Stent thrombosis in real-world patients: a comparison of drug-eluting with bare metal stents

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Background. Although the introduction of drug-eluting stents (DES) has been associated with an impressive reduction in target vessel revascularisation, there has been concern about the safety profile. The aim of this study was to determine the incidence of stent thrombosis in real-world patients and evaluate the contribution of drug-eluting stents.

Methods. A prospective observational cohort study was conducted at a high-volume centre in Utrecht, the Netherlands. All patients who underwent a percutaneous coronary intervention (PCI) between 1 January and 31 December 2005 were evaluated. The patients were pretreated with aspirin and clopidogrel, which was continued for six months in bare metal stents (BMS) and 12 months in DES.

Results. In 2005, 1309 patients underwent a percutaneous coronary intervention procedure with stent implantation. After a median follow-up of nine months, 1.8% (n=23) of the patients had suffered from stent thrombosis. Two cases could be attributed to incorrect use of antiplatelet agents. In 8/23 cases, a technical reason was found such as an unrecognised dissection or stent under-expansion. The timing of stent thrombosis was acute in 1/23 patients, subacute in 20/23 patients and late in 2/23 patients. In both cases of late stent

thrombosis, a BMS had been used. There were no differences in stent thrombosis rates between DES and BMS (1.4 vs. 1.9%, ns.). This is remarkable since DES were used in more complex and longer lesions.

Conclusion. The use of DES in routine daily practice does not appear to be associated with a higher rate of stent thrombosis than BMS. (*Neth Heart J* 2007;15:382-6).

Keywords: PCI, stent, subacute thrombosis

The introduction of drug-eluting stents (DES) has been associated with an impressive reduction in target vessel revascularisation. This has led to a rapid and widespread adoption throughout the world. However, there has been concern about the safety profile.¹ The most dramatic outcome is stent thrombosis, a condition associated with a high mortality rate. In 2003, the FDA published a web notification after receiving numerous reports of subacute stent thrombosis with the sirolimus-eluting stent.² Theoretically, this may be expected because of the combination of delayed endothelialisation of the drug-eluting stent with an increased tendency to platelet aggregation on sirolimus.^{3,4} The randomised clinical trials, although carried out in selected patients with a relatively short follow-up, could not confirm the suspicion raised.⁵⁻⁷ The question remains whether DES can be applied safely in real-world patients with more complex lesions. The aim of this study was to determine the incidence of stent thrombosis in an unselected cohort of patients and evaluate the contribution of DES.

Patients and methods

A prospective observational cohort study was conducted at a high-volume centre in Utrecht, the Netherlands. All patients who underwent a percutaneous coronary intervention (PCI) between 1 January and 31 December 2005 were evaluated. The indications for PCI included stable angina pectoris, unstable angina (NSTEMI-ACS) and acute myocardial infarction (STEMI-ACS). We applied the following

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Table 1. Baseline characteristics

	Overall (n=1309)²	BMS (n=1015)	DES (n=294)	P value¹
Age (years)	63±12	63±12	61±11	0.036
Male sex	0.74	0.74	0.73	ns
Indication				
- Stable angina pectoris	0.48	0.44	0.65	0.000
- NTSE-ACS	0.23	0.24	0.22	ns
- STE-ACS	0.27	0.31	0.12	0.000
Multivessel PCI	0.12	0.11	0.17	0.009
Current smoking	0.61	0.64	0.48	0.007
Hypercholesterolaemia	0.50	0.49	0.53	ns
Hypertension	0.45	0.44	0.51	ns
Diabetes	0.19	0.11	0.42	0.000
Positive family history	0.48	0.47	0.50	ns
Renal dysfunction	0.15	0.13	0.18	ns
Previous MI	0.26	0.25	0.32	0.015
Previous PCI	0.20	0.22	0.41	0.000
Previous CABG	0.06	0.06	0.07	ns
Good LV function	0.78	0.78	0.79	ns
Procedural characteristics				
Segments, no.	1681	1321	360	
Vessel				
- Left main	0.01	0.01	0.01	ns
- Left anterior descending	0.42	0.38	0.55	0.000
- Right circumflex	0.23	0.24	0.20	ns
- Right anterior descending	0.33	0.35	0.23	0.000
- Graft	0.02	0.02	0.01	ns
Lesion characteristics				
- Type A/B1	0.43	0.46	0.30	0.000
- Type B2/C	0.57	0.54	0.70	0.000
TIM1 3 flow	0.70	0.70	0.73	ns
Thrombus	0.25	0.29	0.12	0.000
GP IIb/IIIa-I	0.23	0.25	0.17	0.004
Stent thrombosis	0.018	0.019	0.014	ns

¹ The probability value refers to the difference between the drug-eluting stent (DES) and the bare metal stent (BMS) group. ² 75 out of 1384 patients were treated with balloon angioplasty or attempt to recanalisation, without the use of stents; this results in a study cohort of 1309 patients. NTSE-ACS=unstable angina, STE-ACS=acute myocardial infarction, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, LV=left ventricle.

criteria for the use of DES: in-stent restenosis, long lesions (>20 mm), vessel diameter <3 mm and diabetes mellitus.⁸ DES usage was discouraged in STE-ACS and poor patient compliance.

In case of elective PCI procedures, the patients were on 100 mg aspirin and 75 mg clopidogrel daily for at least one week before the procedure. Emergency PCI was carried out by administration of a loading dose of 450 to 900 mg aspirin intravenously, 300 to 600 mg clopidogrel orally and an intravenous bolus

of 5000 units of unfractionated heparin. At the start of the PCI, a weight-adjusted initial dose of 70 U/kg of unfractionated heparin was administered. GP IIb/IIIa inhibitors (tirofiban and abciximab) were used at the discretion of the interventionalist. Aspirin was continued indefinitely and clopidogrel for six months with bare metal stents (BMS) and 12 months in DES. Angiographic and procedural outcome were documented by the interventional cardiologist. The clinical outcome was recorded by the clinician on the

ward before discharge. Clinical follow-up was carried out for an average of nine months (range 3 to 15 months). If complications occurred, medical records at our hospital and elsewhere were reviewed to characterise clinical events during the study period.

Stent thrombosis was defined as the occurrence of angiographically confirmed partial or total stent occlusion or sudden cardiac death after successful stent implantation. Stent thrombosis was categorised according to the timing of the occurrence into acute (<1 day), subacute (1-30 days) and late (>30 days). The cases with stent thrombosis were reviewed by a panel of three interventionalists to evaluate technical aspects of the PCI procedure. The following technical aspects were scored: stent expansion, side branch event, dissection and residual stenosis >50% in the treated segment. In addition, we evaluated the medical records to document drug prescription during the hospital stay and at discharge, as well as patient adherence to medication.

Categorical variables were compared by the χ^2 test or Fisher's exact test. Continuous variables are presented as mean $\pm$ SD and were compared with the use of Student's *t* test. All statistical analyses were carried out with the software package SPSS version 11.5.0.

Results

Baseline characteristics

In 2005, 1384 patients underwent a PCI procedure. Seventy-five patients were excluded because no stent was implanted. The reason was either balloon angioplasty only or an unsuccessful recanalisation. Thus, 1309 patients were included in the cohort. The patients were followed for an average of nine months. The mean age of the whole group was 63 ± 12 years (table 1). The indication for the PCI was stable angina in 48%, an NSTEMI-ACS in 23% and a myocardial infarction in 27%. Nineteen percent of the patients were diabetic. With regard to lesion characteristics, 43% of the interventions were performed in a type A or B1 lesion whereas 57% concerned a type B2 or C lesion. GP IIb/IIIa inhibitors were administered in 23% of the procedures.

Drug-eluting stents

In accordance with the indications for DES use in our centre, DES were predominantly used in patients with stable angina pectoris, diabetics and multivessel procedures. With regard to lesion characteristics, DES were used more often in complex lesions and more frequently involved the left anterior descending coronary artery (LAD). On the other hand, the right coronary artery (RCA) was treated more frequently with BMS.

Stent thrombosis

Stent thrombosis occurred in 1.8% of the patients (23/1309). The DES group demonstrated a stent thrombosis rate of 1.4% and the BMS group 1.9% (ns).

Table 2. Characteristics of patients with versus patients without stent thrombosis.

	No stent thrombosis (n=1286)	Stent thrombosis (n=23)	P value
Age (years)	62 $\pm$ 12	67 $\pm$ 11	0.047
Male sex	0.73	0.83	ns
Indication			
- Stable angina pectoris	0.49	0.48	0.000
- NSTEMI-ACS	0.23	0.26	ns
- STE-ACS	0.26	0.26	0.000
Multivessel PCI	0.13	0.13	0.009
Current smoking	0.60	0.75	ns
Hypercholesterolaemia	0.50	0.37	ns
Hypertension	0.46	0.42	ns
Diabetes	0.18	0.25	ns
Positive family history	0.47	0.53	ns
Renal dysfunction	0.14	0.29	ns
Previous MI	0.26	0.35	ns
Previous PCI	0.25	0.30	ns
Previous CABG	0.06	0.04	ns
Good LV function	0.78	0.50	ns
Procedural characteristics			
Segments, no.	1658	23	
Vessel			
- Left main	0.01	0.0	ns
- Left anterior descending	0.41	0.70	0.009
- Right circumflex	0.23	0.09	ns
- Right anterior descending	0.33	0.22	ns
Graft	0.02	0.0	ns
Lesion characteristics			
- Type A/B1	0.43	0.35	ns
- Type B2/C	0.57	0.65	ns
TIMI 3 flow	0.70	0.78	ns
Thrombus	0.25	0.22	ns
GP IIb/IIIa inhibitors	0.23	0.17	ns
Stent thrombosis	0.23	0.13	ns

NSTEMI-ACS=unstable angina, STE-ACS=acute myocardial infarction, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, LV=left ventricle.

The only variables that differed significantly between the group with and without stent thrombosis were age and target vessel (table 2). The stent thrombosis group was older and more frequently associated with a PCI of the LAD. Although there was a tendency towards a higher frequency of renal dysfunction, diabetes and poor left ventricular function in the group with stent thrombosis, these variables did not reach statistical significance.

The timing of stent thrombosis was acute in 1/23 patient, subacute in 20/23 patients and late in 2/23 patients. In both cases of late stent thrombosis, a BMS had been used. One of the patients was only taking oral anticoagulants and suffered from a stent thrombosis after 166 days. The second patient with a late stent thrombosis after 80 days initially underwent a PCI of a diffusely diseased LAD. The PCI was technically difficult and resulted in stent underexpansion and a side branch event (dissection of diagonal). Antiplatelet therapy was used as prescribed.

With regard to the reason for stent thrombosis, two cases could be explained by incorrect use of antiplatelet agents. An 80-year-old patient did not take any antiplatelet drugs at home as well as insulin and suffered from a stent thrombosis after ten days. The other patient only took oral anticoagulants and not the aspirin and clopidogrel that were prescribed. In eight cases, a technical reason was identified. In one patient both stent underexpansion and dissection of a side branch were detected. Three patients had stent underexpansion only, one patient had a side branch event only and two patients had an unrecognised dissection at the stent edge. The last patient concerned a primary PCI in a patient with an anterior wall infarction. This case was particularly complex because of a diffusely diseased LAD and incessant ventricular fibrillation. This resulted in a difficult and prolonged PCI procedure in which a residual stenosis of >50% was accepted. In the remaining 13 patients, no technical comments could be made.

Discussion

In this unselected cohort of 1309 consecutive patients undergoing stent implantation, a 1.8% cumulative incidence of stent thrombosis was noted. There were no differences between the DES and BMS group (1.4 and 1.9% respectively). The incidence is higher than the reported incidence of stent thrombosis of 0.4% at one year for sirolimus, and 0.6% at nine months for paclitaxel in major clinical trials.⁵⁻⁷ However, it appears to be comparable with registries and observational cohort trials that more closely reflect real-world patients. For example, Iakovou et al.⁹ conducted a prospective multicentre study to evaluate the incidence, predictors and outcome of stent thrombosis after implantation of drug-eluting stents in routine daily practice and reported an incidence of 1.3% at nine months.

Of interest is the fact that we could not demonstrate a difference between BMS and DES. A comparison is difficult to make because DES were used in specific patient categories that were considered to be prone to in-stent restenosis (such as diabetes, in-stent restenosis, long lesions and small vessel diameter). This selection has biased this study. On the other hand, it reflects the daily practice and is applied in most budget-limited centres. Despite differences in baseline characteristics, it is at least remarkable that there were no differences

in stent thrombosis rates because DES were used in more complex and longer lesions.

The majority of the cases with stent thrombosis occurred within a month. Only 2/23 cases presented as late stent thrombosis. Both cases were initially treated with BMS. Although it is well known that late stent thrombosis can occur in DES, it should be emphasised that BMS can also be involved in late stent thrombosis.

In 2/23 patients with stent thrombosis there was an apparent relation with incorrect use of antiplatelet agents. This is in accordance with other studies that have demonstrated that withdrawal of antiplatelet agents is associated with a 90-fold increase in risk of stent thrombosis.⁹ It is therefore of utmost importance that patients who receive a stent are well informed and receive proper instructions about medication use. In one third of the cases we could identify certain technical flaws. Dissection at the edges of the stent, stent underexpansion and side branch events are well-known risk factors for stent thrombosis and may have predisposed to stent thrombosis in these patients. In more than half of the patients we had no explanation for the occurrence of stent thrombosis. In these patients, an uneventful PCI was performed in combination with correct use of antiplatelet therapy. We speculate that these patients may be resistant to the antiplatelet effects of aspirin and clopidogrel.¹⁰ Variability between patients to platelet inhibition is well known. Up to 10% of patients treated with clopidogrel are resistant to its effects and as many as 25% are only partially responsive.¹¹ Muller et al.¹¹ evaluated platelet inhibition in a group of patients undergoing elective PCI, and demonstrated that among the group of non-responders there were two incidents of subacute stent thrombosis after PCI. Also several other studies have demonstrated an association between resistance to antiplatelet drugs and clinical outcome.¹² Future research is needed to evaluate the role of antiplatelet resistance to aspirin and clopidogrel in the occurrence of stent thrombosis.

There are several limitations to this study. The number of stent thromboses is low which has an important impact on the statistical power of our analysis. Second, a follow-up period of nine months is relatively short. It is feasible that the incidence of stent thrombosis in the long term may be higher. Data are scarce because most trials have a follow-up time of nine to 12 months. Recent data from the Basket-Late trial, evaluating DES vs. BMS at 18 months in real-world patients, did not show differences in primary endpoints death / myocardial infarction but event rates of 8% were reported.¹³ In addition, a recent meta-analysis by Camenzind,¹⁴ concerning all available data of the randomised double-blind clinical trials comparing first-generation DES with the respective BMS control, reported a higher incidence of death and myocardial infarctions in the DES group. Because of these concerns, an FDA Circulatory System Devices Panel gathered on 7 December 2006. They recommended several strategies to improve the quality and usefulness of research on

stents, including large registries with matched controls, more randomised trials comparing DES with outcomes with BMS, coronary artery bypass grafts or medical therapies. A few months later an entire issue of the New England Journal of Medicine was dedicated to this topic with five original articles about stent thrombosis and DES. There were four meta-analyses by different groups evaluating the safety of both sirolimus- and paclitaxel-eluting stents as compared with BMS.¹⁵⁻¹⁸ Although the number of revascularisation procedures was lower in the DES group, no differences in mortality and myocardial infarctions could be demonstrated. Although the studies were underpowered, there was a tendency to a higher rate of stent thrombosis in the DES group. New data were provided by a large Swedish registry comprising 19,771 patients who underwent a PCI in 2003 or 2004.¹⁹ Interestingly, up to six months a lower event rate was noted in the DES group which can be translated into less in-stent restenosis and less re-interventions. However, after the first six months, a higher event rate was noted in the DES group and at three years, mortality was 18% higher in the patients treated with DES. It is obvious that we need large randomised trials to evaluate the long-term safety of drug-eluting stents and determine the optimum duration and dose of dual antiplatelet therapy. Until these questions are answered, a more restrictive use of DES seems advisable with attention for the current 'on label' indications approved by the FDA. ■

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