reported. Two presumed late stent thromboses related to clopidogrel discontinuation were reported in the TAXUS-II trial (6). With SES, there has been one published report of LAST from the European multicenter, randomized, double-blind study of the SIRolImUS-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS)

Table 3. Treatment of Patients With LAST

Pt. No.	Age, Gender	IVUS	Glycoprotein IIb/IIIa Use	Treatment	Post-LAST Clopidogrel Recommendation
1	74, Male	No	Abciximab	Balloon angioplasty, SES 2.75*18 mm	Lifelong
2	57, Male	Yes	Abciximab	Thrombectomy, balloon angioplasty, PES 3.5*20 mm	1 year
3a	64, Male*	Yes	Abicixmab	Balloon angioplasty, PES 2.25*8mm, 3.5*8 mm, 3.5*8 mm	Lifelong
3b	64, Male*	No	Abciximab	Balloon angioplasty, PES 3*32 mm	Lifelong
4	74, Male	No	No	Thrombectomy, balloon angioplasty, PES 3.5*12 mm	Not stated
5	39, Male	No	No	Balloon angioplasty, inotropes, atropine	Not stated
6	63, Male	No	Integrellin	Balloon angioplasty, PES 2.5*24 mm, intra-aortic balloon pump, inotropes	—
7	71, Male	No	No	Balloon angioplasty, PES 3*20 mm, 3*8 mm, 3*12 mm, intra-aortic balloon pump, inotropes	—

*This patient had two separate episodes of late stent thrombosis.
IVUS = intravascular ultrasound; other abbreviations as in Tables 1 and 2.

trial, with accompanying histological findings showing acquired aneurysm formation with eosinophilic infiltrates; the investigators concluded that LAST was due to a hypersensitive reaction to the polymer coating of the stent (7). Two of the LAST events we report occurred more than two years after SES implantation and both patients died. The timing of the events and the intraprocedural difficulty in wiring the lesion in both patients are potentially compatible with a similar etiology of LAST.

Late stent thrombosis was a major problem with the now discontinued QP2 stent program (8). The ongoing occurrence of stent thrombosis (3.2%, 7.1%, and 10.3% at 1, 6, and 12 months) in the Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial was attributed to the long duration of high-dose drug release and proinflammatory nature of the polymer sleeves.

Several mechanisms of LAST have been postulated: a local drug effect delaying endothelialization or results in the formation of a dysfunctional endothelium, a hypersensitivity, or inflammatory reaction to the polymer, or the development of neointimal hyperplasia with occlusive thrombus formation as the acute event. Furthermore, it is known that previous treatment with brachytherapy is associated with an increased risk of late stent thrombosis when on mono-antiplatelet therapy (4); however, no patient in this report had previous brachytherapy in the stented segment. The use of IVUS, if clinically feasible at the time of stent thrombosis, may help facilitate the elucidation of its etiology. However, their clinical condition often precludes a pre-intervention IVUS.

In patients with documented LAST, we empirically prescribe long-term dual antiplatelet therapy in an attempt to reduce recurrence. The use of long-term dual antiplatelet therapy for the primary prevention of LAST is more problematic. Although it would seem intuitive to do so, there is debate in published literature. There are data from the pre-DES era to suggest that in selected patients, prolonged dual antiplatelet therapy is associated with a reduction in major adverse cardiac events (9,10); however, such potent inhibition of platelet function is associated with an increased risk of major bleeding complications (11,12).

It is difficult to compare the incidence we have reported with that from the bare stent era due to the paucity of reports; a single center registry reported a late stent thrombosis incidence (defined as >30 days) of 0.76%, a figure not dissimilar to this report (13).

The results of this preliminary report expand our previous observations that LAST occurs with DES, demonstrate that it may occur when patients are receiving antiplatelet monotherapy, and provide an estimate of the expected rate in an unselected DES population. Its incidence is low, but potentially problematic given the rapid uptake of such stents. It is imperative that cardiologists and other doctors who treat these patients are aware of this potential late complication, and any decision to stop antiplatelet therapy for whatever reason must take this into account.

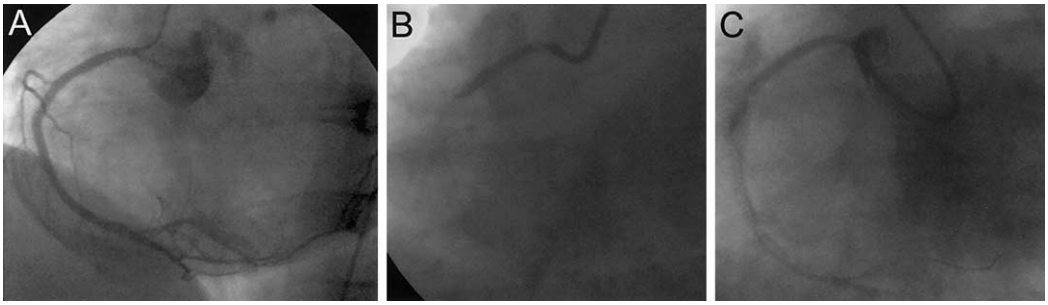

Figure 1. Representative film of late angiographic stent thrombosis (LAST). **(A)** Index procedure, post-stent implantation, right coronary artery. **(B)** Late angiographic stent thrombosis with ST-segment elevation. **(C)** After wire passage, LAST demonstrating large thrombus burden.

Study limitations. This report is confined to patients who presented with acute symptoms and angiographically proven late stent thrombosis. The low frequency of postmortem studies performed in the Netherlands, which would have accurately determined the cause of death, precluded an accurate assessment of the overall rate of late stent thrombosis.

Reprint requests and correspondence: Prof. Patrick W. Serruys, Thoraxcenter, Ba-583, Dr. Molewaterplein 40, 3015-GD Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

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