Characteristics and prognosis of patients with angiographic stent thrombosis: comparison between drug-eluting and bare-metal stents

Caractéristiques et pronostic des patients avec thrombose angiographique d’un stent : comparaison entre stents actifs et conventionnels


Institut de cardiologie, Département de cardiologie médicale, Groupe hospitalier Pitié-Salpêtrière, Paris.

KEYWORDS
Drug-eluting stent; Thrombosis.

Summary

Introduction. — Conflicting data exist on the risk of stent thrombosis with drug-eluting stents (DES) versus bare-metal stents (BMS). Little is known about the potential different characteristics and outcomes of DES versus BMS thrombosis.

Objective. — To compare the characteristics, timing and outcomes of patients with angiographic stent thrombosis according to type of stent implanted.

Methods. — The population comprised consecutive patients who underwent BMS or DES implantation (January 2003-April 2007) at Pitié-Salpêtrière Hospital. Data from patients with and without a stent thrombosis were compared to identify predictors of thrombosis. Timing of thrombosis (acute, <24 hours; subacute, <30 days; late, >30 days; very late, >1 year), clinical, angiographic and procedural characteristics, and outcomes were compared between patients with a BMS or DES thrombosis.

Results. — A total of 3579 patients received a BMS (2815 lesions, 2318 patients) or a DES (1536 lesions, 1261 patients). Documented angiographic stent thrombosis occurred in 52 (1.4%) patients, 16 (1.3%) with a DES and 36 (1.6%) with a BMS. Rates of acute (0.1% versus 0.2%), subacute (1% versus 0.7%), late (both 0.2%) and very late (both 0.2%) thrombosis were similar in patients with BMS and DES thrombosis. Factors predictive of stent thrombosis were similar, including left ventricular failure (P<0.0001), initial percutaneous coronary intervention (PCI) for acute myocardial infarction (P<0.0001), initial percutaneous coronary intervention (PCI) for acute myocardial infarction (P<0.0001), multivessel PCI (P<0.0001), and balloon dilatation before stenting (P<0.04). Eleven (21%) cases of BMS (n=8, 22%) or DES (n=3, 19%) thrombosis arose soon after stopping antiplatelet therapy. Thirteen of 52 (25%) patients died a few hours after the event. Twenty-seven (52%) major adverse cardiac events occurred at 18 months, 7 in patients with a DES and 20 in those with a BMS (44% versus 55%, P=NS). These included 16 deaths (31%), 7 repeat PCIs and 4 myocardial infarctions. There were no independent predictive factors of death after stent thrombosis.

* C. Le Feuvre, Institut de cardiologie, Département de cardiologie médicale, Groupe hospitalier Pitié-Salpêtrière, 47-83, bd de l’Hôpital, 75651 Paris cedex 13.
E-mail : claude.lefeuvre@psl.aphp.fr
Introduction

The introduction of drug-eluting stents (DES) has led to a dramatic reduction in the rate of restenosis in comparison with bare-metal stents (BMS) [1]. By the end of 2004, DES were used in nearly 80% of percutaneous coronary interventions (PCI) in the USA, and within 3 years, several million DES had been implanted worldwide. A meta-analysis of 10 randomized trials confirmed the efficacy and safety profile of these devices, but the trials were not powered to detect or exclude the effect of DES on rare events such as stent thrombosis [2].

The timing of stent thrombosis is highly variable, ranging from “acute” to “late”. Conflicting results have been reported on an increased risk of late stent thrombosis with DES compared with BMS [3-10]. In several pooled analyses of randomized studies [3-5], for example, the rates of stent thrombosis did not differ between BMS and DES, whereas late thrombosis appeared to be more frequently associated with DES in one trial [6]. Similarly, no statistically significant difference was found between the two devices in rates of stent thrombosis in three registry studies [8-10], whereas DES were associated with an increased risk in a Swedish registry [7]. The aim of our study was to compare the clinical, angiographic and procedural characteristics, timing of stent thrombosis, and clinical outcomes of patients with stent thrombosis according to whether they had a DES or BMS.

Methods

The study population comprised 3,579 consecutive patients who underwent BMS (2,815 lesions treated in 2,318 patients) or DES (1,536 lesions in 1,261 patients) implantation at our institution between January 2003 and April 2007. All patients were treated with aspirin and clopidogrel (chronic treatment or loading dose at least 6 hours before the intervention). The type of stent (BMS or DES) selected and the use of glycoprotein IIb/IIIa inhibitors was at the physician’s discretion. In most cases, DES were selected in accordance with French guidelines which took into account proximal left anterior descending artery, diabetes, vessel diameter <3 mm, lesion length >15 mm, and in-stent restenosis. After stent implantation, all patients were treated with clopidogrel and aspirin. Treatment with aspirin was continued indefinitely. In most patients, clopidogrel treatment was stopped 1 month after BMS implantation, and 6 to 12 months after DES implantation.

Conclusions. — BMS and DES thrombosis are similar in terms of timing of thrombosis, characteristics and outcomes, and share the same risk of late thrombosis after interruption of antiplatelet therapy.

© 2008 Published by Elsevier Masson SAS.
Definitions
Stent thrombosis was defined as in-stent thrombosis confirmed angiographically, with or without vessel occlusion, and associated with clinical or electrocardiographic signs of acute ischaemia or elevation of creatinine kinase levels to twice the normal value within 48 hours of angiography (i.e. “definite” stent thrombosis according to the Academic Research Consortium [ARC] definition, 2006). Partial thrombosis referred to an intrastent filling defect with a TIMI flow of 1 to 3 in the coronary artery, and total stent occlusion referred to intrastent thrombosis with a TIMI flow of 0. Patients with probable or possible stent thrombosis according to the ARC y.

Timing of stent thrombosis was categorized according to the ARC definitions as acute (<24 hours), subacute (<30 days), late (>30 days) and very late (>1 year) after implantation. Clinical definition, which corresponded to unexplained death ≤30 days or >30 days after initial PCI, were not included in this study, angiographic and procedural characteristics were compared in patients with or without stent thrombosis, and according to the type of stent used in those with a thrombosis.

Continuous variables are presented as means (standard deviations). Categorical data are presented as per cent frequencies. Univariate analyses were performed using the χ² test for categorical data with Yates correction if needed, and analysis of variance for continuous variables with Fisher’s exact test if needed. A univariate analysis that included 23 clinical, biological, angiographic and procedural variables (tables 1, 2 and 3) was performed to identify the best set of predictors for occurrence of cardiac death after stent thrombosis. A Cox model was performed to identify independent predictors of cardiac death after stent thrombosis. Survival curves were constructed using the Kaplan-Meier actuarial method, and comparisons between groups were obtained with the log-rank statistic. All calculations were performed with StatView 5.0 (SAS institute Inc., Cary, NC). A probability of P <0.05 was considered statistically significant.

Results
Over a follow-up period of 51 months, a documented angiographic stent thrombosis occurred in 52 (1.4%) patients, 16 (1.3%) with a DES and 36 (1.6%) with a BMS. The rates of acute (n=3, 0.1% versus n=2, 0.2%), subacute (n=24, 1% versus n=9, 0.7%), late (n=5, 0.2% versus n=2, 0.2%) and very late thrombosis (n=4, 0.2% versus n=3, 0.2%) were similar in patients with BMS or DES thrombosis.

The baseline characteristics of patients with and without stent thrombosis are listed in table 1. Stent thrombosis was more frequent in men (P<0.04), in patients with a previous myocardial infarction (P<0.0001), with clinical left ventricular failure before the initial PCI (P<0.0001), initial
PCI for acute myocardial infarction (P<0.0001), balloon dilatation before stenting (P<0.04), smaller diameter stents (P<0.02), and multivessel PCI (P<0.0001).

The baseline characteristics of patients with BMS or DES thrombosis are compared in table 2. Eleven (21%) cases of BMS (n=8) or DES (n=3) thrombosis arose soon after antiplatelet therapy was interrupted. Most of the predictive factors for stent thrombosis, including male sex, prior myocardial infarction, prior left ventricular failure and balloon dilatation prior to stenting, were encountered similarly with BMS and DES (table 2). Initial PCI for a bifurcation lesion and initial PCI with more than one stent were more frequent in patients with a DES thrombosis, whereas initial PCI for acute myocardial infarction was performed more frequently in patients with a BMS thrombosis (table 2). Peak concentrations of creatinine kinase and troponin following stent thrombosis, as well as those of inflammatory markers, did not differ between the two groups (table 3).

Thirteen (25%) of the 52 patients with a stent thrombosis died within a few hours of the thrombotic event. A total of 27 (52%) major adverse cardiac events occurred within 18 months: 16 deaths (31%), 7 repeat PCIs, and 4 non-fatal myocardial infarctions. The composite outcome (death, recurrent stent thrombosis, myocardial infarction, repeat revascularization) was also similar 18±6 months after BMS or DES thrombosis (44% versus 55%, P=NS; table 3 and figure 1). Most events occurring after 4 months were related to a repeat revascularization procedure in patients with a BMS thrombosis. Overall, at the end of follow-up, 17 (33%) patients died after a stent thrombosis.

Factors predictive of survival in univariate analysis were direct stenting during the first PCI (66% versus 35%, P<0.04) and the upper level of fibrinogen after stent thrombosis (4.9±1.6 g/L versus 6.1±2.3 g/L, P<0.04). There was a trend towards a lower rate of previous myocardial infarction (47% versus 74%, P=0.06) and a higher concentration of creatinine kinase after stent thrombosis (3 629 versus 1667 IU/L, NS: non-significant.

### Table 2 Baseline characteristics and procedural data according to type of stent thrombosis.

<table>
<thead>
<tr>
<th></th>
<th>DES thrombosis (n=16)</th>
<th>BMS thrombosis (n=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)±SD</td>
<td>57±15</td>
<td>62±14</td>
<td>NS</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>14 (88)</td>
<td>34 (94)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (37)</td>
<td>14 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>28 (54)</td>
<td>1799 (51)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>7 (44)</td>
<td>20 (56)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>8 (50)</td>
<td>26 (72)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>1 (6)</td>
<td>5 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial PCI for acute MI, n (%)</td>
<td>5 (31)</td>
<td>23 (64)</td>
<td>0.03</td>
</tr>
<tr>
<td>Initial PCI for bifurcation lesion, n (%)</td>
<td>6 (37)</td>
<td>4 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Initial multivessel PCI, n (%)</td>
<td>13 (81)</td>
<td>11 (31)</td>
<td>0.03</td>
</tr>
<tr>
<td>Initial PCI with &gt;1 stent, n (%)</td>
<td>10 (62)</td>
<td>12 (33)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stent diameter (mm)±SD</td>
<td>2.9±0.3</td>
<td>2.9±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>24±8</td>
<td>19±7</td>
<td>0.06</td>
</tr>
<tr>
<td>Direct stenting, n (%)</td>
<td>7 (44)</td>
<td>22 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Antiplatelet discontinuation, n (%)</td>
<td>3 (19)</td>
<td>8 (22)</td>
<td>NS</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; NS: non-significant; PCI: percutaneous coronary intervention; SD: standard deviation.

### Table 3 Biological characteristics and clinical events according to type of stent thrombosis.

<table>
<thead>
<tr>
<th></th>
<th>DES thrombosis</th>
<th>BMS thrombosis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin, μg/L</td>
<td>82±89</td>
<td>158±457</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine kinase, IU/L</td>
<td>1790±1646</td>
<td>2443±4168</td>
<td>NS</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>31±49</td>
<td>43±63</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.7±1.6</td>
<td>5.5±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Long-term follow-up (18±6 months), n (%)</td>
<td>6 (37)</td>
<td>11 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>6 (37)</td>
<td>11 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrent stent thrombosis</td>
<td>1 (6)</td>
<td>4 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-fatal reinfarction</td>
<td>1 (6)</td>
<td>3 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>1 (6)</td>
<td>8 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>7 (44)</td>
<td>20 (55)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: non-significant.
Survival rates (A) after BMS or DES thrombosis, and (B) without major cardiac events after BMS or DES thrombosis.

P=0.08) in patients who died. Multivariable analysis identified no independent predictors of death after stent thrombosis.

**Discussion**

Stent thrombosis remains a rare but dramatic event. Timing of stent thrombosis, clinical, angiographic and procedural characteristics, and clinical outcomes appear similar irrespective of whether a DES or BMS is used. Interruption of antiplatelet therapy was encountered in a similar percentage of cases in those with a DES or BMS thrombosis. To our knowledge, this is the first clinical study comparing the characteristics and outcomes of documented angiographic stent thrombosis according to type of stent used.

Some reports have warned of a possible increase in the risk of stent thrombosis after implantation of DES in comparison with BMS [6,7]. Despite this fear and theoretical concerns that DES could be associated with a higher rate of stent thrombosis, the rates of stent thrombosis for DES have been shown to be similar to those for BMS [3-5,8-14]. More recently, attention has focused on late stent thrombosis, especially with DES [6,7]. Late stent thrombosis after implantation of sirolimus- and paclitaxel-eluting stents has been reported up to 17 months [15]. Late stent thrombosis may also occur when patients are stable on single antiplatelet therapy [16]. However, it is difficult to compare the incidence of late stent thrombosis reported in the DES era from that reported in the BMS era due to the paucity of published reports. For example, a pooled analysis of multicentre coronary stent clinical trials demonstrated in 2001 that stent thrombosis occurred in <1.0% of patients undergoing bare-metal stenting of native coronary artery lesions, but this analysis - like others - was limited to stent thrombosis occurring within 30 days after implantation [13]. A single-centre registry study reported a late stent thrombosis incidence of 0.76% with BMS, which is similar to the figure reported with DES [17]. Several mechanisms of late stent thrombosis have been postulated. Farb et al reported pathological descriptions and showed that stenting across branch ostia, disruption of adjacent vulnerable plaques, and extensive plaque prolapse can precipitate late stent thrombosis. They stated that late stent thrombosis has probably been under-recognized clinically in the BMS era [18]. According to an interesting study on angiographic patterns of restenosis, occluded in-stent restenosis occurred in 7% of cases [19]. In-stent restenoses with total occlusion are difficult to distinguish from late stent thrombosis. Even if thrombotic occlusion of the stent up to 2 years after implantation has been described without platelet treatment discontinuation [20], less attention has been paid to late stent thrombosis before the expansion of coated stents. Another study, in which 10 (20%) patients developed a stent thrombosis, has drawn attention to the fact that late stent thrombosis can occur after aspirin withdrawal in patients with a BMS [21]. Hence, the true incidence of late stent thrombosis with BMS in the “real world” remains unclear.

In a large cohort of consecutive patients undergoing DES implantation, premature discontinuation of antiplatelet therapy was the most important predictor of stent thrombosis. Other key predictors were renal failure, diabetes and low ejection fraction [22]. In our study, previous myocardial infarction, left ventricular failure and PCI for acute myocardial infarction were more often encountered in patients with stent thrombosis. Multivessel stenting and balloon dilatation before stenting were also more frequent in patients with stent thrombosis. Discontinuation of antiplatelet therapy was demonstrated in 21% of cases and was associated with both DES and BMS stent thrombosis. Baseline characteristics of patients with and without stent thrombosis show similar predictive factors for stent thrombosis with these devices, except multivessel PCI, which was more common among patients with a DES. This finding concurs with recent data showing the high occurrence of stent thrombosis among patients treated with DES for multivessel disease [23].

**Timing of stent thrombosis**

Thirty-eight (1%) cases of stent thrombosis occurred within a month of stent implantation and 14 (0.4%) occurred after 4 weeks (i.e. “late” stent thrombosis). This higher rate of stent thrombosis during the first month is in accordance with a previous report by Ong et al, in which the rate of acute/subacute stent thrombosis was higher than that for late stent thrombosis (mean follow-up of 1.5 years) (1.0% versus 0.35%, n=2006) [16].

In the present study, the proportion of late stent thrombosis versus other stent thrombosis appears similar with DES (5/16, 31%) and BMS (9/36, 25%). This is in agreement with recent data showing that DES implantation is not associated with a higher rate of stent thrombosis than with BMS, especially if patients adhere to the recommended dual antiplatelet therapy regimen [3-5, 24]. However, in a pooled analysis of four randomized trials including 5261 patients with a follow-up of 4 years, stent thrombosis after
Characteristics and prognosis of patients with angiographic stent thrombosis

1 year was more common with DES than with BMS, with five stent thromboses in patients with sirolimus-eluting stents versus none in patients with BMS, and nine episodes in patients with paclitaxel-eluting stents versus two in patients with BMS [6].

Presentation and follow-up

Cardiac death occurred in one-third of patients, mainly in the first few hours following stent thrombosis, and a major adverse cardiac event occurred by 18 months in more than half of the patients. These findings are in agreement with the known clinical consequences for patients with stent thrombosis, including short-term mortality rates of up to 25% [13]. In our series, no significant difference in terms of outcome according to the type of stent was noted, and no independent predictive factors for cardiac death after stent thrombosis were identified.

Limitations

This report is confined to patients who presented with acute symptoms and angiographically proven stent thrombosis (“definite” stent thrombosis according to the ARC definition). The data allow us to compare the timing of thrombosis, characteristics and clinical outcomes of patients with stent thrombosis according to the type of stent - BMS or DES. Patients with “probable” or “possible” stent thrombosis (corresponding to unexplained death within 30 days or more than 30 days after initial PCI) were excluded. The cohort represents 3 527 consecutive patients from a single centre who underwent BMS or DES implantation. Subclinical stent thrombosis may have occurred in some patients but remained undetected. Conversely, sudden deaths related to stent thrombosis were not taken into account.

Conclusions

In our centre, BMS and DES angiographic thrombosis (“definite”) are very similar in terms of the timing of thrombosis, clinical, angiographic and procedural characteristics, and clinical outcomes, with the same risk of late thrombosis after interruption of antiplatelet therapy in patients with DES or BMS.

References