Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Joost Daemen, Peter Wenaweser, Keiichi Tsuchida, Linda Abrecht, Sophia Vaina, Cyrill Morger, Neville Kukreja, Peter Jüni, Georgios Sianos, Gerrit Hellige, Ron T van Domburg, Otto M Hess, Eric Boersma, Bernhard Meier, Stephan Windecker, Patrick W Serruys

Summary

Background **Stent thrombosis is a safety concern associated with use of drug-eluting stents. Little is known about occurrence of stent thrombosis more than 1 year after implantation of such stents.**

Methods **Between April, 2002, and Dec, 2005, 8146 patients underwent percutaneous coronary intervention with sirolimus-eluting stents (SES; n=3823) or paclitaxel-eluting stents (PES; n=4323) at two academic hospitals. We assessed data from this group to ascertain the incidence, time course, and correlates of stent thrombosis, and the differences between early (0–30 days) and late (>30 days) stent thrombosis and between SES and PES.**

Findings **Angiographically documented stent thrombosis occurred in 152 patients (incidence density 1·3 per 100 person-years; cumulative incidence at 3 years 2·9%). Early stent thrombosis was noted in 91 (60%) patients, and late stent thrombosis in 61 (40%) patients. Late stent thrombosis occurred steadily at a constant rate of 0·6% per year up to 3 years after stent implantation. Incidence of early stent thrombosis was similar for SES (1·1%) and PES (1·3%), but late stent thrombosis was more frequent with PES (1·8%) than with SES (1·4%; p=0·031). At the time of stent thrombosis, dual antiplatelet therapy was being taken by 87% (early) and 23% (late) of patients (p<0·0001). Independent predictors of overall stent thrombosis were acute coronary syndrome at presentation (hazard ratio 2·28, 95% CI 1·29–4·03) and diabetes (2·03, 1·07–3·83).**

Interpretation **Late stent thrombosis was encountered steadily with no evidence of diminution up to 3 years of follow-up. Early and late stent thrombosis were observed with SES and with PES. Acute coronary syndrome at presentation and diabetes were independent predictors of stent thrombosis.**

Lancet 2007; 369: 667–78

See **Comment** page 619

Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Dr Molewaterplein 40,3015 GD Rotterdam, Netherlands (J Daemen MD, K Tsuchida MD, S Vaina MD, N Kukreja MBBS, G Sianos MD, R T van Domburg PhD, E Boersma PhD, Prof P W Serruys MD); **Department of Cardiology, University Hospital Bern, Bern, Switzerland** (P Wenaweser MD, L Abrecht MD, C Morger MD, G Hellige MD, Prof O M Hess MD, Prof B Meier MD, Prof S Windecker MD); **and Division of Clinical Epidemiology and Biostatistics, Department of Social and Preventive Medicine, University of Bern, Bern, Switzerland** (P Jüni MD)

Correspondence to:
Prof Patrick W Serruys
p.w.j.c.serruys@erasmusmc.nl

Introduction

Drug-eluting stents significantly reduce rates of restenosis and target lesion revascularisation compared with bare metal stent. Since the publication of pivotal randomised trials on the two DES approved by the US Food and Drug Administration (polymer-based sirolimus-eluting stents [SES] and polymer-based paclitaxel-eluting stents [PES]),[1–4] these devices have been widely used in the percutaneous treatment of coronary artery disease worldwide.[5–8] However, several pre-clinical and clinical safety concerns[9–15] related to the use of drug-eluting stents have been expressed since then. One of the most important issues raised is stent thrombosis, a catastrophic, albeit infrequent, complication that results in abrupt coronary artery closure, which can lead to myocardial infarction or sudden cardiac death. This problem is not restricted to drug-eluting stents, and its incidence does not seem to exceed that seen with bare metal stents up to 1 year of follow-up.[16–22] However, case reports and observational studies have noted that some patients develop stent thrombosis unusually late after implantation of drug-eluting stents.[23–25]

To date, no large-scale study has focused on late stent thrombosis later than 1 year after drug-eluting stent implantation. Although variables such as acute coronary syndromes, bifurcation stenting, diabetes, discontinuation of antiplatelet therapy, renal failure, and stent length seem to be consistently associated with overall stent thrombosis,[19,26–28] predictors specific for late stent thrombosis have not yet been identified. We therefore assessed all angiographically documented stent thrombosis following unrestricted use of SES and PES in routine clinical practice at two academic referral hospitals between April, 2002, and December, 2005. The purposes of this investigation were to: estimate the incidence and time course of stent thrombosis with drug-eluting stents in routine clinical practice; identify predictors of stent thrombosis; identify differences between early and late stent thrombosis; and assess differences between SES and PES.

Methods

Study group and design

Between April 16, 2002, and Dec 31, 2005, a total of 8146 consecutive patients underwent percutaneous coronary intervention with SES or PES at two academic referral hospitals in the Netherlands and Switzerland. 3823 patients were treated with SES (Cypher, Cordis Corporation, Johnson and Johnson, Warren, NJ, USA) and 4323 patients with PES (TAXUS, Express2, or Liberté, Boston Scientific, Natick, MA, USA). In the Dutch

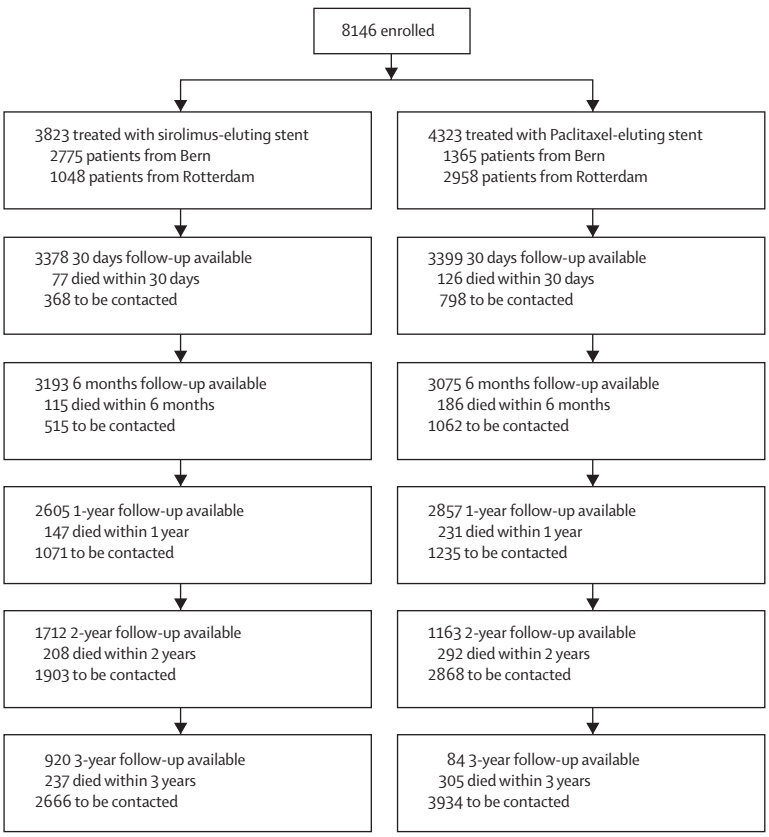

Figure 1: **Study profile**

institution, SES have been used as a default strategy for PCI as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry[7] since April, 2002. From the first quarter of 2003, PES became commercially available and replaced SES as default device for such procedures, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry.[5] In the Swiss institution, SES have been used since April, 2002, and PES since March, 2003. Between April, 2003, and May, 2004, a randomised trial was done to compare the devices.[6] Between June, 2004, and March, 2005, the use of SES and PES was alternated on a daily basis. Since April, 2005, the use of PES has been abandoned and SES have been used as the default device. Patients treated with both types of stents (SES and PES) in one lesion, and lesions previously treated with brachytherapy, were excluded from the study population. The study was designed during a conference between the Bern and Rotterdam investigators. Baseline clinical and angiographic variables, procedural characteristics, and endpoints of interest were identified, and a template with all variables of interest for this study was supplied to the two study sites. Data from both sites were then entered into a database, held at the Thoraxcenter, Rotterdam, The Netherlands, generating all analyses presented in this manuscript.

This study was approved by the local ethics committee at both hospitals and was done in accord with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Procedures

All interventions were done according to current practice guidelines for percutaneous coronary intervention.[29] The operator was responsible for the decision to choose a specific treatment strategy. Patients were prescribed aspirin plus clopidogrel 75 mg per day (after a loading dose of 300 mg or 600 mg) before or during baseline coronary

	Overall (n=8146)	SES (n=3823)	PES (n=4323)	p
Age (years)	62·6 (11·6)	62·5 (11·5)	62·7 (11·6)	0·31
Male	6065/8146 (75%)	2859/3823 (75%)	3206/4323 (74%)	0·53
Hypertension	3745/8144 (46%)	1965/3821 (51%)	1780/4323 (41%)	<0·0001
Family history	2279/8144 (28%)	1112/3821 (29%)	1167/4323 (27%)	0·04
Current smoking	2993/8144 (37%)	1721/3821 (45%)	1272/4323 (29%)	<0·0001
Dyslipidaemia	4079/8144 (50%)	2087/3821 (55%)	1992/4323 (46%)	<0·0001
Diabetes	1315/8144 (16%)	697/3821 (18%)	618/4323 (14%)	<0·0001
Renal failure	134/3309 (4%)	97/2253 (4%)	37/1056 (4%)	0·30
Left ventricular ejection fraction (%)	55 (12)	54 (12)	55 (11)	0·01
Acute coronary syndrome at presentation	2853/4859 (59%)	795/1481 (54%)	2058/3378 (6 1%)	<0·0001
Bifurcation treatment	781/4889 (16%)	267/1488 (18%)	514/3401 (15%)	0·01
Number of stents per patient	1·96 (1·23)	1·87 (1·13)	2·03 (1·31)	<0·0001
Total stent length per patient (mm)	35·9 (25·3)	33·6 (22·6)	37·9 (27·4)	<0·0001
Average stent diameter per patient (mm)	2·93 (1·4)	2·90 (2·1)	2·95 (0·5)	0·11
Duration of clopidogrel prescription (months)*	5·94 (3·1)	4·72 (4·0)	6·36 (2·6)	<0·0001

Data are mean (SD) or n/total with data available (%). *Based on Rotterdam cohort.

Table 1: **Clinical and procedural characteristics of study population stratified by stent type**

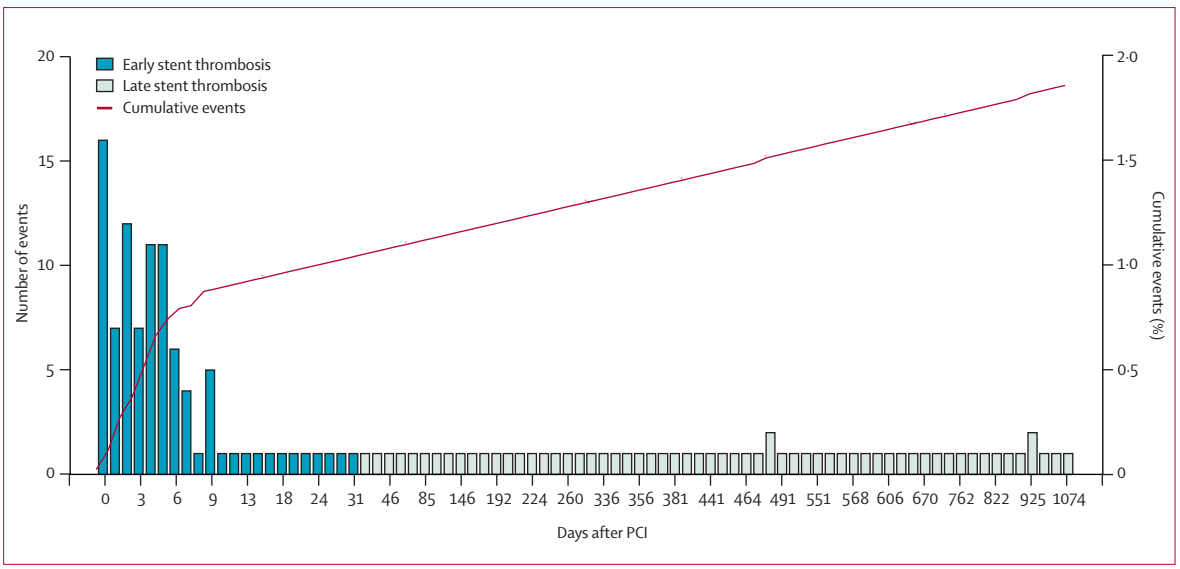

Figure 2: **Occurrence and frequency of stent thrombosis over time**

interventions. After the procedure, all patients were advised to maintain lifelong use of aspirin. In the Dutch institution, patients treated with PES were prescribed at least 6 months of clopidogrel (75 mg per day), on the basis of existing data from a randomised controlled trial.[30] For patients treated with SES, clopidogrel was prescribed for at least 3 months, unless one of the following was present, in which case clopidogrel was maintained for at least 6 months: multiple SES implantation (≥3 stents), total stent length 36 mm or longer, chronic total occlusion, and bifurcations.[5] In the Swiss institution, 12 months of clopidogrel was prescribed irrespective of the stent type used.[6] In a few patients who were on oral anticoagulation therapy, doctors recommended a shorter duration of clopidogrel (eg, 3-month triple therapy with aspirin, clopidogrel, and warfarin).

Patients were contacted according to follow-up schedules specific for each institution for the occurrence of major adverse cardiac events, including all-cause death, myocardial infarction, and repeat revascularisation. Survival data for all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on re-admission and major adverse cardiac events. For patients who had an adverse event at another centre, medical records or discharge summaries from other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. Data were based on a registry at two institutions entered into a database. There was no independent or external monitoring of data entry. However, data were carefully verified and adjudicated by clinicians. Mean follow-up was 1·73 years. Figure 1 shows flow of patients during various follow-up times.

Myocardial infarction was defined as increased creatine kinase by twice the upper limit of normal value and three times the upper limit of normal value of creatine kinase-MB fraction. Repeat revascularisation included target lesion revascularisation (TLR) and non-TLR, irrespective of whether the procedure was clinically or angiographically driven.

Only patients with angiographically proven stent thrombosis were included in the present study. Stent thrombosis was judged to have occurred if thrombolysis

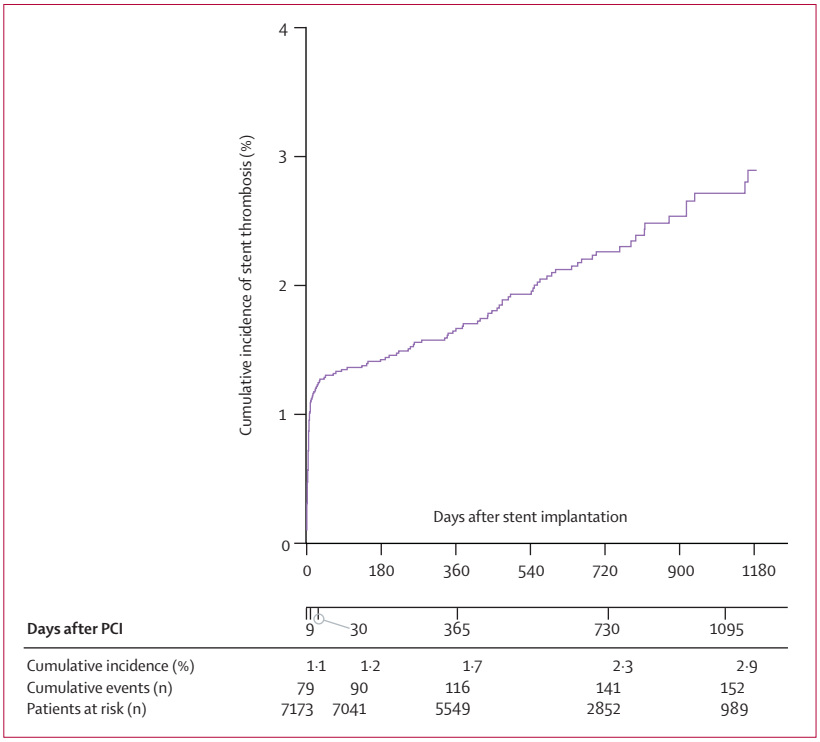

Figure 3: **Kaplan-Meier survival curve showing cumulative incidence of stent thrombosis in patients with SES or PES**

Slope of linear portion of cumulative incidence curve between 30 days and 3 years was 0·6% per year.

in myocardial infarction (TIMI) flow was grade 0 with occlusion originating in the peri-stent region, or grade 1, 2, or 3 in the presence of a thrombus originating in the peri-stent region. Angiographic evidence of thrombus was defined as a discrete, intraluminal filling defect with defined borders and separated from the vessel wall.[31] Additionally, at least one of the following criteria had to be met: acute ischaemic symptoms (typical chest pain with duration >20 min); ischaemic ECG changes (ST-segment elevation in territory of implanted stent, ST-segment depression or T-wave inversion in territory of implanted stent); typical rise and fall in cardiac biomarkers.[32]

All cases of angiographically proven stent thrombosis were reviewed independently by two experienced interventional cardiologists. In case of disagreement, a consensus was established between the two reviewers, or a third interventional cardiologist was consulted.

Stent thrombosis was categorised dependant on the timing of emergence into early (within 30 days) and late (>30 days).

Risk factors and co-morbidities in each patient were determined as classified by the treating physicians. Acute coronary syndrome was defined as the group of clinical symptoms, electrocardiographic changes, and elevation of cardiac biomarkers that is compatible with acute myocardial ischaemia and encompasses an acute myocardial infarction (ST-segment elevation and non-ST segment elevation myocardial infarction) as well as unstable angina.[32] Hypertension was defined as blood pressure of 140 mm Hg or greater systolic or 90 mm Hg or greater diastolic, or current use of antihypertensive treatment. Dyslipidaemia was classified as a concentration of cholesterol in serum of 6·2 mmol/L or greater, or the use of lipid-lowering drugs.

Angiographic success was defined as: achievement of 30% or less residual diameter stenosis within the stented segment by visual assessment; no evidence of residual dissection; no evidence of thrombus; and achievement of final TIMI flow grade 3. For the quantitative angiographic analysis, in-segment analysis was defined as the stented segment plus the adjacent proximal and distal 5-mm peri-stent regions. Premature discontinuation of antiplatelet therapy was characterised as cessation of either aspirin or clopidogrel before the end of the recommended duration of prescription.

	ST (n=152)	No ST (n=7994)	p
Age (years)	60·3 (12·0)	62·5 (11·5)	0·01
Male	115/152 (76%)	5950/7994 (74%)	0·78
Hypertension	63/152 (41%)	3682/7992 (46%)	0·29
Family history	44/152 (29%)	2235/7992 (28%)	0·79
Current smoking	57/152 (38%)	2936/7992 (37%)	0·87
Dyslipidaemia	74/152 (49%)	4005/7992 (50%)	0·74
Diabetes	29/152 (19%)	1286/7992 (16%)	0·32
Renal failure	9/152 (6%)	132/3242 (4%)	1·00
Left ventricular ejection fraction (%)	52 (12)	55 (12)	0·07
Acute coronary syndrome at presentation	67/95 (71%)	2786/4764 (59%)	0·02
Bifurcation treatment	27/96 (28%)	754/4793 (16%)	0·003
Number of stents per patient	2·35 (1·73)	1·95 (1·22)	<0·0001
Total stent length per patient (mm)	42·3 (34·0)	35·8 (25·1)	0·002
Average stent diameter per patient (mm)	2·83 (0·35)	2·93 (1·44)	0·48

Data are mean (SD) or n/total with data available (%). ST=stent thrombosis.

Table 2: **Comparison of clinical and procedural characteristics between patients with and without stent thrombosis**

	Hazard ratio (95% CI)			
	Bern		Rotterdam	
	Univariate	Multivariate	Univariate	Multivariate
Overall stent thrombosis				
Age	0·99 (0·97–1·00)	0·98 (0·96–1·01)	0·98 (0·96–1·00)	0·97 (0·95–1·00)
Male sex	1·06 (0·63–1·79)	1·32 (0·65–2·66)	1·05 (0·62–1·75)	0·90 (0·51–1·58)
Family history	0·74 (0·44–1·25)	0·67 (0·35–1·28)	1·25 (0·77–2·02)	1·23 (0·74–2·15)
Diabetes	1·04 (0·58–1·85)	1·30 (0·67–2·51)	1·43 (0·81–2·53)	2·03 (1·07–3·83)
Hypertension	0·83 (0·54–1·30)	0·78 (0·45–1·34)	0·72 (0·44–1·19)	0·68 (0·38–1·21)
Smoking	1·05 (0·67–1·63)	0·87 (0·50–1·51)	0·89 (0·51–1·55)	0·78 (0·43–1·44)
Dyslipidaemia	0·77 (0·50–1·20)	0·76 (0·44–1·30)	0·93 (0·58–1·47)	1·07 (0·63–1·82)
Left ventricular ejection fraction	0·98 (0·96–0·99)	*	‡	‡
Renal failure†	1·00 (0·24–4·10)	0·96 (0·23–3·99)	‡	‡
Acute coronary syndrome at presentation	‡	‡	1·80 (1·07–3·05)	2·28 (1·29–4·03)
Bifurcation treatment	‡	‡	1·87 (1·04–3·37)	1·47 (0·79 –2·72)
Paclitaxel-eluting stents	1·26 (0·80–1·97)	1·25 (0·73–2·12)	1·47 (0·86–2·51)	1·38 (0·79–2·44)
Number of stents per patient	1·21 (0·97–1·51)	1·11 (0·74–1·67)	1·27 (1·12–1·43)	1·27 (0·98–1·64)
Total stent length per patient	1·01 (1·00–1·02)	1·01 (0·98–1·03)	1·01 (1·01–1·02)	1·00 (0·99–1·01)
Average stent diameter per patient	0·64 (0·26–1·60)	‡	0·70 (0·46–1·07)	0·72 (0·42–1·22)
Absence of clopidogrel	‡	‡	0·59 (0·77–4·48)	0·77 (0·09–6·24)

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Early stent thrombosis				
Age	1·01 (0·98–1·04)	1·00 (0·97–1·04)	0·98 (0·96–1·01)	0·96 (0·94–0·99)
Male sex	1·02 (0·50–2·08)	1·04 (0·44–2·49)	0·82 (0·45–1·52)	0·70 (0·35–1·39)
Family history	0·50 (0·22–1·12)	0·41 (0·14–1·18)	0·94 (0·50–1·78)	0·83 (0·40–1·70)
Diabetes	1·43 (0·70–2·90)	2·03 (0·91–4·52)	1·94 (1·01–3·73)	2·29 (1·07–4·90)
Hypertension	0·51 (0·28–0·94)	0·40 (0·19–0·86)	0·97 (0·54–1·76)	0·80 (0·39–1·63)
Smoking	0·76 (0·41–1·38)	0·85 (0·41–1·78)	0·40 (0·16–1·01)	0·37 (0·14–0·97)
Dyslipidaemia	0·68 (0·37–1·24)	0·82 (0·39–1·68)	1·03 (0·59–1·82)	1·29 (0·66–2·56)
Left ventricular ejection fraction	0·98 (0·95–1·00)	*	‡	‡
Renal failure†	1·64 (0·39–6·82)	1·23 (0·29–5·28)	‡	‡
Acute coronary syndrome at presentation	‡	‡	1·64 (0·86–3·14)	2·29 (1·16–4·52)
Bifurcation treatment	‡	‡	3·17 (1·66–6·05)	2·52 (1·26–5·02)
Paclitaxel-eluting stents	1·11 (0·60–2·05)	1·28 (0·63–2·59)	0·93 (0·49–1·76)	0·86 (0·44–1·71)
Number of stents per patient	1·32 (1·00–1·74)	1·39 (0·85–2·26)	1·34 (1·17–1·55)	1·18 (0·85–1·63)
Total stent length per patient	1·01 (1·00–1·03)	1·00 (0·98–1·03)	1·02 (1·01–1·02)	1·01 (0·99–1·02)
Average stent diameter per patient	0·63 (0·20–1·95)	‡	0·70 (0·45–1·11)	0·66 (0·35–1·24)
Absence of clopidogrel	‡	‡	¶	*
Late stent thrombosis				
Age	0·96 (0·94–0·99)	0·96 (0·92–0·99)	0·97 (0·94–1·01)	0·99 (0·95–1·03)
Male sex	1·11 (0·50–2·43)	1·93 (0·56–6·63)	1·93 (0·66–5·63)	1·52 (0·51–4·56)
Family history	1·06 (0·51–2·15)	1·04 (0·45–2·43)	2·07 (0·95–4·55)	2·40 (1·03–5·58)
Diabetes	0·61 (0·22–1·73)	0·67 (0·20–2·27)	0·69 (0·20–2·30)	1·22 (0·34–4·34)
Hypertension	1·53 (0·77–3·06)	1·75 (0·75–4·09)	0·36 (0·14–0·98)	0·43 (0·15–1·24)
Smoking	1·52 (0·78–2·97)	0·92 (0·40–2·11)	2·13 (0·97–4·70)	1·70 (0·70–4·11)
Dyslipidaemia	0·88 (0·46–1·70)	0·72 (0·32–1·62)	0·80 (0·37–1·76)	0·89 (0·37–2·04)
Left ventricular ejection fraction	0·98 (0·96–1·01)	*	‡	‡
Renal failure†	..	..	‡	‡
Acute coronary syndrome at presentation	‡	‡	2·34 (0·94–5·87)	2·46 (0·87–7·00)
Bifurcation treatment	‡	‡	0·31 (0·04–2·30)	0·22 (0·03–1·72)
Paclitaxel-eluting stents	1·39 (0·72–2·70)	1·21 (0·54–2·75)	2·43 (0·96–6·17)	2·36 (0·92–6·04)
Number of stents per patient	1·07 (0·75–1·54)	0·73 (0·35–1·56)	1·14 (0·90–1·45)	1·57 (1·00–2·46)
Total stent length per patient	1·00 (0·99–1·02)	1·01 (0·98–1·05)	1·00 (0·99–1·01)	0·99 (0·96–1·01)
Average stent diameter per patient	0·63 (0·13–3·00)	‡	0·85 (0·33–2·15)	0·82 (0·33–2·06)
Absence of clopidogrel	‡	‡	0·74 (0·07–7·42)	1·03 (0·08–13·03)

*Not used for multivariate analysis because of colinearity problems. †Defined as creatinine >150 µmol/L. ‡Not used in analysis, <75% of variables available. ¶Could not be estimated.

Table 3: **Univariate and multivariate Cox proportional hazards analysis**

A creatinine value of 150 µmol per L or chronic haemodialysis qualified for the definition of renal impairment.

Statistical analysis

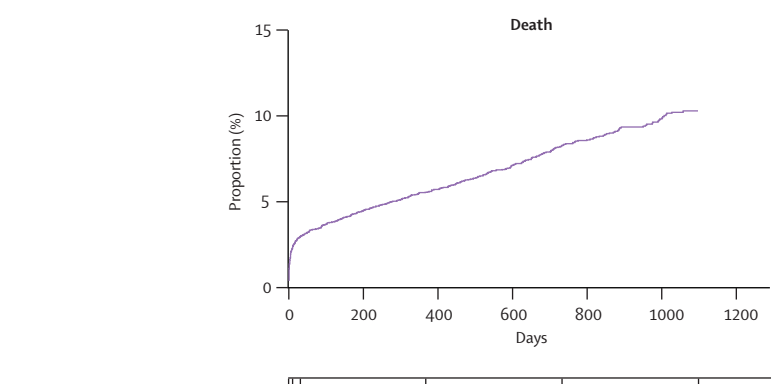
Continuous variables are described as mean and SD or median values with IQR. Dichotomous variables are described as counts and percentages. Continuous variables were compared between SES and PES and between early and late thrombosis with Student's *t* test (for parametric variables) or Mann-Whitney U test (for non-parametric variables) as appropriate in terms of the clinical, angiographic, and procedural demographics.

The incidence of stent thrombosis was calculated as incidence density and as cumulative incidence. Incidence density was defined as the number of patients with stent thrombosis divided by the total number of patient-years, and expressed as a number per 100 patient-years of observation.[33,34] Cumulative incidence was estimated by the Kaplan Meier method and differences were assessed with the log-rank test. A Cox proportional hazards model was used to identify independent predictors of stent thrombosis, with these variables: age, sex, family history of cardiovascular disease, diabetes, hypertension, current smoking, dyslipidaemia, renal impairment, left ventricular ejection fraction, acute coronary syndrome at presentation, stent type (SES or PES), number of stents, total stent length, average stent diameter, bifurcation treatment, and prescribed duration of clopidogrel. Data

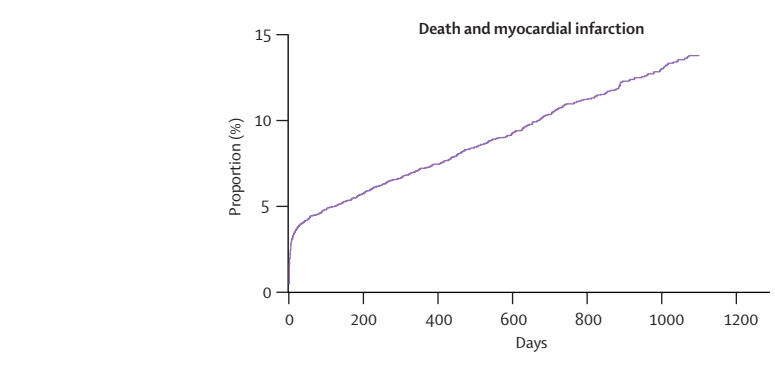
on acute coronary syndrome, bifurcation treatment, and average stent diameter in the Bern cohort, and on left ventricular ejection fraction and renal impairment in the Rotterdam cohort, were available in less than 75% of the patients; therefore, we stratified univariate and multivariate Cox regression analysis by centre. Statistical analyses were done with SPSS 12.0.1 for Windows. All p values were two-sided and values less than 0·05 were judged statistically significant.

Role of the funding source

There was no industry involvement in the study design, data collection, data analysis, or writing of the report. The study was supported by research grants from the two institutions; data from both institutions were entered into a common database held at the Thoraxcenter, Rotterdam, the Netherlands. As principal investigators, PWS and SW had full access to the data and take final responsibility for the data as presented in the manuscript.



Days after PCI	9	30	365	730	1095
Incidence (%)	2·1	2·7	5·3	8·0	10·1
Cumulative events (n)	152	203	378	500	542
Patients at risk (n)	7242	7116	5628	2904	1009



Days after PCI	9	30	365	730	1095
Incidence (%)	3·0	3·8	7·2	10·0	13·7
Cumulative events (n)	224	284	507	669	729
Patients at risk (n)	7173	7039	5522	2824	975

Figure 4: **Kaplan Meier survival curves showing (A) all-cause mortality and (B) all-cause mortality or myocardial infarction in overall population**

	Overall ST (n=152)	Early ST (n=91)	Late ST (n=61)	p
PCI for stent thrombosis	148 (97%)	87 (96%)	61 (100%)	0·51
Additional stenting	59 (39%)	30 (33%)	29 (48%)	0·13
Adjunctive thrombolysis	9 (6%)	5 (6%)	4 (7%)	0·83
Adjunctive thrombectomy	18 (12%)	11 (12%)	7 (12%)	9·85
In-hospital outcome				
Death	11 (7%)	8 (9%)	3 (5%)	0·53
Periprocedural myocardial infarction*	106 (70%)	62 (68%)	44 (72%)	0·99
Reinfarction	2 (1%)	1 (1%)	1 (2%)	0·77
Repeat revascularisation	5 (3%)	3 (3%)	2 (3%)	0·97
Emergency bypass surgery	3 (2%)	2 (2%)	1 (2%)	1·00
Recurrent stent thrombosis	2 (1%)	1 (1%)	1 (2%)	0·77
30-day outcome				
Death	13 (9%)	9 (10%)	4 (7%)	0·40
Reinfarction	3 (2%)	2 (2%)	1 (2%)	1·00
Repeat revascularisation	7 (5%)	4 (4%)	3 (5%)	1·00
Recurrent stent thrombosis	3 (2%)	2 (2%)	1 (2%)	1·00
6-month outcome				
Death	17 (11%)	12 (13%)	5 (8·2%)	0·24
Reinfarction	3 (2%)	2 (2%)	1 (1·6%)	1·00
Repeat revascularisation	10 (7%)	5 (6%)	5 (8·2%)	0·52
Recurrent stent thrombosis	3 (2%)	2 (2%)	1 (1·6%)	1·00
Hierarchical MACE†	117 (76%)	70 (77%)	47 (75·4%)	0·99

PCI=percutaneous coronary intervention. ST=stent thrombosis. MACE=major adverse cardiac events (defined as the composite of death, periprocedural myocardial infarction, reinfarction, and repeat revascularisation). *Myocardial infarction due to stent thrombosis. †Including periprocedural myocardial infarction due to stent thrombosis.

Table 4: **Periprocedural and postprocedural clinical outcomes of patients with stent thrombosis**

Results

Between April, 2002, and December, 2005, 8146 patients underwent percutaneous coronary intervention with SES (3823 patients) or PES (4323 patients) at the two academic hospitals. Table 1 summarises clinical and procedural characteristics of the overall study population. Compared with patients treated with PES, those who received SES were more likely to have hypertension, a family history of coronary heart disease, dyslipidaemia, and diabetes, and were more frequently smokers. Left ventricular ejection fraction was somewhat lower in the SES group than in the PES group. By contrast, patients treated with PES presented more often with an acute coronary syndrome, and received more and longer stents than SES patients.

Angiographically proven stent thrombosis was recorded in 152 of 8146 patients at a median of 9 days (IQR 3–342) after DES implantation during a follow-up period of more than 3 years (mean 1·73 years, SD 0·99). The incidence density of stent thrombosis was 1·3 per 100 person-years. Stent thrombosis occurred early (at 0–30

days) in 91 of 152 (60%) patients, and late (after 30 days) in 61 of 152 (40%) patients. The cumulative incidence of early ST was 1·1% (91 events), whereas late ST occurred at a rate of 0·6 per 100 person-years of observation (61 events). The median time to occurrence of early stent thrombosis was 4 days (IQR 1–6). Of the 61 late ST cases, 36 (59%) patients developed stent thrombosis 1 year or later after stent implantation (median 451 days; IQR 211–665; figure 2). The cumulative incidence of stent thrombosis over time showed an initial steep rise with 50% of cases occurring within 9 days, followed by an almost linear increase in the remaining events up to 3 years. The cumulative incidence of stent thrombosis was 1·2% at 30 days, 1·7% at 1 year, 2·3% at 2 years, and 2·9% at 3 years. The slope of the linear portion of the cumulative incidence curve between 30 days and 3 years was 0·6% per year (figure 3).

Patients with stent thrombosis were younger, presented more often with an acute coronary syndrome, and were treated more frequently for bifurcation lesions, compared with those without stent thrombosis (table 2). The number of stents and total stent length were greater in patients with stent thrombosis than in those without (table 2).

Table 3 summarises the results of Cox proportional hazards analysis. In the Bern group, no independent predictors of overall stent thrombosis emerged. Hypertension was the only independent predictor of early stent thrombosis, and age was the only independent predictor of late stent thrombosis. In the Rotterdam group, acute coronary syndrome at presentation and diabetes were independent predictors of overall stent thrombosis. Age, hypertension, smoking, acute coronary syndrome at presentation, and bifurcation treatment were independently associated with early stent thrombosis. Family history of coronary heart disease was an independent predictor of late stent thrombosis in the Rotterdam group. Absence of clopidogrel treatment did not seem to be associated with an increased risk of total and late stent thrombosis.

In the overall group (n=8146), 3-year cumulative incidences were 10·3% for all-cause mortality, 13·7% for death or myocardial infarction (figure 4), 4·1% for myocardial infarction, 11·7% for target vessel revascularisation, and 22·3% for major adverse cardiac events (ie, death, periprocedural myocardial infarction, reinfarction, and repeat revascularisation). Percutaneous coronary intervention was the initial treatment strategy in almost all patients who developed stent thrombosis (table 4). The majority of patients who presented with stent thrombosis developed myocardial infarction. Notably, recurrent stent thrombosis in two patients and multiple stent thromboses in a different vessel in another patient caused three reinfarctions within 6 months after treatment of stent thrombosis. We noted no differences in clinical outcome between patients with early and late stent thrombosis.

Table 5 shows baseline clinical, angiographic, and procedural characteristics stratified for early or late stent thrombosis. Compared with patients who had late stent thrombosis, patients with early stent thrombosis were slightly younger, more frequently diabetic, less frequently smokers, and had more bifurcation lesions treated, smaller reference vessel diameter, smaller final minimum luminal diameter, and a higher residual diameter stenosis.

Clinical, procedural, and angiographic characteristics of the 152 patients with stent thrombosis are shown in table 6, along with the comparison between SES and PES. More than 70% of stent thrombosis cases occurred in patients who underwent the index percutaneous coronary intervention in the context of acute coronary syndromes. Patients' characteristics, apart from sex and hypertension, were similar for both stent types. The groups were also similar in terms of time course (table 6), 3-year cumulative incidence of total stent thrombosis (SES 2·5%, PES 3·2%, p=0·07; figure 5), and cumulative incidence of early stent thrombosis (SES 1·1%, PES 1·3%, p=0·49). Late stent thrombosis, however, occurred later in the SES group than in the PES group (table 6) and cumulative incidence at 3 years was significantly higher in the PES group (1·9%) than in the SES group (1·4%; p=0.031).

Of patients who had early stent thrombosis, 79 (87%) were on dual antiplatelet therapy, eight (9%) were on a

	Early ST	Late ST	p
Baseline clinical characteristics			
n	91	61	
Age (years)	61·9 (11·7)	58·0 (12·2)	0·05
Male sex	66/91 (73%)	49/61 (80%)	0·34
Clinical presentation			
Stable angina	28/91 (31%)	15/61 (25%)	
Acute myocardial infarction	41/91 (45%)	28/61 (50%)	1·00
Unstable angina	22/91 (24%)	18/61 (30%)	0·57
Cardiogenic shock	8 (9%)	5 (8%)	1·00
Hypertension	35/91 (39%)	28/61 (46%)	0·40
Family history	20/91 (22%)	24/61 (39%)	0·03
Current smoking	25/91 (28%)	32/61 (53%)	0·002
Dyslipidaemia	41/91 (45%)	33/61 (54%)	0·32
Diabetes	25/91 (28%)	5/61 (8%)	0·003
Non-insulin-dependent	18/91 (20%)	4/61 (7%)	0·03
Insulin-dependent	7/91 (7%)	1/61 (2%)	0·15
Renal insufficiency	8/91 (9%)	1/61 (2%)	0·09
Multivessel disease	55/91 (60%)	33/61 (54%)	0·50
Multivessel stenting	31/91 (34%)	17/61 (28%)	0·48
Left ventricular ejection fraction (%)	51 (12)	53 (12)	0·41
Number of stents per patient	2·52 (1·85)	2·08 (1·51)	0·12
Total stent length per patient (mm)	46·4 (37·5)	36·1 (27·2)	0·07
Average stent diameter per patient (mm)	2·82 (0·37)	2·85 (0·32)	0·72
Timing of ST (days)			
Mean (SD)	5·5 (6·5)	459·4 (274·7)	..
Median (IQR)	4·0 (1–6)	442·0 (235–652)	..

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Lesion and procedural characteristics			
n*	98	63	
Pre-procedure			
Treated vessel			
Left main coronary artery	0/98 (0%)	1/63 (2%)	..
Left anterior descending artery	53/98 (54%)	34/63 (54%)	0·989
Left circumflex artery	19/98 (19%)	6/63 (10%)	0·092
Right coronary artery	26/98 (27%)	21/63 (33%)	0·378
Saphenous vein graft	0	1 (2%)	..
ACC/AHA lesion class B2/C	81/89 (91%)	51/63 (81%)	0·089
Bifurcation lesions	34/95 (36%)	8/63 (13%)	0·002
Diameter stenosis (%)	81 (17)	82 (19)	0·740
Lesion length (mm)	20·11 (13·36)	20·30 (13·83)	0·940
MLD (mm)	0·49 (0·41)	0·55 (0·57)	0·465
MLD, excluded total occlusion (mm)	0·68 (0·33)	0·77 (0·53)	0·332
RVD (mm)	2·70 (0·53)	2·87 (0·43)	0·041
Periprocedure or postprocedure			
Number of stents per lesion	1·59 (0·87)	1·63 (1·04)	0·746
Average stent diameter per lesion (mm)	2·95 (0·32)	2·94 (0·29)	0·902
Total stent length per lesion (mm)	32·39 (23·05)	31·08 (23·11)	0·729
Maximum balloon inflation pressure (atm)	16·9 (3·7)	16·2 (3·7)	0·250
Periprocedural bolus heparin (units)	7·4 (3·5)	7·3 (2·9)	0·753
In-stent diameter stenosis (%)	14 (14)	10 (8)	0·046
In-stent MLD (mm)	2·39 (0·52)	2·58 (0·40)	0·024
In-segment diameter stenosis (%)	18 (12)	13 (10)	0·030
In-segment MLD (mm)	2·14 (0·51)	2·38 (0·45)	0·006
Ratio of SES to PES	0·8 (43:55)	0·8 (27:36)	0·899
Direct stenting	29/98 (30%)	17/63 (27%)	0·653
Stent overlap	41/98 (42%)	24/63 (38%)	0·392
Use of glycoprotein IIb/IIIa inhibitors	38/98 (39%)	19/63 (30%)	0·218

Data are mean (SD) or n/total with data available (%), unless otherwise specified. MLD=minimum lumen diameter. PCI=percutaneous coronary intervention. RVD=reference vessel diameter. ACC/AHA=American College of Cardiology/American Heart Association. *Multiple lesions in the same patient counted separately.

Table 5: **Clinical, procedural, and angiographic characteristics for patients with early and late stent thrombosis (ST)**

single antiplatelet drug, and four (4%) were not on antiplatelet therapy. By contrast, late stent thrombosis occurred during dual antiplatelet therapy in 14 (23%) patients, during single-drug therapy in 31 (51%), and in 16 (26%) who were not on antiplatelet therapy (p<0·0001 for the comparison of early *vs* late). Stent thrombosis occurred late in 31 patients on aspirin monotherapy, and 97% (30 of 31) experienced the event after the recommended prescription period of clopidogrel had ended. 23 patients prematurely discontinued one or both of the two antiplatelet drugs (seven of 91 early, 16 of 61 late, p=0·008). The reasons for premature discontinuation were poor compliance in 11 patients (48%), surgery in 7 (30%), bleeding in four (17%), and allergy in one (4%).

Discussion

Our findings from a large cohort of patients with stent thrombosis after implantation of drug-eluting stents add to the evidence about late stent thrombosis[23–28,35] with the following observations: stent thrombosis occurred with an incidence density of 1·3 per 100 person-years and a cumulative incidence of 2·9% at 3 years; the incidence of late stent thrombosis did not diminish, but continued at a steady rate of 0·6% per year during the first 3 years; acute coronary syndrome at presentation and diabetes were independent predictors of overall stent thrombosis; and early and late stent thrombosis occurred with both types of drug-eluting stent, but late stent thrombosis was more frequently observed with PES than with SES.

The principal aim of this study was to assess the incidence of stent thrombosis during a follow-up period of up to 3 years in a large group of patients treated with the unrestricted use of drug-eluting stents. Previous data on stent thrombosis after drug-eluting stent implantation were derived from randomised trials and registries, in which low rates of events were reported and early stent thrombosis seemed to occur with similar frequency in drug-eluting and bare metal stents.[17,19–22,36] Similarly, a recent meta-analysis reported similar event rates for drug-eluting and bare metal stents up to 1 year of follow-up.[18] The incidence of early stent thrombosis (1·2%) and the median time to stent thrombosis (9 days) in the present study were similar to rates previously reported in patients treated with bare metal stents.[16,35]

Of more interest are adverse events during long-term follow-up and the occurrence of late stent thrombosis encountered with drug-eluting stents. Late stent thrombosis has also been shown in the long-term follow-up results of early trials comparing SES and PES with bare metal stents. A pooled analysis of RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS revealed five cases of late stent thrombosis between 1 year and 4 years of follow-up with SES, but no such case with bare metal stents (survival free from stent thrombosis at 3 years: 98·8% *vs* 99·4%, p=0·20).[37] Similarly, a pooled analysis of TAXUS II, IV, V, and VI showed eight cases of late stent thrombosis between 9 months and 3 years with PES and only one case with bare metal stents (survival free from stent thrombosis at 3 years 98·7% *vs* 99·2%, p=0·36).[22] However, concerns have been raised as to whether these data are truly applicable to everyday clinical practice, because of the small number of patients, and the exclusion of acute coronary syndromes and complex lesions in randomised controlled trials. The complexity of the present population is reflected in the high mortality rates. The cumulative incidence of all-cause mortality was 10·3% in the present study, which is higher than the mortality rates reported in previous studies. However, the results of the present study suggest that late stent thrombosis with drug-eluting stents occurs more frequently than expected[19–22,36] and that rates increase steadily during long-term follow-up. The sustained occurrence over a long-term period might be explained in part by the delayed healing response after implantation of drug-eluting stents, as indicated by delayed re-

	Overall (n=152)	SES (n=69)	PES (n=83)	p
Age (years)	60·3 (12·0)	61·3 (13·4)	59·5 (10·8)	0·37
Male sex	115/152 (76%)	46/69 (67%)	69/83 (83%)	0·02
Hypertension	63/152 (41%)	40/69 (58%)	23/83 (28%)	<0·0001
Family history	44/152 (29%)	23/69 (33%)	21/83 (25%)	0·29
Current smoking	57/152 (38%)	27/69 (39%)	30/83 (36%)	0·74
Dyslipidaemia	74/152 (49%)	33/69 (48%)	41/83 (49%)	0·87
Diabetes	29/152 (19%)	16/69 (23%)	13/83 (16%)	0·30
Renal insufficiency	9/143 (6%)	6/68 (9%)	3/84 (4%)	0·30
Left ventricular ejection fraction (%)	52 (12)	53 (12)	51 (13)	0·61
Acute coronary syndrome at presentation	67/95 (71%)	24/35 (69%)	43/60 (72%)	0·82
Multivessel disease	88/149 (59%)	42/65 (65%)	45/83 (54%)	0·24
Bifurcation treatment	27/96 (28%)	9/36 (25%)	18/60 (30%)	0·65
Timing of early ST (days)				
Mean (SD)	5·5 (6·5)	5·9 (6·3)	5·1 (6·4)	0·58
Median (IQR)	4·0 (1–6)	4·0 (2–8)	4·0 (1–5)	
Timing of late ST (days)				
Mean (SD)	459·4 (274·7)	564·8 (310·1)	375·7 (212·5)	0·007
Median (IQR)	442·0 (235–652)	585 (381–801)	343·5 (214–509)	
Recommended duration of clopidogrel (months)				
Mean (SD)	7·9 (3·5)	8·1 (4·1)	7·9 (3·1)	0·84
Median (IQR)	6·0 (6·0–12·0)	6·5 (3·8–12·0)	6·0 (6·0–12·0)	
Number of stents per patient	2·35 (1·73)	2·20 (1·64)	2·47 (1·80)	0·35
Average stent diameter per patient (mm)	2·83 (0·35)	2·75 (0·28)	2·89 (0·39)	0·051
Total stent length per patient (mm)	42·3 (34·0)	38·5 (28·0)	45·5 (38·2)	0·22

Data are mean (SD) or n/total with data available (%), unless otherwise specified.

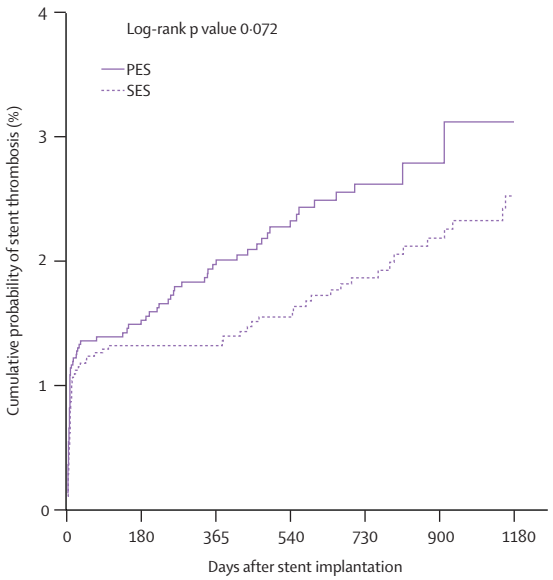
Table 6: **Clinical, procedural, and angiographic characteristics of patients with stent thrombosis (ST) overall and by type of stent**

endothelialisation[38] and hypersensitivity reactions to the antiproliferative drugs or, more probably, to the synthetic polymers.[12,13]

Stent thrombosis is a multifactorial occurrence that has been attributed to a range of angiographic, lesion-related and vessel-related, technical and clinical factors.[39] Acute coronary syndrome, bifurcation treatment, diabetes and premature discontinuation of anti-platelet therapy were the strongest predictors of overall ST in several previous studies.[19,26–28,40] The present study confirms the predictive value of diabetes and acute coronary syndrome at presentation.

Several clinical risk factors were predictive for development of early stent thrombosis. The increased risk in diabetic patients might be related to the more diffuse and aggressive nature of atherosclerosis, accompanied by longer lesion lengths, smaller vessel size, and greater plaque burden, which might incur less optimal procedural results.[41–44] Additionally, the detrimental effects of smoking on endothelial function[45,46] and the long-term impairment of peri-stent vasoreactivity after drug-eluting stent implantation[14,15] are well known. However, the fact that smoking was independently associated with lower rates of early stent thrombosis might be related to the high number of patients with acute coronary syndrome in the present population. Smokers are likely to stop smoking immediately after such an event, which might remove from their risk-factor profile one of the major determinants of atherosclerosis.[47,48] The fact that the use or implementation of an antihypertensive treatment at the time of percutaneous coronary intervention was sufficient to qualify patients as hypertensive might have resulted in the so-called protective predictive value of hypertension for early stent thrombosis and the trend towards a lower risk for late stent thrombosis. However, overall, late stent thrombosis seemed difficult to predict and its cause remains largely unknown.

Although the cumulative incidence of overall and early stent thrombosis was similar for the two types of drug-eluting stent, late stent thrombosis occurred more frequently in patients treated with PES than in those treated with SES during the 3-year observation period. Up to 90% of paclitaxel remains indefinitely sequestered within the polymer, while 10% of the drug is released in a bimodal manner during a 2-week period. In contrast, sirolimus is completely released from the polymer and slowly elutes over a 90-day period. Whether the differences in drug-release kinetics,[49] distribution within the vessel wall, mechanisms of action,[50] or design of the stent platforms[51] affect the incidence and time course of late stent thrombosis remains unclear. PES were implanted in more complex lesions in this study group,



Days after PCI	9	30	365	730	1095
Incidence, SES (%)	1·0	1·1	1·3	1·9	2·5
Cumulative events (n)	36	41	47	60	69
Patients at risk (n)	3535	3508	2671	1710	903
Incidence, PES (%)	1·2	1·3	2·0	2·7	3·2
Cumulative events (n)	43	49	69	81	83
Patients at risk (n)	3626	3493	2667	1131	68

Figure 5: **Kaplan Meier survival curves showing cumulative incidence of stent thrombosis stratified by type of drug-eluting stent**

whereas SES had been used from an earlier time than had PES, and subsequently the length of follow-up differed between the two devices. Only randomised clinical trials will be able to fairly address potential differences in safety between the two stent types.

In this study, 30 of 31 patients who had late stent thrombosis while on single antiplatelet therapy received lifelong aspirin. Although absence of clopidogrel was not associated with a higher risk of stent thrombosis, 80% of patients with late stent thrombosis developed the problem after completion of the recommended duration of clopidogrel treatment. The question of whether extended or indefinite adjunctive clopidogrel treatment, if well tolerated, might be considered for patients who undergo drug-eluting stent implantation remains open. The effect of antiplatelet treatment on the pathophysiology of stent thrombosis is well established. Platelet aggregation studies have shown that an impaired response to antiplatelet treatment[52] and high post-treatment platelet reactivity[53] are associated with stent thrombosis. Furthermore, late stent thrombosis after cessation of clopidogrel has been reported in several studies.[23,25–27,35] In particular, the withdrawal of antiplatelet treatment in patients undergoing non-cardiac procedures seems problematic, because perioperative stress enhances platelet aggregation and thus the risk of thrombotic stent occlusion.[23,54] In this study, seven patients (one early; six late) discontinued both aspirin and clopidogrel before elective dental work or non-cardiac surgery. However, further evidence of the limited ability of clopidogrel to prevent all stent thrombosis is provided in our study, in which 13 of 61 of patients had late stent thrombosis despite dual antiplatelet therapy with aspirin and clopidogrel. Despite the longer duration of clopidogrel prescription (12 months) in the patients from Bern compared with those in Rotterdam (6 months), the incidence of both early and late stent thrombosis was similar in both centres. Additionally, the increased risk of bleeding complications and the economic burden imposed by long-term clopidogrel administration must be carefully weighed in light of these findings.

Effective antiplatelet treatment has a key role in the prevention of stent thrombosis and randomised controlled trials should be appropriately designed to prospectively address the following questions: which drugs are essential and for how long, what is the role of platelet function tests in patients undergoing drug-eluting stent implantation, and what are the therapeutic consequences?

Our study has several limitations. First, this was a non-randomised cohort study, with the decision about stent type and antiplatelet therapy largely determined by local institutional practice. The main purpose of the present study was to investigate the incidence and time course of stent thrombosis in unselected patients treated with drug-eluting stents. A comparison with stent thrombosis after bare metal stent implantation was beyond the scope of the present manuscript. The study was observational in nature and has the same disadvantages as any other observational study, including confounding by indication.[55] SES and PES have been used in both centres at different times, and PES were available for commercial use 1 year later than were SES. This difference in follow up might have biased our results. Nevertheless, results from comparisons of these two stent types should be viewed as hypothesis-generating and have to be confirmed in long-term follow-up of randomised controlled trials directly comparing these devices. Longer-term follow-up of the group of patients we studied will be needed to better understand the time course and incidence of this overall rare problem.

Second, our data provide an estimate of the incidence of stent thrombosis after drug-eluting stent implantation during routine clinical practice at two tertiary care centres. In this study we recorded a high number of stents per patient, small average stent diameter, and overall long total stent length, so our findings might not apply to institutions with more restricted use of drug-eluting stents. Nevertheless, previous randomised trials certainly underestimated the true incidence of stent thrombosis because of their less complex population of patients. Some stent thrombosis might have been undetected in our study despite our attempts at an active surveillance of harms.[56]

Additionally, we only reported angiographically documented cases, using a definition consistent with our previous reports on stent thrombosis after drug-eluting or bare metal stent implantation.[16,17,19–22,36] This practice might have led to an underestimation of the actual incidence of stent thrombosis—for example, if patients had sudden cardiac death or silent stent occlusion. Because of resource limitations it was impossible to ascertain retrospectively characteristics of patients and procedures that were not prospectively collected as part of routine procedures. Therefore, some variables were unavailable. In particular, the actual use of clopidogrel at each time point was not available for a substantial proportion of patients and therefore was not used in the final analysis. By contrast, the duration of clopidogrel prescription was available for all patients in Rotterdam and was included in the final Cox regression models. The value of clopidogrel in preventing stent thrombosis needs to be established in sufficiently powered dedicated trials. Intravascular ultrasound examination was not routinely done and the underlying mechanism contributing to the occurrence of stent thrombosis was not specifically investigated.

In conclusion, our data suggest that late stent thrombosis occurs at a steady rate during follow-up up to 3 years, tends to be more frequent with PES than with SES, and can unpredictably occur at any time point despite antiplatelet therapy. Late stent thrombosis complicating the use of drug-eluting seems to be a distinct entity with pathophysiological factors that differ from those of early stent thrombosis.

Contributors

The first two authors contributed equally to the manuscript. K Tschuchida, P Wenaweser, J Daemen, S Windecker, and P W Serruys were responsible for conception and design of the study, analysis and interpretation of data, and drafting of the manuscript. S Vaina, L Abrecht, C Morger, K Kukreja, P Jüni, G Sianos, G Hellige, R T van Domburg, O M Hess, E Boersma, and B Meier critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. Statistical expertise was provided by J Daemen, P Jüni, R T van Domburg, and E Boersma. S Windecker, B Meier, and P W Serruys obtained public funding. Administrative, technical, and logistic support were provided by O M Hess, R T van Domburg, B Meier, S Windecker, and P W Serruys. K Tschuchida, P Wenaweser, J Daemen, S Vaina, L Abrecht, C Morger, N Kukreja, G Sianos, and G Hellige acquired data.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The study was funded by research grants from the University Hospital Bern, Bern, Switzerland, and the Thoraxcenter, Rotterdam, the Netherlands.

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