BRIEF REPORT

Stent Thrombosis in the Modern Era: Incidence, Outcome, and Predictive Factors

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Coronary stent thrombosis is a catastrophic complication of percutaneous coronary intervention. Its incidence is reported to be about 1%, though it can occur more frequently in high-risk patients, in high-risk lesions, and in multivessel procedures.

We investigated the occurrence of stent thrombosis in 404 consecutive patients in a period when conventional and drug-eluting stents were both being used. We found an overall incidence of 2.23%, a mortality rate of 22.2%, and a non-fatal myocardial infarction rate of 66.6%. Predictors of stent thrombosis were acute myocardial infarction, multiple stent placement, poor ejection fraction, small stent diameter, the presence of residual dissection, and premature discontinuation of clopidogrel.

Key words: *Stent. Thrombosis. Percutaneous coronary intervention.*

Trombosis del *stent* en la era moderna: incidencia, consecuencias y factores predictores

La trombosis del *stent* (TS) es una complicación temida del intervencionismo coronario percutáneo por sus consecuencias catastróficas, cuya incidencia aproximada es del 1% y que puede ser más frecuente en procedimientos realizados en pacientes/lesiones de alto riesgo o procedimientos multivaso.

Analizamos la aparición de TS en una población de 404 pacientes consecutivos en un período en el que se utilizaron tanto *stents* recubiertos como *stents* convencionales, con una incidencia global del 2,23%, una mortalidad del 22,2% y una tasa de infarto agudo de miocardio no fatal del 66,6%. Los factores predictores de aparición de TS fueron: indicación por infarto agudo de miocardio, implante de múltiples *stents,* peor fracción de eyección, diámetro de *stent* más pequeño, presencia de disección residual y abandono precoz de clopidogrel.

Palabras clave: *Stent. Trombosis. Intervencionismo coronario percutáneo.*

INTRODUCTION

Stent thrombosis (ST) is a clinical event with high associated mortality and morbidity.[1] Despite optimization of the implant technique and use of dual antiplatelet therapy with aspirin and clopidogrel, the incidence of ST has not been eliminated.[2] In the modern era of antiproliferative drug-eluting stents and conventional stents, the former have not obtained higher rates of ST in the randomized clinical trials initially published,[3,4] or in recent publications with consecutive "real world" patients,[5-7] even though it was initially postulated that the delay in the endothelialization of the covered segment could lead to higher rates of ST.

The purpose of our study was three-fold: *a)* analyze the incidence of stent thrombosis in an unselected population of consecutive patients percutaneously revascularized with conventional, drug-eluting, or both kinds of stents at a time when both types of devices were used concomitantly; *b)* analyze the morbidity and mortality associated with stent thrombosis in this population; and *c)* identify possible predictors of the development of thrombosis.

METHODS

Study Population

Between June 2003 an June 2004 a total of 404 consecutive patients who received 762 stents for 625

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lesions (1.22 stent/lesion) with a successful outcome (residual stenosis <50% and absence of death, infarction, or need for emergency coronary artery bypass grafting during the procedure) from our hospital were included: 321 (42.13%) drug-eluting stents (200 Cypher, 121 Taxus) and 441 (57.87%) conventional stents.

The population susceptible to follow-up was composed of patients revascularized with conventional stents alone (200 patients; 45%), patients revascularized with drug-eluting stents alone (148 patients; 36.6%), and patients revascularized with both types of stents (56 patients; 13.8%).

All demographic, clinical, angiographic, and technical data were obtained at the time of the procedure. After hospital discharge, all patients were assessed at 30 days and 6 months post-implant by phone or outpatient visit, with the latter consisting of an interview, physical examination, electrocardiogram, and chest x-ray.

Coadjuvant Therapy

All procedures were performed according to the current guidelines for coronary interventional procedures.[8] All patients were given a 300-mg loading dose of clopidogrel in the catheterization laboratory along with aspirin, and after the procedure, were prescribed a combined antiplatelet regimen consisting of aspirin (200 mg every 24 h) and clopidogrel (75 mg every 24 h) for at least 9 months. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the interventional cardiologist.

Definitions

Stent thrombosis was considered to have occurred when there was recurrence of ischemia with angiographic evidence of vessel occlusion (TIMI 0-1 flow) or the presence of a flow-limiting thrombus (TIMI 1-2) at the site of the previous stent implant. Depending on the time of onset, subacute thrombosis was defined as occurring 24 h after the procedure up to day 30, and late thrombosis as occurring after day 30 and up to month 6.

Statistical Analysis

Categorical variables were compared by Fisher's exact test and continuous variables, by Student's *t* test following verification of the normality assumption; if not met, the nonparametric test was used (Mann-Whitney U test). Statistical significance was set at a $P<.05$. The statistical analysis was done with SPSS (version 11.0, SPSS Inc., Chicago, Illinois, USA.).

RESULTS

Baseline Characteristics

Table 1 shows the clinical and angiographic characteristics of the population. Most implants were done in the clinical context of unstable angina (49.7%), 79% of the patients were men, 25% were diabetic, and 25% presented three-vessel disease. Glycoprotein IIb/IIIa inhibitor use during the procedure was 46.3%, and more than one stent was implanted in half the cases (50.7%). There was a high percentage of complex lesions (62.8% of lesions were Type B2 or C).

Incidence, Time, Form of Presentation, and Clinical Events Associated With Stent Thrombosis

At 6 months of follow-up (available for all patients), ST was angiographically documented in 9 of the 404 patients included in the study (2.23%). Four cases occurred in the group of 200 patients in whom only conventional stents were implanted (2%) and another 5 cases occurred in the group of 147 patients in whom only drug-eluting stents were implanted (3.4%). No patient with both types of stents had ST. Of the 5 cases of ST in drug-eluting stents, 3 occurred in paclitaxel-eluting stents and 2 in sirolimus-eluting stents. Most

TABLE 1. **Baseline Clinical and Lesion Characteristics***

Age, y	62.5±11.4
Men	319 (79%)
Diabetes	188 (25%)
Prior MI	80 (19.8%)
Prior surgery	23 (5.7%)
Prior PTCA	44 (10.9%)
Unstable angina	201 (49.7%)
Acute MI	36 (8.9%)
Ejection fraction, %	59±13.7
Three-vessel disease	101 (25%)
GP IIb/IIIa inhibitors	187 (46.3%)
>1 stent	205 (50.7%)
Lesions (n=625)	
Anterior descending	235 (37.6%)
Bypass	9 (1.4%)
Left main coronary artery	2 (0.3%)
B2 or C lesion	392 (62.8%)
Complete occlusion	57 (9.1%)
Restenosis	25 (4%)
Residual dissection	24 (3.8%)
Diameter <3 mm	192 (30.7%)
Length >20 mm	187 (29.9%)
Stent diameter, mm	3±0.5
Total stent length, mm	19.5±8.8
Stents/lesion	1.22±0.51

*Values are expressed as number (%) or as mean ± standard deviation. GP indicates glycoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

TABLE 2. **Clinical and Angiographic Characteristics of Patients With Stent Thrombosis***

No.	Sex	Age	Artery	Diameter	Segment	EF %	No. Stents	Stent Type	Stent Diameter, mm	Total Stent Length, mm	GP IIb/IIIa	Time, days
1	M	83	Cx	2.33	Prox	55%	2	Conventional	2.5	20	Yes	3
2	M	47	Cx	2.67	Prox	37%	1	Paclitaxel	2.75	16	No	1
3	M	52	LAD	2.61	Mid	66%	3	Sirolimus	3.0	39	No	1
4	M	39	RCA	2.57	Mid	53%	2	Sirolimus	2.75	61	Yes	7
5	M	70	LAD	2.38	Mid	30%	2	Paclitaxel	2.5	24	Yes	2
6	M	58	LAD	2.51	Mid	42%	2	Conventional	2.5	21	No	8
7	M	49	LAD	2.54	Mid	53%	1	Conventional	2.5	12	Yes	3
8	M	54	Diag	2.54	Prox	30%	1	Conventional	2.5	16	No	11
9	M	71	LAD	2.52	Prox	62%	1	Paclitaxel	2.5	16	Yes	85

*AD indicates anterior descending; CX, circumflex artery; Diag, diagonal; EF, ejection fraction; M, male; Mid, middle; Prox, proximal; RCA, right coronary artery.

ST occurred in the first 11 days after the procedure (median, 3 days). There were 8 subacute thromboses (1.98%) with a mean of 4.5±3.7 days (range, 1 to 11 days) and 1 late thrombosis (0.25%) that occurred 85 days after the procedure. The clinical and angiographic characteristics of the patients with ST are shown in Table 2.

Of the 9 patients with ST, there were 2 in-hospital deaths (22.2%) and 6 patients presented nonfatal acute myocardial infarction (66.6%).

On follow-up, 4 patients presented non-Q-wave myocardial infarction but did not undergo a new coronary angiography, and there were 3 out-of-hospital deaths.

Predictors of Stent Thrombosis

Table 3 indicates the clinical, angiographic, and procedure variables for the patients with and without ST. The mean ejection fraction was significantly lower in the ST group, the indication for acute myocardial infarction was also significant in the group of patients with ST compared to those without, and the implant of more than one stent/patient was also another statistically significant factor in the ST group. In addition, early discontinuation of clopidogrel was also highly significant (*P*=.002) in the group with onset of ST. The drug-eluting stents did not reach statistical significance compared to conventional stents for the development of ST. The number of stents/lesion showed a significant correlation with the onset of ST, and stent diameter was significantly smaller in the ST group. The presence of residual dissection after lesion dilation was also statistically significant in the ST group versus the subjects without ST.

TABLE 3. **Clinical, Angiographic, and Procedural Characteristics of Patients With and Without Stent Thrombosis***

	Thrombosis		Significance
	No	Yes	*P*
Patients	n=395	n=9	
Age, y	62.6±11.4	58.2±1.9	.256
Men	310 (78.5%)	9 (100%)	.214
Diabetes	104 (26.3%)	4 (44.4%)	.256
Unstable angina	188 (47.6%)	2 (22.2%)	.182
Acute MR	33 (8.4%)	3 (33.3%)	.038
GP IIb/IIIa inhibitors	183 (46.3%)	4 (44.4%)	1.00
>1 stent/patient	197 (49.9%)	8 (88.9%)	.037
Three-vessel disease	97 (24.6%)	4 (44.4%)	.236
EF, %	59.2±13.8	51.2±11.8	.049
Drug-eluting	143 (43.2%)	5 (55.6%)	.503
Clopidogrel discontinuation	10 (2.5%)	3 (33.3%)	.002
Lesions	n=616	n=9	
Stent/lesion	1.2±0.5	1.5±0.7	.037
Balloon inflation pressure	12.5±2.4	12.5±2.0	.965
Stent diameter, mm	2.98±0.47	2.69±0.24	.047
Length, mm	19.4±8.7	24.9±15.3	.224
B2 or C lesion	386 (62.7%)	6 (66.7%)	1.00
Complete occlusion	55 (8.9%)	2 (22.2%)	.194
Residual dissection	22 (3.6%)	2 (22.2%)	.043
Ulcer	7 (1.1%)	0	.903
Thrombus	33 (5.4%)	0	.612
Restenosis	25 (4.1%)	0	.691
Length >30 mm	64 (10.4%)	2 (22.2%)	.244

*EF indicates ejection fraction; GP, glycoprotein; MI, myocardial infarction.

DISCUSSION

In our study, which samples a representative population from daily clinical practice, i.e., consecutive patients in whom drug-eluting and conventional stents were used, we observed a 2.23% incidence of angiographic thrombosis at 6 months of follow-up. This figure is comparable to the incidence of ST observed in these patients in the various published studies on conventional stents[9] or drug-eluting stents alone[5,6] in the current era of dual antiplatelet therapy (aspirin and clopidogrel).

Although we observed a higher incidence of ST among patients with drug-eluting stents, the difference was not significant.

The clinical consequences of the ST were severe: 22.2% mortality and 66.6% nonfatal acute myocardial infarction. These findings are consistent with the published studies[1,10] and are, at the very least, surprising, since when ST occurs, the patient is usually still hospitalized; nevertheless, the consequences remain catastrophic despite prompt restoration of coronary flow.

As in previous studies on the use of conventional stents[1,10] or drug-eluting stents alone,[5,6] in our study a poorer ejection fraction, indication of acute myocardial infarction, implant of smaller diameter stents, use of more stents per lesion, more than one stent per patient, and presence of residual dissection were variables associated with the onset of ST. Additionally, we should mention early discontinuation of clopidogrel, a risk factor repeatedly cited in recent studies[5,6] and highly significant in the ST group. Ten patients dropped out of our study for lack of adherence and the other 3, for economic reasons. Therefore, the prescribing physician plays an important role in stressing the importance of therapeutic compliance by the patient.

Limitations

Because the incidence of ST is low, a small sample may underestimate or overestimate the true incidence.

Considering its incidence, the definition of ST can significantly influence the results of the study. Angiographic evidence of vessel occlusion is a reasonable definition, but cases of thrombosis among patients with adverse events who do not undergo a new coronary angiography may be missed, thereby underestimating the actual incidence of ST. Likewise, the use of major cardiac events to define ST overestimates the actual incidence because not all patients who die suddenly or present myocardial infarction present ST.

Conclusions

The incidence of angiographic stent thrombosis in a "real-world" population, i.e., an unselected population of consecutive patients percutaneously revascularized by the implant of conventional stents, drug-eluting (sirolimus and paclitaxel) stents, or both, continues to be low (2.23%), without exceeding the incidence of thrombosis obtained when only conventional stents were available or when drug-eluting stents alone are used.

Angiographically confirmed ST in this population continues to be associated with elevated morbidity (66% myocardial infarction) and mortality (22%).

Stent thrombosis in this population appears to be related to procedures performed in patients with an indication of acute myocardial infarction, implant of multiple stents, poorer ejection fraction, smaller diameter stent, presence of residual dissection, and early discontinuation of clopidogrel.

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