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Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry

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Aims To evaluate the occurrence of late and very late stent thrombosis (ST) following elective drug-eluting stent (DES) implantation in unprotected left main coronary artery (LMCA) stenosis in a large multicentre registry.

Methods and results All 731 consecutive patients who had sirolimus- or paclitaxel-eluting stent electively implanted in *de novo* lesions on unprotected LMCA in five centres were included. ST was defined according to Academic Research Consortium definitions. Four (0.5%) patients had a definite ST: three early (two acute and one subacute) and one late ST, no cases of very late definite ST were recorded. All patients survived from the event. Three patients had a probable ST. Therefore, 7/731 (0.95%) patients had a definite or a probable ST and all were on dual antiplatelet therapy at the time of the event. Possible (eight late and 12 very late) ST occurred in 20 (2.7%) patients. At 29.5 $\pm$ 13.7 months follow-up, a total of 45 (6.2%) patients had died; 31 (4.2%) of cardiac death. Ninety five (12.9%) patients had a target-vessel and 76 (10.4%) a target-lesion revascularization. Angiographic follow-up was performed in 548 patients (75%): restenosis occurred in 77 (14.1%) patients.

Conclusion Elective treatment of LMCA stenosis with DES appears safe with a 0.9% incidence of definite and probable ST at 29.5 $\pm$ 13.7 months.

Keywords Stent • Left main coronary artery • Drug-eluting stents • Stent thrombosis

Introduction

Some concerns have recently been raised regarding the risk of late and very late stent thrombosis (ST) following drug-eluting stent (DES) implantation.[1–10] Registry data of percutaneous coronary interventions (PCI) with DES use in unprotected left main coronary artery (LMCA) lesions showed that, at mid-term clinical follow-up, this is a feasible and safe approach.[11–19] To date, no study has specifically addressed the prevalence and predictors of late and very late ST following elective DES implantation in unprotected LMCA lesions. The aim of the present study is therefore to evaluate the occurrence of late and very late ST following elective DES implantation in unprotected LMCA stenosis in a large multicentre registry.

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Methods

This study included all consecutive patients with a stenosis in an unprotected LMCA electively treated with PCI and sirolimus- (SES, Cypher, Cordis, Johnson & Johnson Company, Warren, NJ, USA) or paclitaxel-eluting stent (PES, Taxus, Boston Scientific, Natick, MA, USA) implantation in five centres (San Raffaele Hospital and EMO Centro Cuore Columbus in Milan; San Giovanni Battista Hospital in Turin, Italy; Erasmus Medical Center – Thoraxcenter, The Netherlands; the Asan Medical Center, Korea and University of California, Los Angeles Medical Center) between March 2002 and March 2006. The data were prospectively collected in the single centres and retrospectively entered into a common database. Patients with ST or non-ST elevation myocardial infarctions (MIs) were excluded from the analysis. The decision to perform PCI instead of surgery was considered when one of these two conditions was present: suitable anatomy for stenting and preference by patient for a percutaneous approach or suitable anatomy for stenting and disincentive for surgery defined as a Euroscore $\geq$6 and/or prior coronary artery bypass grafting (CABG) with failure of all conduits.

Coronary angioplasty and DES implantation were performed according to the practice of fully covering the diseased segment.[20,21] At the start of the procedure, a bolus of unfractionated heparin was administered at 100 IU/kg to achieve an activated clotting time of $>$250 s. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator. Clinical follow-up was scheduled and obtained for all patients at 1, 6, 12, and 24 months by office visit or direct telephone call to the patients. Patients eligible for longer clinical follow-up were contacted at 36, 48, and 60 months.

Dual antiplatelet therapy (DAT) (i.e. aspirin 100 mg daily and clopidogrel 75 mg daily or ticlopidine 250 mg twice daily) was administrated according to local practice (for at least 6 months after the procedure in Rotterdam and Turin and 12 months in Milan, Seoul, and Los Angeles). All patients were advised to remain on aspirin (100 mg die) lifelong. In addition, cilostazol was also given to some patients for 1 month (in Seoul).

Detailed information on adherence as well as reasons and date for discontinuation of DAT was obtained in all patients.

Angiographic follow-up was scheduled between 4 and 9 months or earlier if non-invasive evaluation or clinical presentation suggested the presence of ischaemia.

Definitions

ST was defined on the basis of the Academic Research Consortium definitions according to the timing of presentation as early (0–30 days), late (31–360 days), or very late ($>$360 days) and to the following trilevel of certainty:

Definite ST in the presence of an acute coronary syndrome and either angiographic or pathological (autopsy) confirmation of ST;

Probable ST in case of an acute MI involving the target-vessel territory without angiographic confirmation of thrombosis or other identified culprit lesion and/or any unexplained death within 30 days;

Possible ST in the case of any unexplained death after 30 days.

The following major adverse cardiac events (MACE), during hospital stay and at follow-up, were also analysed: death, CABG, MI, target lesion revascularization (TLR), and target vessel revascularization (TVR).

Deaths were classified as either cardiac or non-cardiac. Cardiac death was defined as any death due to a cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), procedure-related deaths, and death of unknown cause.

Non-Q-wave MI was defined as an elevation of serum creatine kinase (CK) MB isoenzyme that was three times the upper limit of normal (ULN) in the absence of pathological Q-waves.

Restenosis was defined as $>$50% luminal narrowing at the segment site (stent and 5 mm proximal and distal) demonstrated at the follow-up angiography, regardless of clinical symptoms.

TLR was defined as any revascularization performed on the treated segment; TVR was defined as any re-intervention performed on the treated vessel considering also treatment of any segment in the left anterior descending and circumflex arteries.

The European system for cardiac operative risk evaluation (Euroscore) was used to stratify the risk of death at 30 days.[22] The patients were stratified as high risk in the presence of a Euroscore $\geq$6.

Unstable angina was defined according to the presence of: (i) rest angina (usually $>$20 min); (ii) new onset ($<$2 months) severe exertion angina of at least Canadian Cardiovascular Society Classification (CCSC) class III in severity; (iii) recent ($<$2 months) acceleration of angina as reflected by an increase of at least one CCSC class to at least CCSC class III.

Event adjudication

All the events in patients included in this registry were first evaluated by at least two co-authors from the participating centres and then by two co-authors of the coordinating centre on the basis of detailed reports from each of the participating centres.

Statistical analysis

Continuous data were reported as mean $\pm$ standard deviation (SD) or median [interquartile range (IQR)] as appropriate. In general, differences in proportions were tested with χ^2 test or Fisher's exact test, while differences in continuous variables with Student's *t*-test or Wilcoxon rank sum test.

At univariate logistic regression analysis the following covariates were assessed: age, gender, diabetes, left ventricular ejection fraction (LVEF), unstable angina, Euroscore, DAT, duration of DAT ($<$6 months, 6–12 months, $>$12 months), distal LMCA, intravascular ultrasound (IVUS) guidance, baseline reference vessel diameter, baseline minimal luminal diameter, stent type, both branch stenting, crush technique, stent length, final kissing balloon inflation, and maximum inflation pressures. Among continuous variable, no pre-specified cut-off was employed. Because of the small number of events observed in a dataset of 731 patients, exact odds ratios (OR) with associated 95% confidence intervals (CI) and two-tailed *P*-values were computed using permutation resampling.

In order to obtain parameter estimates adjusted for potential collinearity among covariates, exact conditional analyses were carried out re-running the exact logistic regressions with one covariate at a time as a fixed factor and treating the remaining as nuisance parameters.[23] The Statistical Analysis System program version 9.1 (SAS Institute, Cary, NC, USA) was used for data analysis.

All authors have read and agreed to the manuscript as written.

Results

Baseline clinical, lesion, and procedural characteristics are summarized, respectively, in *Tables 1* and *2*. A total of 731 patients with unprotected LMCA were electively treated in our centres with DES implantation. One hundred and seventy six (24.0%) patients were diabetic and 333 (45.5%) had unstable angina. Mean age was 63.1 $\pm$ 11.8 years and LVEF 54.8 $\pm$ 10.9%. Median and IQR of Euroscore was 3.0 (2.0–6.0); a Euroscore $\geq$6 was present in

Table 1 Clinical characteristics of the study population

	***n* = 731 patients**
Age (years)	63.1 ± 11.8
Female gender, *n* (%)	189 (25.8)
Hypertension, *n* (%)	427 (58.4)
Hypercholesterolaemia, *n* (%)	368 (50.3)
Smoking, *n* (%)	247 (33.8)
Diabetes mellitus, *n* (%)	176 (24.0)
Unstable angina, *n* (%)	333 (45.5)
LVEF (%)	54.8 ± 10.9
Chronic renal failure, *n* (%)	40 (5.5)
Euroscore, median (IQR)	3.0 (2.0–6.0)
Euroscore ≥6, *n* (%)	262 (35.8)

LVEF, left ventricular ejection fraction (%).
Continuous data were reported as mean ± SD or median and interquartile range (IQR) as appropriate.

Table 2 Lesion and procedural characteristics

	***n* = 731 patients**
Distal, *n* (%)	559 (76.5)
Number of vessels treated	2.2 ± 0.8
Number of lesions treated	2.3 ± 1.5
IABP, *n* (%)	96 (13.1)
GP IIb/IIIa inhibitors usage, *n* (%)	102 (13.9)
IVUS guidance, *n* (%)	337 (46.1)
DCA or rotablator, *n* (%)	24 (3.3)
Cypher stent implantation, *n* (%)	536 (73.3)
Taxus stent implantation, *n* (%)	196 (26.8)
Both branches stented/distal, *n* (%)	276 (49.4)
Stent length (mm)	25.0 ± 15.1
Maximum balloon diameter (mm)	3.7 ± 0.6
Maximum pressure inflation (atm)	17.5 ± 3.7

IABP, intra-aortic balloon pump implantation; GP IIb/IIIa inhibitors usage, use of glycoprotein IIb/IIIa inhibitors during the procedure; IVUS, intravascular ultrasound; DCA, directional coronary atherectomy.
Data are presented as percentages and mean ± SD.

36% of the patients. The number of treated vessels was 2.2 ± 0.8 and the number of lesions 2.3 ± 1.5; 27% of the patients also had right coronary artery disease. An intra-aortic balloon pump was used in 96 (13.1%) patients. In 337 (46.1%) patients IVUS guidance was performed. Reference vessel diameter of the LMCA was 3.7 ± 0.6 mm. At least one SES was implanted in 536 (73.3%) and PES in 196 (26.8%) patients; in one patient both PES and SES were used. In 559 (76.5%) patients the stenosis was located at the distal segment of the LMCA. When the distal left main was treated, the stenting strategy adopted was provisional (cross-over) approach in 283 (50.6%) patients, 'crush' in 120 (21.5%), 'V' stenting in 80 (14.3%), 'modified T' in 52 (9.3%) and 'culotte' in 24 (4.3%). Final kissing balloon inflation was performed in 64% of the cases.

The median duration of DAT was 8.8 months (IQR, 6.0–20.7).

Stent thrombosis

Definite stent thrombosis

Four (0.54%) patients had a definite ST. Three patients had an early (two acute and one subacute) and only one a late definite ST.

Early definite stent thrombosis

Among the three patients with early definite ST: one had an intra-procedural ST successfully treated with intravenous administration of abciximab, intracoronary administration of recombinant tissue plasminogen activator (r-TPA) and additional stent implantation (the patient was found to be a poor responder to clopidogrel); the second occurred some hours after the PCI and was successfully treated with emergency CABG; and the last occurred 12 days after the index procedure. All the three patients had the thrombotic event while on DAT and all of them are alive at the time of this report.

Late and very late definite stent thrombosis

Only one patient had a definite late ST at 3.9 months while on DAT. The patient had an acute anterior MI and angiographically proven ST in the proximal left anterior descending artery successfully treated with repeat PCI. This patient died of lung cancer 10 months after the thrombotic event. No cases of very late definite ST were recorded.

Probable stent thrombosis

Probable ST occurred in three patients. In all the three, the event occurred early and was adjudicated because of the occurrence of sudden death within 30 days from the procedure, in the absence of an autopsy or control angiography.

Therefore, a total of 7/731 (0.95%) patients had a definite or probable ST. Characteristics of patients with definite or probable ST are illustrated in *Table 3*; baseline, lesion, procedural characteristics of patients with definite or probable ST vs. patients without definite or probable ST are illustrated in *Table 4*.

At univariate exact logistic (unconditional) analysis, age (OR = 1.07, CI 95% 1.00–1.16; $P = 0.03$), LVEF (OR = 0.94, CI 95% 0.90–0.98; $P = 0.007$) and Euroscore (OR = 1.19, CI 95% 1.07–1.34; $P = 0.003$) were correlated to definite or probable ST. At conditional univariate analysis, only LVEF (OR = 0.94, CI 95% 0.89–0.99; $P = 0.03$) and Euroscore (OR = 1.22, CI 95% 1.06–1.41; $P = 0.008$) were associated with definite or probable ST (*Table 5* and *Figure 1A*).

Possible stent thrombosis

Possible stent thrombosis was adjudicated in 20 patients in whom the cause of death was unexplained (no autopsy or control angiography was performed).

Late possible ST occurred in eight and very late possible ST in 12 of these patients. Eight of these patients were on DAT at the time of the event and 12 had suspended DAT (10 because of the hospital protocol, one because of gastric symptoms and

Table 3 Characteristics of the patients with definite and probable stent thrombosis

Patient	Euro score	Age (years)	LVEF (%)	Unstable angina	Lesion location	Stent type	Stenting technique	Time of the event (days)	DAT at the time of the event
Definite ST									
1	1	55	55	No	Distal	Taxus	Crush	0	Yes
2	9	72	30	Yes	Distal	Cypher	Cross-over	0	Yes
3	10	71	45	Yes	Distal	Taxus	V	12	Yes
4	11	71	35	No	Distal	Taxus	Crush	116	Yes
Probable ST									
1	12	76	40	Yes	Distal	Cypher	Crush	12	Yes
2	15	78	39	Yes	Ostium	Taxus	Cross-over	1	Yes
3	10	85	30	Yes	Distal	Cypher	Cross-over	3	Yes

LVEF, left ventricular ejection fraction; DAT, dual antiplatelet therapy; ST, stent thrombosis.

Table 4 Baseline, lesion, procedural characteristics of patients with definite or probable stent thrombosis vs. patients without definite or probable stent thrombosis

	Patients with definite or probable stent thrombosis ($n = 7$)	Patients without definite or probable stent thrombosis ($n = 724$)
Age (years)	72.5 ± 9.2	63.1 ± 11.8
LVEF (%)	39.1 ± 8.8	54.9 ± 10.8
Male gender	5 (71.5%)	537 (74.1%)
Unstable angina	5 (71.5%)	328 (45.3%)
Diabetes	2 (28.5%)	174 (24.1%)
Euroscore	9.6 ± 4.6	4.0 ± 3.0
Distal location	6 (85.7%)	554 (76.5%)
Both branch stenting[a]	4 (66.6%)	272 (49.1%)
Stent length (mm)	25.8 ± 14.0	25.0 ± 15.8
Reference vessel (mm)	3.32 ± 1.0	3.4 ± 0.5
IVUS done	3 (42.1%)	334 (46.8%)
DAT	7 (100%)	117 (16.1%)
Myocardial infarction[b]	4 (57.1%)	9 (1.24%)
Target lesion revascularization	4 (57.1%)	74 (10.2%)
Cardiac death	3 (42.8%)	28 (3.86%)

DAT, dual antiplatelet therapy at the time of the thrombotic event [in patients with definite or probable stent thrombosis (ST)] or at the time of last clinical follow-up (in patients without definite or probable ST).
[a]Both branch stenting: the percentages are calculated considering only patients with distal lesion location.
[b]In myocardial infarctions are excluded peri-procedural myocardial infarctions unless occurred following ST.

one because of abdominal surgery). Clinical characteristics were unfavourable in most of these patients: 8/20 (40%) were >75 years old, 13/20 (65%) patient had a LVEF <40% and a Euroscore ≥6 (*Table 6*).

In-hospital and long-term major adverse cardiac events

In-hospital and long-term clinical outcomes are illustrated in *Table 7*.

During hospitalization, five (0.68%) patients died; all of them were >75 years and had a Euroscore >6. None of these patients had an angiographically or pathologically proven ST. Sudden death occurred in 2/5, and probable ST cannot be excluded. Non-Q-wave MI occurred in 69 (9.4%) of the patients.

At 29.5 ± 13.7 months, cumulatively 45 (6.2%) patients died; 31 (4.2%) of cardiac death. During the follow-up period, 11 patients experienced a MI and nine of them were not in the target vessel (two were due to angiographically proven ST in a stent not in the target vessel). Seventy six (10.5%) patients underwent TLR and 95 (13.0%) a TVR (83 re-PCIs and 12 CABG). Angiographic follow-up was performed in 548 patients (75%); restenosis occurred in 77 (14.1%) of these patients. Notably, the range and extent of clinical follow-up did not differ among the different centres.

At univariate exact logistic (unconditional) analysis, age (OR = 1.06, CI 95% 1.03–1.09; $P = 0.0001$), LVEF (OR = 0.94, CI 95% 0.92–0.96; $P < 0.0001$), Euroscore (OR = 1.21, CI 95% 1.13–1.30; $P < 0.0001$), unstable angina (OR = 3.73, CI 95% 1.54–11.6; $P = 0.002$) and IVUS guidance (OR = 0.93, CI 95% 0.16-0.93; $P = 0.03$) were correlated to cardiac death. At conditional analysis, only unstable angina (OR = 3.25, CI 95% 1.33–9.05; $P = 0.007$), LVEF (OR = 0.79, CI 95% 0.87–0.97; $P = < 0.0001$) and Euroscore (OR = 1.18, CI 95% 1.04–1.23; $P = 0.003$) were correlated to cardiac death (*Figure 1B*).

Discussion

The main findings of this study are: (i) the incidence of definite ST is relatively low (0.5%): 75% of the cases occurred within 30 days and none after 1 year; all the patients were successfully treated and survived from the event; (ii) the cumulative occurrence of definite and probable ST is 0.95% and at conditional analysis exact logistic analysis was correlated with the Euroscore and LVEF, but not with

Table 5 Unconditional and conditional analysis of the predictors of definite and probable stent thrombosis

	Unconditional analysis			Conditional analysis		
	OR	95% exact CI	*P*	OR	95% exact CI	*P*
DES type	0.5174	0.1950–1.2693	0.1728	0.5531	0.2081–1.3732	0.2420
Gender	0.8708	0.1409–9.2236	1.0000	0.6773	0.1044–7.4699	0.9417
Age (years)	1.0783	1.0052–1.1620	0.0343	1.0649	0.9860–1.1595	0.1154
Diabetes	1.2503	0.1182–7.7574	1.0000	0.8982	0.0814–5.8378	1.0000
Unstable angina	3.0184	0.4903–31.9183	0.3171	2.7247	0.4283–29.6316	0.4045
LVEF (%)	0.9436	0.9027–0.9829	0.0072	0.9417	0.8894–0.9934	0.0280
Reference vessel (mm)	1.1958	0.5949–2.9384	0.7899	1.2420	0.5879–3.4065	0.7482
MLD (mm)	0.9489	0.2923–3.0104	0.9327	1.2245	0.3775–3.9770	0.7357
Maximum pressure (atm)	1.1592	0.9807–1.3545	0.0798	1.1639	0.9775–1.3656	0.0862
Stent length (mm)	1.0055	0.9552–1.0474	0.7544	1.0152	0.9573–1.0656	0.5395
Distal location	1.8425	0.2208–85.4474	0.9695	0.7260	0.0460–55.1541	1.0000
Kissing balloon inflation	1.9497	0–4.9615	1.0000	2.2424	0–6.0158	1.0000
Type of stenting technique	1.9465	0.3910–9.6902	0.6171	1.5316	0.2979–7.8749	1.0000
Both branch stenting	3.1327	0.4454–34.8600	0.3339	2.2919	0.3134–26.3552	0.5863
Euroscore	1.1996	1.0758–1.3422	0.0026	1.2193	1.0577–1.4124	0.0076
IVUS	0.8758	0.1273–5.2108	1.0000	1.4492	0.2006–9.1331	0.9194
DAT discontinuation	0.1464	0.0219–0.8813	0.0347	0.1524	0.0196–0.9889	0.0485
DAT duration, 12 months	0.6076	0.1193–2.2452	0.8555	0.4343	0.0836–1.6713	0.3823
DAT duration, 6 months	1.2958	0.2753–4.4804	1.0000	1.3891	0.2899–4.9297	1.0000

DES, drug-eluting stent; MLD, minimal lumen diameter, IVUS, intravascular ultrasound; DAT, dual antiplatelet therapy.

the duration of DAT (at the time of the thrombotic event all patients were on DAT); (iii) there was a 4.2% cumulative cardiac mortality and 6.2% cumulative total mortality rate at 29.5 $\pm$ 13.7 months follow-up.

According to current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines the presence of a stenosis in the LMCA (if a patient is not eligible for CABG) is considered a Class IIb or IIa indication for PCI, respectively.[24,25] According to these guidelines, when a patient is eligible for CABG, PCI has a class III indication, irrespective of the lesion location. Some retrospective studies evaluating surgical treatment for this disease reported an in-hospital mortality varying from 1.7 to 7.0% and a 1-year mortality of 6–14%.[26–30] Recently, encouraging results have been reported with elective DES implantation in LMCA with a 1-year mortality of 0–5%.[11,13,17,31] The need for TLR in these registries varied from 0 to 14%.[11,13,17,19,31] Indeed, the presence of ostial and mid-shaft lesions in the LMCA was associated with a more favourable outcome and an extremely low restenosis rate.[12,32]

Recently some concerns have been raised about the long-term safety of DES implantation.[1–10] A multicentre registry analysing >3000 patients electively treated with DES (in 67% for an off-label indication) reported a ST incidence, at 18 months, of 1.9% (which included definite and possible ST).[1] Half of the events occurred within 30 days. Similarly, another registry reported that most (60%) ST occurs within 30 days.[3] In this study, which included patients with acute coronary syndromes, a 2.9% cumulative incidence of definite ST was reported in 8146 patients at 3 years. The presence of an acute coronary syndrome was an independent predictor of ST.

No study has thus far addressed the issue of ST following DES implantation in the subset of unprotected LMCA lesions. Our study represents the largest ($n = 731$) series of patients with unprotected LMCA lesions electively treated with DES. According to clinical and lesion characteristics, our study population was at moderately low surgical risk (Euroscore ≥ 6 in almost 36% of the patients), but at intermediate risk for angioplasty (distal left main in 76% of the patients). The occurrence of in-hospital MACE, which included non-Q-wave MI (defined as an elevation of serum CK MB isoenzyme that was three times ULN), was in accordance with previous reports. Only four (0.5%) patients had a definite ST and all of them were on DAT at the time of the event. This finding may point out the importance of evaluating individual responsiveness to antiplatelet therapy.[33] Interestingly one patient, who developed intra-procedural ST and in whom we measured platelet inhibition, was found to be a non-responder to clopidogrel. In three (75%) patients, definite ST occurred within 30 days and only in one at 3.9 months. All the four patients who had definite ST survived from the event after having been successfully treated: three with repeat PCI and one with CABG. Three of the patients are still alive at the time of this report and one died because of lung cancer.

Even if we consider definite and probable ST together (which included three deaths within 30 days in the absence of angiographic or pathological confirmation of ST) the low incidence of 0.95% is still quite reassuring. Again, all patients had the event while on

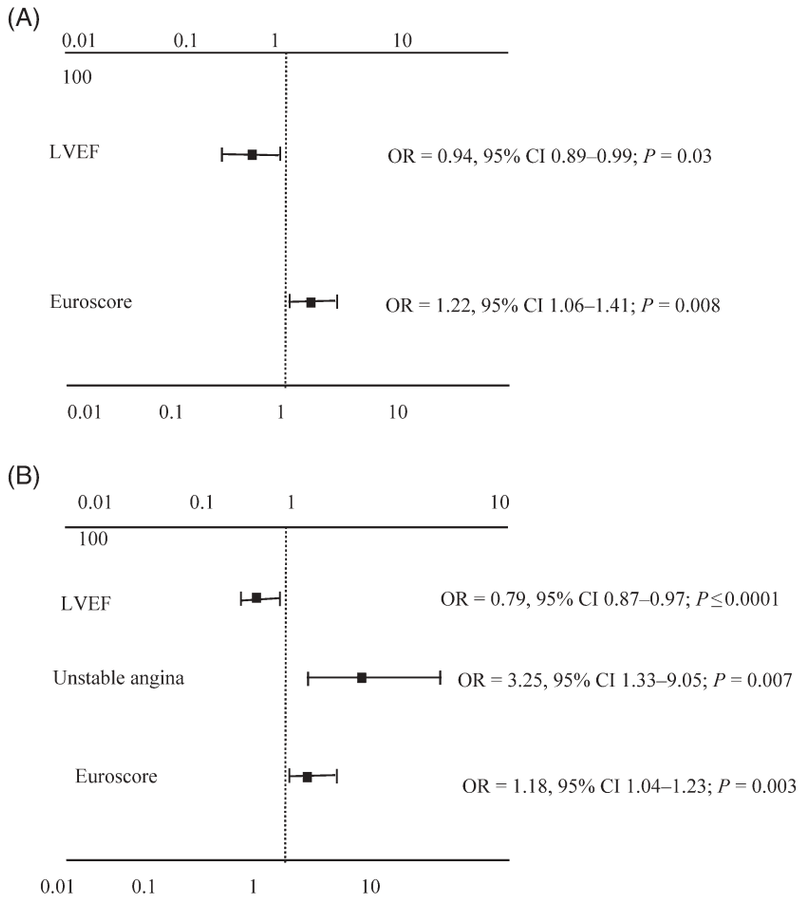

Figure 1 Predictors at conditional analysis of definite or probable stent thrombosis (*A*) and cardiac death (*B*).

DAT. At conditional exact logistic analysis, the occurrence of definite and probable ST was correlated with Euroscore and LVEF. This finding is consistent with predictors identified in general PCI populations.[1,3] Therefore, no unique ST predictor among LMCA lesions was identified in our analysis.

Regarding the 20 (2.7%) patients with possible ST (unexplained deaths after 30 days) we need to take into account that many of these patients had high risk characteristics for cardiac death unrelated to ST (*Table 6*); at conditional exact logistic analysis, cardiac death was correlated to Euroscore and LVEF. Moreover, at least nine of the patients with probable ST would meet the inclusion criteria for MADIT II (multicentre automatic defibrillator implantation trial), which reported an expected overall mortality of 19.8% and a sudden cardiac death rate of 9.8% at 2 years in the control group.[34,35] Eight patients were still on DAT at the time of death and 12 were not (10 suspended DAT according to the hospital protocol and only two prematurely).

Furthermore, the cumulative occurrence of death (cardiac and non-cardiac) at 29.5 $\pm$ 13.7 months follow-up was 4.2 and 6.2%, respectively. These rates are encouraging if compared with mortality rates following CABG at a similar clinical follow-up time period.

The low rates of cardiac death in our study could also be justified by the exclusion of patients presenting with a MI. In addition, we cannot exclude that the low rate of cardiac events reported in our study were due to the fact that LM stenting was performed in highly experienced centres.

Additionally, only 11 (1.5%) patients experienced a MI during follow-up, nine of which were not in the target vessel. Interestingly, two were due to angiographically proven ST not in the target vessel.

In our registry the long-term efficacy of DES in this subset of lesions is confirmed by a TLR and TVR rate (83 re-PCIs and 12 CABG) of 10 and 13%, respectively, and a restenosis rate of 14% even with 76% of lesions involving the distal LMCA. So far, no randomized data comparing PCI with DES implantation vs. CABG are available.[11,15,16] The 'Synergy between Percutaneous Intervention with TAXUS® and Cardiac Surgery' (SYNTAX) trial was recently conducted and included 710 patients with left main disease randomized to receive either a PES or CABG. Interestingly, the study was not powered to detect any difference between CABG and PCI with DES in the subset of unprotected LMCA lesions but only in triple-vessel disease.

Table 6 Characteristics of the patients with possible stent thrombosis

Patient	Euro score	Age (years)	LVEF (%)	Unstable angina	Lesion location	Stent type	Stenting technique	Time of the event (days)	DAT at the time of the event
1	8	72	26	No	Distal	Cypher	Cross-over	1162	No
2	5	65	55	No	Distal	Cypher	V	175	No
3	0	48	57	Yes	Distal	Cypher	Cross-over	790	No
4	3	53	61	Yes	Distal	Cypher	Crush	546	No
5	13	82	28	Yes	Distal	Cypher	Crush	154	No
6	7	66	35	Yes	Distal	Cypher	Cross-over	1390	Yes
7	11	71	20	Yes	Distal	Taxus	Crush	443	Yes
8	4	63	65	No	Distal	Taxus	Crush	955	No
9	5	54	35	No	Distal	Cypher	V	986	Yes
10	4	72	30	No	Distal	Cypher	Cross-over	623	Yes
11	9	77	30	Yes	Distal	Taxus	Cross-over	270	No
12	11	80	30	Yes	Distal	Taxus	Culotte	156	No
13	6	56	40	Yes	Distal	Taxus	Cross	699	No
14	8	75	45	Yes	Ostium	Cypher	N/A	1149	No
15	10	72	40	Yes	Distal	Taxus	Culotte	352	No
16	9	80	30	Yes	Distal	Taxus	Cross-over	243	No
17	4	78	60	Yes	Distal	Taxus	Cross-over	482	Yes
18	11	82	30	No	Distal	Taxus	Cross-over	180	Yes
19	10	51	25	Yes	Distal	Cypher	Cross-over	757	Yes
20	25	81	50	Yes	Ostium	Taxus	N/A	99	Yes

LVEF, left ventricular ejection fraction; DAT, dual antiplatelet therapy; N/A, not applicable.

Table 7 Major adverse cardiac event at hospitalization and at long-term clinical follow-up

	In-hospital, *n* = 731	Follow-up, *n* = 726
Cardiac death, *n* (%)	5 (0.7)	26 (3.6)
Total death, *n* (%)	5 (0.7)	40 (5.5)
MI, *n* (%)	69 (9.4)	11 (1.5%)
TLR, *n* (%)	2 (0.3)	76 (10.5)
TVR, *n* (%)	2 (0.3)	95 (13.0)
MACE, *n* (%)	73 (9.9%)	138 (19.0)

MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiac events.
Data are presented as percentages.

Study limitations

This is a retrospective multicentre registry. No '*a priori*' sample size has been calculated. Another limitation is the length of clinical follow-up. Moreover we cannot exclude that some of the unexplained deaths that occurred at follow-up could have been a ST because of the absence of an angiographic and/or pathological examination. Different durations of DAT were prescribed among the centres due to different institutional practices.

Conclusions

In this multicentre registry, the elective use of DES in unprotected LMCA stenosis appears to be safe and effective at 29.5 $\pm$ 13.7 clinical follow-up. Definite and probable ST occurred in 0.9% of the patients. Further studies with longer durations of follow-up as well as uniform and prespecified durations of DAT are needed in order to better clarify the issue of safety following DES implantation in unprotected LMCA lesions.

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