
**Drug-Eluting Stent Thrombosis: Results From the Multicenter Spanish Registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivos)**

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# Drug-Eluting Stent Thrombosis

## Results From the Multicenter Spanish Registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivos)

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**Objectives** This study sought to assess the incidence, predictors, and outcome of drug-eluting stent (DES) thrombosis in real-world clinical practice.

**Background** The DES thromboses in randomized trials could not be comparable to those observed in clinical practice, frequently including off-label indications.

**Methods** We designed a large-scale, nonindustry-linked multicentered registry, with 20 centers in Spain. The participant centers provided follow-up data for their patients treated with DES, reporting a detailed standardized form in the event of any angiography-documented DES-associated thrombosis occurring.

**Results** Of 23,500 patients treated with DES, definite stent thrombosis (ST) developed in 301: 24 acute, 125 subacute, and 152 late. Of the late, 62 occurred >1 year (very late ST). The cumulative incidence was 2% at 3 years. Antiplatelet treatment had been discontinued in 95 cases (31.6%). No differences in incidences were found among stent types. Independent predictors for subacute ST analyzed in a subgroup of 14,120 cases were diabetes, renal failure, acute coronary syndrome, ST-segment elevation myocardial infarction, stent length, and left anterior descending artery stenting, and for late ST were ST-segment elevation myocardial infarction, stenting in left anterior descending artery, and stent length. Mortality at 1-year follow-up was 16% and ST recurrence 4.6%. Older age, left ventricular ejection fraction <45%, nonrestoration of Thrombolysis In Myocardial Infarction flow grade 3, and additional stenting were independent predictors for mortality.

**Conclusions** The cumulative incidence of ST after DES implantation was 2% at 3 years. No differences were found among stent types. Patient profiles differed between early and late ST. Short-term prognosis is poor, especially when restoration of normal flow fails. (J Am Coll Cardiol 2008;51:986–90) © 2008 by the American College of Cardiology Foundation

Mortality rates, myocardial infarction, and stent thrombosis (ST) with drug-eluting stents (DES) in the combined analyses of multiple randomized trials are comparable to those observed with bare-metal stents (BMS), although patients included in these trials had a low risk profile (1,2).

Initial clinical practice registries provided data on thrombosis rates, frequently including off-label indications for DES. In these studies the incidence of stent thrombosis was around 1.3%, with a late thrombosis rate of 0.35% to 0.8% depending on the definitions applied, and different predictors for thrombosis were identi-

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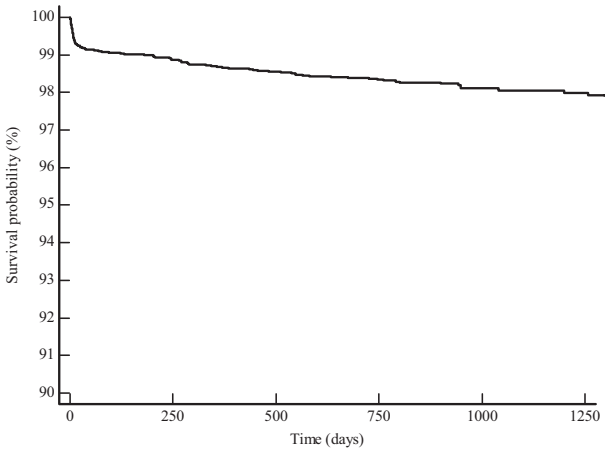


| Follow up time | 1 year | 2 years | 3 years |
|---|---|---|---|
| Cumulative incidence (100 minus survival) | 1.2% | 1.6% | 2% |
| Patients at risk | 17040 | 11180 | 4110 |

**Figure 1** **Cumulative Incidence of ST**

A Kaplan-Meier curve shows the survival free of definite stent thrombosis (ST) for the overall cohort and the subsequent cumulative incidence of ST. This incidence was 1.2%, 1.6%, and 2% at 1, 2, and 3 years, respectively.

fied (3–6). Nevertheless, there is a paucity of data on the magnitude of DES-associated thrombosis in standard cardiology practice, its incidence years after implantation, and the predisposing factors, specifically for late ST.

The current study was designed as a multicenter industry-independent registry with the aim of resolving these areas of doubt regarding DES thrombosis in real-world cardiology practice.

## Methods

This is an industry-independent prospective registry. All coordination between the 20 participating centers across Spain, the adjudication process, and analyses were performed centrally at the Hospital Universitario Marques de Valdecilla in Santander.

**Patient selection.** Since the introduction of DES in Spain in June 2002, its penetration has increased from 5% in 2002 to 59% in 2006 and has varied widely in different centers (7). All of the participating centers were required to fill in a detailed standardized form in the event of any angiographically-documented DES-associated thrombosis occurring since the introduction of DES. Patients gave informed consent for the inclusion of their data in the registry, and anonymity was guaranteed.

**Definitions.** Stent thrombosis was considered to have occurred when confirmed by angiography: either Thrombolysis In Myocardial Infarction flow grade 0 or 1 or the presence of flow-limiting thrombus (Thrombolysis In Myocardial Infarction flow grade 1 or 2) occurring at any time after stent implantation. Acute coronary syndrome would need to have been present for those cases with ST >1 month post-procedure. This was defined as the presence of at least 1 of the following: new onset of typical chest pain at rest >20 min, new acute ischemic electrocardiographic changes, or typical rise and fall in cardiac biomarkers.

**Abbreviations and Acronyms**

**BMS** = bare-metal stent(s)
**DES** = drug-eluting stent(s)
**LAD** = left anterior descending artery
**PES** = paclitaxel-eluting stent(s)
**SES** = sirolimus-eluting stent(s)
**ST** = stent thrombosis
**STEMI** = ST-segment elevation myocardial infarction

**Follow-up.** Clinical follow-up data were obtained from the hospital registries and medical records in which the data from the scheduled visits of patients, hospital admissions, and procedural reports are collected. The appropriate medical records and discharge summaries were solicited for patients who had suffered events at another hospital.

**Statistical analysis.** Continuous variables are presented as mean ± standard deviation or as median followed by 25th to 75th percentile. Categorical variables are expressed as percentages. Continuous variables were compared with the Student *t* test if the data followed a normal distribution and with Wilcoxon tests if the data were skewed. Categorical variables were compared with the chi-square square test or the Fisher exact test where indicated. We planned ahead to perform a multivariate analysis in a subgroup within the total cohort of patients (at least from 6 centers). Multivariate analyses were done

**Table 1** **Clinical, Angiographic, and Procedural Characteristics of Patients With and Without Documented ST**

| | No ST (n = 23,199) | ST (n = 301) | p Value |
|---|---|---|---|
| Age, yrs | 63 ± 11 | 60.4 ± 12 | <0.0001 |
| Female | 5,568 (24%) | 71 (23.6%) | 0.92 |
| Diabetes | 6,964 (30%) | 93 (30.8%) | 0.81 |
| Hypertension | 10,790 (46.5%) | 148 (49.2%) | 0.38 |
| Hypercholesterolemia | 10,555 (45%) | 145 (48.2%) | 0.29 |
| Renal failure | 696 (3%) | 15 (5%) | 0.06 |
| LVEF, % | 57 ± 11 | 50.9 ± 12 | <0.0001 |
| ACS | 13,306 (57.4%) | 247 (82%) | <0.0001 |
| STEMI | 2,540 (11%) | 112 (37.2%) | <0.0001 |
| LAD lesion | 11,656 (50.3%) | 220 (73%) | <0.0001 |
| Total occlusion | 2,313 (10%) | 63 (21%) | <0.0001 |
| Restenosis | 1,855 (8%) | 26 (8.6%) | 0.74 |
| Bifurcation (2 stents) | 694 (3%) | 13 (4.3%) | 0.25 |
| Stent length, mm | 20 ± 7 | 25.3 ± 14.6 | <0.0001 |
| Stent diameter, mm | 2.94 ± 0.3 | 2.83 ± 0.36 | <0.0001 |
| Abciximab | 3,424 (14.8%) | 80 (26.5%) | <0.0001 |
| Number of lesions treated per patient | 1.45 ± 0.7 | 1.53 ± 0.8 | 0.049 |

Values are mean ± standard or n (%).

ACS = acute coronary syndrome; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; ST= stent thrombosis; STEMI = ST-segment elevation myocardial infarction.

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**Table 2** Characteristics of the Patients With Acute/Subacute and Late ST

| | Acute/Subacute ST (n = 149) | Late ST (n = 152) | p Value |
|---|---|---|---|
| Age, yrs | 62.5 ± 11 | 58.4 ± 13 | 0.003 |
| Female | 45 (30%) | 26 (17%) | 0.011 |
| Diabetes | 60 (40%) | 33 (21.7%) | 0.0009 |
| Renal failure | 11 (7.4%) | 4 (2.6%) | 0.099 |
| Hyperlipidemia | 64 (43%) | 81 (53.3%) | 0.10 |
| Hypertension | 79 (53%) | 69 (45.4%) | 0.20 |
| ACS | 127 (85%) | 120 (79%) | 0.22 |
| STEMI | 57 (38%) | 55 (36.2%) | 0.80 |
| EF | 50 ± 12 | 51.7 ± 11 | 0.21 |
| Restenosis | 12 (8%) | 14 (9.2%) | 0.86 |
| Total occlusion | 26 (17.4%) | 37 (24.3%) | 0.17 |
| Bifurcation (2 stents) | 9 (6%) | 4 (2.6%) | 0.24 |
| LAD | 107 (72%) | 113 (74.3%) | 0.79 |
| Multiple lesions treated | 45 (30%) | 57 (37.5%) | 0.21 |
| Abciximab | 34 (23%) | 46 (30.2%) | 0.19 |
| Stent length | 25.8 ± 14 | 24.8 ± 14 | 0.52 |
| Stent diameter | 2.79 ± 0.3 | 2.87 ± 0.38 | 0.044 |
| Suboptimal result* | 39 (26%) | 16 (10.5%) | 0.0008 |
| Stent underexpansion | 29 (19%) | 14 (9.2%) | 0.022 |
| Median time to stent thrombosis | 6 (2 to 10) | 287 (168 to 552) | |

Values are presented as mean ± standard deviation, n (%), or median (interquartile range). *Any of the following: stent underexpansion noted by angiography defined as in-stent residual stenosis >10%; final Thrombolysis In Myocardial Infarction flow grade <3; noncovered dissection at stent margins; significant disease in the adjacent reference segments defined as a stenosis >25%.
EF = ejection fraction; other abbreviations as in Table 1.

using those variables with $p < 0.25$ in the univariate analysis, but variable of antiplatelet therapy discontinuation was not included because the data were not available for all cases without ST. A stepwise Cox proportional hazards model was used to identify independent predictors of mortality and recurrent thrombosis after the ST event. Kaplan-Meier survival curves analyses were used to show the cumulative incidence of ST and in comparing mortality and recurrent thrombosis of late versus early events. All probability values were 2-sided, and values of $p < 0.05$ were considered statistically significant. The statistical package SPSS 11.0 (SPSS Inc., Chicago, Illinois) was used throughout.

## Results

Between June 2002 and January 2007, a total of 23,500 patients were treated with 34,075 DES: 37% with sirolimus-eluting stents (SES) and 63% with paclitaxel-eluting stents (PES) in 20 centers. With a median follow-up of 22 months (11 to 32, 25th percentile and 75th percentile, respectively), 301 patients (1.28%) had documented ST: 24 (8%) were acute (<24 h), 125 (41.5%) were subacute (24 h to 30 days), 90 (30%) were late (1 month to 12 months), and 62 (20.6%) were very late (>1 year). Figure 1 shows the cumulative survival free of ST. Cumulative incidence at 3 years was 2% without differences between stent types (1.97% for PES and 2.03% for SES; $p = 0.8$). The clinical characteristics of the groups with and without thrombosis are described in Table 1. The clinical and procedural characterization of the ST types are summarized in Table 2. Compared with the acute/subacute ST, the cases with late ST were younger men, with a lower incidence of diabetes, with larger vessels and less frequent suboptimal angiographic outcomes. Antiplatelet treatment at the time of the event is presented in Table 3. At discharge from hospital, the duration of combined antiplatelet therapy was 8 ± 3 months. Overall, 95 patients (31.6%) were not taking the prescribed antiplatelet therapy. The reason for treatment cessation was bleeding in 12 patients, surgical intervention in 11, allergic reaction to antiplatelet drugs in 6, and noncompliance in 66 patients. Among those with late ST, 70 patients had ST after properly completing the dual antiplatelet treatment period, a median time of 6.3 months (3 to 15.8 months) after discontinuation of clopidogrel, and only 5 (7.1%) within the first month.

Multivariate analysis was performed in a subgroup of 14,120 patients (Table 4). This subgroup was comparable in all analyzed characteristics to the overall cohort. The independent predictors for acute/subacute thrombosis were acute coronary syndrome, ST-segment elevation myocardial infarction (STEMI), renal failure, stent in left anterior descending artery (LAD), stent length, and diabetes and for late thrombosis were STEMI, stent in LAD, and stent length.

**Table 3** Antiplatelet Treatment at the Time of ST

| Antiplatelet Administered | Acute/Subacute ST (n = 149) | Late ST (n = 90) | *p Value | Very Late ST (n = 62) | †p Value | ‡p Value |
|---|---|---|---|---|---|---|
| ASA + clopidogrel | 110 (74%) | 20 (22%) | 0.001 | 5 (8%) | 0.038 | 0.0001 |
| ASA alone | 15 (10%) | 54 (60%) | 0.001 | 43 (69.3%) | 0.32 | 0.0001 |
| Clopidogrel alone | 11 (7.4%) | 3 (3.3%) | 0.30 | 3 (4.8%) | 0.96 | 0.69 |
| Coumadin | 0 | 1 (1.1%) | 0.80 | 1 (1.6%) | 0.64 | 0.65 |
| No antiplatelet therapy | 11 (7.4%) | 11 (12.2%) | 0.31 | 10 (16.1%) | 0.66 | 0.094 |
| Early dual therapy cessation | 38 (25.5%) | 30 (33.3%) | 0.25 | 5 (8%) | 0.0006 | 0.007 |
| Cessation of ASA monotherapy | 0 | 7 (7.7%) | 0.002 | 15 (24.2%) | 0.009 | 0.0001 |

Values are presented as n (%). Early dual therapy cessation was the discontinuation of clopidogrel and/or ASA within the prescribed dual-therapy period; cessation of ASA monotherapy was the discontinuation of ASA once the prescribed dual-therapy period had passed. *Acute/subacute versus late. †Late versus very late. ‡Acute/subacute versus very late.
ASA = aspirin; other abbreviations as in Table 1.

**Table 4** Multivariate Analysis for Predictors of ST in a Subgroup of 14,120 Patients

| Predictor | Hazard Ratio | 95% Confidence Interval | p Value |
|---|---|---|---|
| Acute-subacute ST | | | |
| ACS | 2.6 | 1.3–4.9 | 0.0027 |
| STEMI | 6.9 | 4–12 | <0.0001 |
| Renal failure | 3.1 | 1.05–9.2 | 0.038 |
| Diabetes | 1.75 | 1.04–2.95 | 0.035 |
| Stent length | 1.08 | 1.06–1.1 | 0.0001 |
| LAD | 2.2 | 1.4–3.7 | 0.0011 |
| Late ST | | | |
| STEMI | 5.2 | 5.5–7.6 | <0.0001 |
| LAD | 3.03 | 2.07–4.4 | <0.0001 |
| Stent length | 1.07 | 1.05–1.09 | <0.0001 |

Abbreviations as in Table 1.

Table 5 summarizes the treatment and outcomes comparing the groups with acute/subacute and late ST. The Kaplan survival analysis for the combined end point of death and recurrent thrombosis did not show significant differences between the groups (hazard ratio 1.2, 95% confidence interval 0.74 to 2.05, p = 0.4). The independent predictors for mortality and thrombosis recurrence after the ST event are shown in Table 6.

## Discussion

The use of DES in cardiology practice has been extended and frequently includes off-label indications. Hence, the incidence of ST in real-world practice is not the same as that observed in the trials. Iakovou et al. (3) found a 1.3% rate in 2,229 patients. The group from Rotterdam reported 1% and 0.35% rates for angiographic subacute and late ST, respectively (4,5). The group from the Washington Hospital Center observed a rate of 1.27% in 2,794 patients with renal failure, bifurcation, in-stent restenosis, and clopidogrel discontinuation as independent predictors (6). Finally, the Bern-Rotterdam registry yielded a cumulative incidence of 2.9% at 3 years in 8,146 patients (8). Diabetes and acute coronary syndrome were identified as independent predictors.

**Table 6** Independent Predictors for Mortality and Recurrent Thrombosis

| Predictor | Hazard Ratio | 95% Confidence Interval | p Value |
|---|---|---|---|
| Predictors of mortality | | | |
| Post-PCI TIMI flow grade <3 | 13 | 4.3–39 | 0.0001 |
| Age | 1.09 | 1.04–1.15 | 0.0001 |
| New stent | 4.04 | 1.36–12 | 0.012 |
| LVEF <45% | 2.66 | 1.01–7 | 0.047 |
| Predictors of recurrent thrombosis | | | |
| Abciximab administration | 0.17 | 0.04–0.65 | 0.018 |
| New stent | 5.08 | 1.07–24 | 0.040 |

LVEF = left ventricular ejection fraction; other abbreviations as in Table 5.

**Predictors for late ST.** Similar to our results, the registries cited above noted that early discontinuation of antiplatelet therapy was a relatively common finding in patients with late ST (3–6,8). The association of STEMI with late ST has been noted in other clinical registries. The Rotterdam group reported a 2-year incidence of 3.2% for angiographic thrombosis in 812 STEMI patients treated with DES (9). Conversely, the recently published randomized trials showed no differences in thrombosis at 1 year between BMS and DES (10,11).

The LAD stent location had been observed, well over a decade ago, as a predictor for ST (12). A review of all

**Table 5** Clinical Presentation, Treatment, and Outcome

| | Overall Sample (n = 301) | Acute/Subacute ST (n = 149) | Late ST (n = 152) | p Value |
|---|---|---|---|---|
| Presentation | | | | |
| STEMI | 252 (83.7%) | 128 (86%) | 124 (81.5%) | 0.36 |
| Shock | 62 (20.5%) | 31 (21%) | 31 (20.4%) | 0.98 |
| Basal TIMI flow grade 0 to 1 | 265 (88%) | 137 (92%) | 128 (84.2%) | 0.056 |
| Treatment | | | | |
| PCI | 283 (94%) | 145 (97%) | 138 (90.7%) | 0.042 |
| Thrombectomy | 110 (39%) | 44 (30%) | 66 (47.8%) | 0.002 |
| New stent | 139 (49%) | 70 (48%) | 69 (50%) | 0.82 |
| Abciximab | 187 (66%) | 99 (68%) | 88 (63.7%) | 0.50 |
| Post-PCI TIMI flow grade 3 | 238 (84%) | 126 (87%) | 112 (81.1%) | 0.20 |
| Outcome | | | | |
| In-hospital | | | | |
| Death | 35 (11.6%) | 20 (13%) | 15 (9.8%) | |
| Thrombosis | 5 (1.66%) | 4 (2.7%) | 1 (0.66%) | |
| Follow-up | 261 (98%) | 128 (99%) | 133 (97%) | |
| Time, months | 11.8 ± 10 | 15 ± 11 | 8.8 ± 7.6 | |
| Death | 48 (16%) | 28 (18.8%) | 20 (13.1%) | |
| Thrombosis | 14 (4.6%) | 9 (6%) | 5 (3.3%) | |

Values are mean ± standard deviation or n (%).
PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

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published case reports of late stent thrombosis shows that 74% of them had had DES implanted in the LAD artery (13). The LAD location in our study was frequently associated with a recent history of infarction in this territory.

**DES versus BMS thrombosis.** Our registry uses angiographic documentation of ST and certainly underestimates the real incidence of ST. The overall incidence of DES-associated documented thrombosis results are slightly higher than reported previously with BMS (14,15). A rate of 0.6% to 0.8% for late-onset thrombosis with BMS has been reported (16); however, these events occurred very exceptionally >12 months post-procedure in the absence of prior brachytherapy.

**Treatment and clinical outcome.** The implantation of an additional stent was associated with an adverse outcome, whereas the infusion of abciximab reduced the recurrence of ST episodes. The use of new stents should be restricted to those with significant residual stenosis after balloon dilatation or with stent-edge dissections. The use of intravascular ultrasound could identify predisposing mechanical factors and could help guide interventions. In fact, detailed intravascular ultrasound studies of 12 of these patients with confirmed DES thrombosis have been previously reported (17).

**Study limitations.** This is the largest registry available to date addressing DES thrombosis; however, several limitations should be noted. The study is observational in nature and has inherent disadvantages. This is a registry of angiographically documented (definite) thrombosis, and as such, the rates of DES are underestimated. The ST incidence would have been closer to reality if we had included probable and possible ST cases (18). However, we felt that clear, clinical, angiographic and procedural characteristics of ST patients were appropriate in defining the profile and variables associated. The multivariate analysis was conducted in a subgroup of patients within the overall cohort; nevertheless, this was a clearly representative group, being the largest multivariate analysis available to date in the literature. Finally, as in other registries (8), it was not possible to ascertain retrospectively the compliance with antiplatelet treatment in patients without ST.

## Conclusions

In this multicenter registry of DES, the cumulative incidence of angiographically documented stent thrombosis was 2% at 3 years. No differences were found between paclitaxel-eluting and sirolimus-eluting stents. The profiles of patients with early and late thrombosis were different. The short-term prognosis is poor, especially when the restoration of normal flow has failed.

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