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**INCIDENCE AND PREDICTORS OF DRUG-ELUTING STENT THROMBOSIS DURING AND FOLLOWING DISCONTINUATION OF THIENOPYRIDINE TREATMENT**

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Abstract **(237 words)**

**Background -** The need for prolonged aspirin and thienopyridine therapy and the risk of stent thrombosis (ST) remain drawbacks associated with drug-eluting stents.

**Methods -** Prospective observational cohort study conducted between June 2002 and January 2004. Detailed patient information was collected on antiplatelet therapy. We analyzed the incidence of ST throughout the 18 month follow-up period and its relationship with thienopyridine therapy.

**Results -** A total of 3021 patients, all successfully and consecutively treated in 5389 lesions with drug-eluting stents were followed for 18 months. ST occurred in 58 patients (1.9%) at 18 months. Forty-two patients (1.4 %) experienced the event within 6 months of stent implantation. Acute myocardial infarction (fatal or non-fatal) occurred in 46 patients (79%) and death in 23 patients (39%) with ST. The median interval from discontinuation of thienopyridine therapy to ST was 13.5 days (IQR, 5.2-25.7) for the first 6 months and 90 days (IQR, 30-365) between 6 and 18 months. On multivariable analysis the strongest predictor for ST within 6 months of stenting was discontinuation of thienopyridine therapy (HR, 13.74; 95% CI, 4.04 to 46.68; P<0.001). Thienopyridine discontinuation after 6 months did not predict the occurrence of ST (HR, 0.94; 95% CI, 0.30 to 2.98; P=0.92).

**Conclusions -** Discontinuation of thienopyridine therapy was the major determinant of ST within the first 6 months but insufficient information is available to determine if there is benefit in continuing a thienopyridine beyond 6 months.

**Key words**: stents, thrombosis, thienopyridine, coronary disease

## Introduction

Drug eluting stents (DES) have significantly reduced the rate of restenosis and the need for repeat revascularizations in comparison to bare metal stents (BMS).[1-5] The implantation of DES has been extended to populations with different clinical and anatomic characteristics from those enrolled in the pivotal trials.[6-10] Although their efficacy in reducing neointimal hyperplasia and clinical restenosis has been maintained in a broad spectrum of clinical conditions, there is an emerging safety concern regarding the risk of stent thrombosis (ST) motivated by a number of reports of late ST in real world patients particularly after the discontinuation of double antiplatelet therapy.[11-13] To date, the incidence and predictors of ST have been evaluated during relatively short follow-up periods, limited to 6-12 months[14-16] and few data are available about ST occurring more than one year after DES implantation. Furthermore, dual antiplatelet therapy to prevent ST has been recommended in the first 3-6 months following DES implantation,[17] but no information is available on its utility over a longer period. While prior studies established that discontinuation of double antiplatelet therapy represents an important risk factor for ST,[14,18,19] little is known about the incidence of ST in patients who continue thienopyridine treatment beyond six months after stenting compared to patients who receive only aspirin. This uncertainty has prevented physicians from establishing the appropriate duration of dual antiplatelet therapy after DES implantation. The present study was conducted with the objective of evaluating the incidence and predictors of ST following successful DES implantation in an unselected population, and to establish the role of double antiplatelet therapy in preventing this adverse event.

## METHODS

The primary endpoint of this prospective observational cohort study was the incidence of ST in patients who received DES. The event and its relationship with thienopyridine were evaluated throughout the 18 months follow-up period. Between June 2002 and January 2004, a total of 6320 patients underwent percutaneous intervention. Among them, we identified 3021 consecutive patients who underwent successful implantation of sirolimus-eluting stents (SES, Cypher, Cordis a Johnson and Johnson Company, Miami Lakes, FL) or paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA). Patients were treated at 3 hospitals in Italy and in one in Germany. All 4 centers involved used exactly the same database and the same definition for risk factors and clinical events. Patients at risk for early discontinuation of double antiplatelet therapy and patients with lesions at low risk for restenosis (large vessels with a short lesion) were treated with BMS. The decision to implant a specific DES was at the discretion of the operator. Only patients with successful DES implantation defined as <20% residual stenosis in the stented segment in the presence of grade 3 Thrombolysis In Myocardial Infarction (TIMI) flow, were considered in the present analysis.[17] Patients with ST-elevation acute myocardial infarction (MI) less than 48 hours before the procedure were excluded because it is not the practice of these institutions to implant DES in patients with MI. All patients were pre-treated with ticlopidine or clopidogrel and aspirin. A loading dose of 300 mg of clopidogrel was given to patients not previously treated with thienopyridines. Aspirin was continued indefinitely and clopidogrel or ticlopidine for at least 3 months after SES implantation and for at least 6 months after PES implantation. Stent implantation methods have been described previously.[20] Glycoprotein IIb/IIIa receptor inhibitors were administered at the physician's discretion. Standard qualitative and quantitative analyses and definitions were used for the angiographic analysis.

Informed consent was obtained from all patients and local institutional review boards approved the study protocol.

**Follow-up and Definitions**

Follow-up data were collected at 30 days, 180 days, 360 days and 540 days after the index procedure either at the time of scheduled clinical visits or by telephone contact. At the time of follow-up contact, data were collected pertaining to patients' clinical status, antiplatelet drug therapy, and interim occurrence of any adverse events. Specifically, patients were asked if they were taking aspirin, ticlopidine or clopidogrel; how many tablets they were taking and how long they were taking them for. If any antiplatelet medication was discontinued, a detailed attempt was made to time this action. In cases of doubt or uncertainty, referring cardiologists or general practitioners were contacted for additional information. Major adverse cardiac events (MACE) include all cause death, MI and repeat revascularization. MI was defined according to current guidelines.[21] Repeat revascularizations were classified as target lesion re-interventions inside the implanted stent or within 5 mm proximally or distally (TLR) or repeated interventions in the same vessel (TVR) by percutaneous coronary interventions (PCI) or by coronary artery bypass graft surgery.

Stent thrombosis (ST) was classified as subacute when it occurred from the end of the procedure up to 30 days, and late when it occurred beyond 30 days. Subacute ST was defined as the occurrence of one of the following events:

1) angiographic documentation of complete or partial stent occlusion with thrombus and target vessel related acute clinical ischemic event.
2) MI in the distribution of the stented vessel.
3) sudden cardiac death

Late ST was defined as the occurrence of one of the following events:

1) angiographic documentation of complete or partial stent occlusion and target vessel related acute clinical ischemic event.
2) autopsy documentation of complete or partial thrombotic stent occlusion
3) MI in the distribution of the stented vessel.

This definition of ST corresponds to the definite and probable definition proposed by the Academic Research Consortium.[22] We separately evaluated the incidence of possible ST by including all unexplained death after 30 days.

**Statistical methods**

A sample of 3000 observations permits the achievement of 80% power at a 2-sided 0.05 significance level to detect a hazard ratio (HR) equal to or greater than 2.5 with a Cox regression of the log HR on a binary risk factor with a 20% or greater prevalence. This power calculation was based on an anticipated event rate of 2%. Categorical variables are presented as raw numbers and percentages and were compared using the $\chi^2$ test or Fisher exact test. Continuous variables are presented as mean ± 1 standard deviation and were compared using the students *t* test. Relationship of thrombosis incidence to the time of antiplatelet therapy discontinuation was initially investigated by means of a stratified Cox regression with two time-dependent covariates (thienopyridine administration during the first 6 months and after 6 months of follow-up) and the following stratification factors: Center, Stent type, Baseline risk status (defined as patients with use of an intra-aortic balloon pump and/or treatment with glycoprotein IIb/IIIa inhibitors and/or family history of coronary artery disease), and Age (≤60, 60-75, >75). Strata were identified based on both prior knowledge of their clinical relevance as confounding factors and preliminary assessment of their statistical association with thrombosis occurrence. Although a causation relationship between stent type and thrombosis cannot be excluded a priori, we treated stent type as a confounder because SES

and PES could have been selectively implanted according to physician preferences based on patient and lesion characteristics. With such manifest selection bias and with relatively few events, any effort to extrapolate the exact amount of risk ascribed to stent type (if any) becomes potentially misleading. Because of the poor predictive ability of this preliminary model, a decision to include more prognostic factors was taken. To accomplish this, a variable selection strategy was carried-out by adding several potential risk factors to the preliminary model one at a time and testing their individual statistical association with thrombosis incidence. The predictive robustness of these "univariate" findings was subsequently tested by means of a bootstrap subset selection method in which a saturated Cox regression analysis using a stepwise elimination process was repeated for each of 1000 bootstrap samples.[23] The relative frequency of selection of variables was used as a criterion to grade their relative "importance". The next step of the model-building process consisted in expanding the initial Cox regression by including further risk factors ranked for their importance and testing each augmented model in order to quantify the overfitting (slope shrinkage) using an internal bootstrapping validation process[24] in which the model was fitted to 1000 bootstrap samples. The final result of the model-building process consisted of the initial Cox regression augmented by 5 prognostic variables (left ventricular ejection fraction coded as ≤30% and >30%, brachytherapy, stent length, reference vessel diameter and final stent implantation pressure). The final model was characterized by a predictive value which had more then doubled when compared with the previous one and, although based on relatively few events, not substantially biased by overfitting. SAS version 9.1 (SAS Institute Inc, Cary, NC) was used for data analysis.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**RESULTS**

The population included 3021 patients treated for 5389 lesions with implantation of a SES in 2853 lesions (52.9%) and a PES in 2536 lesions (47.1%). SES and PES were used in different lesions in the same patient in 165 individuals. Tables 2 and 3 show the baseline clinical, angiographic and procedural characteristics. Complete 18-months follow-up was obtained in 3006 (99.5%) patients. The cumulative rate of angiographic follow-up during this study was 57%. During the follow-up period, 58 patients (1.9%) had ST and this was angiographically documented in 48 patients. Of the remaining 10 patients, 9 had sudden death within 30 days and 1 had a MI without angiographic documentation. Subacute ST occurred in 29 (0.9%) patients and in 20 (69%) of these occurred within 1 week from the procedure. Late ST occurred from day 31 to day 180 in 13 patients (0.4% of the total population); from day 181 to day 360 in 10 (0.3%) and from day 361 to day 540 in 6 (0.2%) patients. The median time of the occurrence of subacute ST was 4 days (interquartile range [IQR], 2-12); late ST occurred after a median period of 210 days (IQR, 119-307) from the index procedure. A detailed schematic of antiplatelet therapy, discontinuation and relation to ST is presented for each patient in Figure 1.

Tables 1 and 2 present the comparisons between patients who developed ST and the patients without ST. Renal failure, treatment with glycoprotein IIb/IIIa inhibitors, use of an intra-aortic balloon pump, and stent implantation in the left anterior descending artery were more frequent in patients who developed ST. Apart from stent length, there were no differences in baseline characteristics between patients who developed ST while on thienopyridines compared to those not on dual antiplatelet therapy at the time of ST (Table 3). Among our patients, 2023 (67%) had stents implanted for off–label indications. In these patients, the occurrence of subacute ST was 1.2% compared to 0.6% in patients with on-label indications (p=0.16), and late ST occurred in 1.0% and 0.9 % respectively (p=0.82).

The adverse events at 30 days and 18 months follow-up are presented in Table 4. The cumulative hierarchical MACE rate at 18 months was 19.9%. MI occurred in 5.3 % of patients and death in 3.7% (2.5 % cardiac death). Repeat revascularization was performed in 14.4% of patients during the follow-up period. Of the 58 cases of ST, 46 (79%) patients had an MI and 23 (39%) died.

**Relationship between antiplatelet therapy and ST**

The proportion of patients taking dual antiplatelet therapy and the incidence of stent thrombosis at 30, 180, 360, and 540 days is presented in Figure 2. After 6 months more than 50% of the patients were taking only aspirin and after 1 year 75% of the patients were taking only aspirin or no antiplatelet therapy. Continuation of thienopyridine therapy after 6 months was more common in males (84.6% on vs. 80.4% off; p=0.01), in patients previously treated with brachytherapy (1.2% on vs. 0.2% off; p=0.02), in patients with an history of previous MI (43.8% on vs. 37.3% off; p=0.005 ), previous bypass surgery (20.6% on vs. 13.6% off; p<0.001 ), previous PCI (39.7% on vs. 26.8% off; p<0.001 ), left main coronary artery stenting (7.4% on vs. 3.2% off; p<0.001), and procedures performed with intra-aortic balloon pump support (2.5% on vs. 1.1% off; p=0.04 ).

While the prevalence of stent thrombosis is higher in patients not taking dual antiplatelet therapy in the first 6 months, after 180 days there is an increasing proportion of patients with thrombosis while on dual antiplatelet therapy (Figure 2). Subacute ST occurred in 29 patients, with 26 (89%) during dual antiplatelet therapy. ST between 1-6 months occurred in 13 patients, with 8 (61%) of these occurring on dual antiplatelet therapy. ST between 6 - 18 months occurred in 16 patients, 9 (56%) taking dual antiplatelet therapy and 7 (44%) on aspirin only. In the first 6 months after DES implantation, the median time from discontinuation of clopidogrel and the occurrence of ST was 13.5 days (IQR, 5.2-25.7) while

after the first 6 months, the median interval was 90 days (IQR, 30-365). When we compared the clinical and lesion characteristics of the patients who sustained ST in the first 6 months following DES implantation to those who had ST after 6 months we only found differences between the 2 groups in age, male gender, hypertension and previous PCI (Table 3).

**Predictors of ST**

Table 5 presents the results of the univariate Cox regression analysis. The stratified multivariable Cox regression analysis (Table 6) found that the discontinuation of thienopyridine therapy was the major predictor of ST within the first 6 months after DES implantation (HR, 13.74; 95% confidence interval [CI] 4.04 to 46.68; P<0.001). Discontinuation of thienopyridine therapy after 6 months from DES implantation was not a predictor of ST (HR, 0.94; 95% CI, 0.30 to 2.98; P=0.92). This finding is graphically presented in Figure 3 which shows that event rates for patients with or without double antiplatelet therapy diverge in the first 6 months after DES implantation and then become similar after 6 months.

Among the baseline characteristics, prior brachytherapy (HR, 9.70; 95% CI, 2.99 to 31.44; P<0.001), and left ventricular ejection fraction ≤30% (HR, 3.72; 95% CI, 1.50 to 9.27; P=0.005) were predictors of ST. A smaller baseline reference vessel diameter (HR, 0.27 per mm increase; 95% CI, 0.06 to 1.13; P=0.07) showed a trend to being predictive of ST. Among the procedural variables, a higher final stent implantation pressure was protective against ST (HR, 0.39 per atmosphere increase; 95% CI, 0.18 to 0.85; P=0.02). A “per 10mm” increase in total stent length per lesion was associated with a significantly higher risk of ST (HR, 2.75; 95% CI, 1.55 to 4.88; P<0.001).

## DISCUSSION

This study analyzed a cohort of over three thousand patients who underwent successful DES implantation, and during a follow-up period of 18 months complete information about duration or cessation of double antiplatelet therapy was collected.

The main findings were:

1) The overall incidence of ST was 1.9%
2) Of patients that suffered ST, half the events occurred during the first 30 days from DES implantation
3) Discontinuation of dual antiplatelet therapy was the most powerful predictor of ST during the first 6 months after stent implantation
4) The risk of ST following discontinuation of thienopyridine treatment after 6 months, if present, seems to be small.

A cumulative 1.9% incidence of ST at 18 months is higher than that reported in the major randomized trials[25-27] or in large registries such as e-Cypher.[16] However, considering the longer follow-up, our rate of ST is comparable to other studies analyzing "real world" populations.[15,28] Unfortunately a precise comparison between different reports is quite difficult because of differences in the definitions applied, especially for late thrombosis. Unexplained death after 30 days occurred in 22 patients in our cohort. If similar to the BASKET-LATE study[29], we include these as possible ST the overall rate of ST in our study would be 2.6%. Eighteen of these deaths occurred after 6 months from stenting, making the rate of late ST (including possible ST) after 6 months 1.2%.

As already reported,[14,16] the severe consequences of this event are apparent, with death occurring in 39% of patients with ST. A very important finding stressing the relevance of other factors such as procedural variables was that 50% of the thrombotic events occurred in the first 30 days after DES implantation. This implies that improved implantation technique

and screening for antiplatelet resistance may have a role in reducing early ST. This may have even greater relevance when DES are implanted for off-label indications as there appears to be a trend to higher rates of ST among this more complex population only in the first 30 days following stent implantation. Unfortunately we do not have data regarding suboptimal stent implantation or antiplatelet resistance in patients who developed ST.

A novel and somewhat provocative finding of our study, contrary to a recent report,[30] is the different weight carried by double antiplatelet therapy in preventing ST in the first 6 months after DES implantation and thereafter. A possible explanation for such differences may be the fact that we obtained complete information about dual antiplatelet therapy in more than 99% of the patients, including the timing of thienopyridine therapy discontinuation. It is interesting to note the temporal relationship between discontinuation and thrombosis; prior to 6 months this is 13.5 days and after 6 months it is 90 days. This questions the temporal and causal link between discontinuation and thrombosis after 6 months and this finding is in agreement with the a recent small study.[29] In many pivotal studies and in some registries[16,26] the relationship between discontinuation of clopidogrel and development of late stent thrombosis is not completely clear. We prefer not to speculate about possible mechanisms for ST occurring after 6 months or about the benefits of extended dual antiplatelet therapy. In addition patients who continued thienopyridine therapy after 6 months from stenting appear to be a higher risk group pointing to a possible bias by the investigators toward extending dual antiplatelet therapy. Ultimately we do not really know if all these very late thrombotic events are really “DES failures” or due to the development of new vulnerable plaques inside a stent which did not allow the development of restenosis. Our findings should not deter physicians from continuing long term thienopyridine therapy in certain high risk patients in whom atherothrombotic protection has been shown beneficial.[31,32]

The main limitation of this report is the lack of randomization between patients who continued thienopyridine therapy and patients who stopped after 6 months. Despite this potential issue we should recognize that the clinical and procedural variables which could have unbalanced the groups were incorporated in the multivariable model. The lack of an independent event committee represents another limitation. Still each case of suspected ST was carefully reviewed by at least 4 physicians. The follow-up truncated at 18 months does not allow us to determine if there is a continuous risk of ST and its relationship to double antiplatelet therapy. The low number of events occurring after 6 months from stenting weakens the power to make a strong statement regarding the safety of thienopyridine discontinuation. Nevertheless we cannot deny that any possible advantage of extended duration of such therapy is likely to be small and needs to be balanced against side effects. Finally, the lack of randomization between SES and PES did not allow us to include the stent type as covariate in the multivariable model.

The main conclusion of this study is that there was a global incidence of 1.9% of ST within 18 months from stenting with 72.4% of these events occurring in the first 6 months. The absence of an obvious relationship, between ST and discontinuation of thienopyridine therapy (HR, 0.94; 95% CI, 0.30 to 2.98; P=0.92) after 6 months from DES implantation, suggests that late ST in DES may be a complex and multifactorial phenomenon.

**Author Contributions:** Dr Colombo and Dr Airoldi (that are both joint first authors) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Airoldi, Colombo, Grube, Briguori, Morici.

*Acquisition of data:* Airoldi, Morici, Latib, Godino, Chieffo, Montorfano, Carlino, Michev, Buellesfeld, Gerckens, Melzi

*Analysis and interpretation of data:* Airoldi, Bonizzoni, Colombo, Morici, Latib

*Drafting of the manuscript:* Airoldi, Colombo, Latib.

*Critical revision of the manuscript for important intellectual content:* Airoldi, Colombo, Latib, Morici, Buellesfeld, Bonizzoni, Chieffo, Carlino, Cosgrave, Gerckens, Godino, Melzi, Montorfano, Michev, Qasim, Sangiorgi, Briguori, Grube.

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**REFERENCES**


1. Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, Guagliumi G, Wijns W, Lindeboom WK, Ligthart J, de Feyter PJ, Morice MC. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. *Circulation.* 2002;106:798-803.

2. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108:788-94.

3. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-23.

4. Stone GW, Ellis SG, O'Shaughnessy CD, Martin SL, Satler L, McGarry T, Turco MA, Kereiakes DJ, Kelley L, Popma JJ, Russell ME. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA.* 2006;295:1253-63.

5. Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: Part II. *Circulation* 2002;106:2859-66.

6. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet.* 2003;362:1093-9.

7. Ong AT, Serruys PW, Aoki J, Hoye A, van Mieghem CA, Rodriguez-Granillo GA, Valgimigli M, Sonnenschein K, Regar E, van der Ent M, de Jaegere PP, McFadden EP, Sianos G, van der Giessen WJ, de Feyter PJ, van Domburg RT. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. *J Am Coll Cardiol.* 2005;45:1135-41.

8. Valgimigli M, van Mieghem CA, Ong AT, Aoki J, Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smits PC, Regar E, Van der Giessen WJ, Sianos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation.* 2005;111:1383-9.

9. Chieffo A, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, Airoldi F, Michev I, Sangiorgi MG, Carlino M, Vitrella G, Colombo A. Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation.* 2005;111:791-5.

10. Suttorp MJ, Laarman GJ, Rahel BM, Kelder JC, Bosschaert MA, Kiemeneij F, Ten Berg JM, Bal ET, Rensing BJ, Eefting FD, Mast EG. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation.* 2006;114:921-8.

11. Stabile E, Cheneau E, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R. Late thrombosis in cypher stents after the discontinuation of antiplatelet therapy. *Cardiovasc Radiat Med.* 2004;5:173-6.

12. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005;45:2088-92.

13. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet.* 2004;364:1519-21.

14. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126-30.

15. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z, Smith K, Fournadjieva J, Suddath WO, Satler LF, Pichard AD, Kent KM, Waksman R. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation.* 2006;113:1108-13.

16. Urban P, Gershlick AH, Guagliumi G, Guyon P, Lotan C, Schofer J, Seth A, Sousa JE, Wijns W, Berge C, Deme M, Stoll HP. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation.* 2006;113:1434-41.

17. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB III, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation.* 2006;113:156-75.

18. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation.* 2006;113:2803-9.

19. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP, Jr., Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation.* 2001;103:1967-71.

20. Colombo A, Orlic D, Stankovic G, Corvaja N, Spanos V, Montorfano M, Liistro F, Carlino M, Airoldi F, Chieffo A, Di Mario C. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. *Circulation.* 2003;107:2178-80.

21. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J.* 2000;21:1502–13.

22. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-51.

23. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med.* 1992;11:2093-109.

24. Harrel FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumption and adequacy, and measuring and reducing errors. *Stat Med.* 1996;15:361-387.

25. Laarman GJ, Suttorp MJ, Dirksen MT, van Heerebeek L, Kiemeneij F, Slagboom T, van der Wieken LR, Tijssen JG, Rensing BJ, Patterson M. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med.* 2006;355:1105-13.

26. Schampaert E, Moses JW, Schofer J, Schluter M, Gershlick AH, Cohen EA, Palisaitis DA, Breithardt G, Donohoe DJ, Wang H, Popma JJ, Kuntz RE, Leon MB. Sirolimus-eluting stents at two years: a pooled analysis of SIRIUS, E-SIRIUS, and C-SIRIUS with emphasis on late revascularizations and stent thromboses. *Am J Cardiol.* 2006;98:36-41.

27. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabate M, Escaned J, Banuelos C, Fernandez-Ortiz A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol.* 2005;45:954-9.

28. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol.* 2005;45:947-53.

29. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C and for the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol.* 2006;48:2584–91.

30. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel Use and Long-term Clinical Outcomes After Drug-Eluting Stent Implantation. *JAMA* 2007 Jan 10;297(2):159-68. Epub 2006 Dec 5.

31. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411–2420.

32. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–533

## FIGURE LEGENDS

**Figure 1**

The relationship between discontinuation of thienopyridine therapy and stent thrombosis. Each line (58) represents a patient who had stent thrombosis. Shaded segments represent time on double antiplatelet therapy, white segments represent time without thienopyridine therapy, black markers and numbers represent the occurrence of stent thrombosis and numbers of days from index procedure.

**Figure 2**

Proportion of patients taking dual antiplatelet therapy and the incidence of stent thrombosis while on or off thienopyridines at 30, 180, 360, and 540 days.

**Figure 3**

Aalen-Nelson estimate of cumulative hazard function in patients on double antiplatelet therapy and in patients who discontinued thienopyridine therapy.

**TABLE 1.** Clinical Characteristics of Patients

| | All patients (n = 3021) | ST (n = 58) | No ST (n = 2963) | P value |
|---|---|---|---|---|
| Age, years | 63.6±28.0 | 65.4±14.6 | 63.5±28.2 | 0.60 |
| Male gender, n (%) | 2528 (83.7) | 47 (81.0) | 2481 (83.8) | 0.57 |
| Hypertension, n (%) | 1903 (63.0) | 36 (62.1) | 1867 (63.0) | 0.83 |
| Diabetes mellitus, n (%) | 799 (26.4) | 19 (32.8) | 780 (26.3) | 0.27 |
| Hypercholesterolemia, n (%) | 1971 (65.2) | 41 (70.7) | 1930 (65.1) | 0.38 |
| Current smoker, n (%) | 377 (12.5) | 8 (13.8) | 369 (12.5) | 0.76 |
| Unstable angina, n (%) | 645 (21.4) | 17 (29.3) | 628 (21.2) | 0.13 |
| Previous MI , n(%) | 1276 (42.2) | 24 (41.4) | 1252 (42.2) | 0.89 |
| Previous bypass surgery, n (%) | 577 (19.1) | 13 (22.4) | 564 (19.0) | 0.52 |
| Previous PCI, n (%) | 1117 (37.0) | 23 (39.7) | 1094 (36.9) | 0.67 |
| Prior brachytherapy | 31 (1.0) | 3 (5.2) | 28 (0.9) | 0.002 |
| Chronic renal failure, n (%) | 166 (5.5) | 7 (17.5) | 159 (7.0) | 0.01 |
| Intra-aortic balloon pump, n (%) | 67 (2.2) | 7 (12.1) | 60 (2.0) | <0.001 |
| Glycoprotein IIb/IIIa inhibitor use, n (%) | 520 (17.2) | 17 (29.3) | 503 (17) | 0.01 |
| LVEF, % | 54.7±10.4 | 53.1±12.3 | 54.8±10.4 | 0.24 |
| LVEF <30%, n (%) | 96 (3.2) | 5 (8.6) | 91 (3.1) | 0.02 |

Abbreviations: ST, stent thrombosis; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction

**TABLE 2.** Angiographic and Procedural Characteristics

| | All lesions (n = 5389) | ST (n = 58)† | No ST (n = 5331) | P value |
|---|---|---|---|---|
| Vessel treated, n | 1.61±0.75 | 1.56±0.58 | 1.61±0.75 | 0.57 |
| Left main coronary artery, n (%) | 210 (3.9) | 4 (6.9) | 206 (3.9) | 0.23 |
| Left anterior descending artery, n (%) | 1776 (33.0) | 30 (51.7) | 1746 (32.8) | 0.002 |
| Left circumflex artery, n (%) | 816 (15.1) | 8 (13.8) | 808 (15.2) | 0.77 |
| Right coronary artery, n (%) | 1113 (20.7) | 10 (17.2) | 1103 (20.7) | 0.52 |
| Saphenous vein grafts, n (%) | 169 (3.1) | 2 (3.4) | 167 (3.1) | 0.89 |
| Internal mammary artery , n (%) | 33 (0.6) | 0 | 33 (0.6) | 0.55 |
| Marginal branch, n (%) | 420 (7.8) | 3 (5.3) | 417 (7.9) | 0.46 |
| Diagonal branch, (%) | 258 (4.7) | 1 (1.8) | 257 (4.9) | 0.27 |
| Ostial location, n (%) | 708 (13.1) | 10 (21.7) | 698 (14.4) | 0.15 |
| Bifurcation, n (%) | 1102 (20.4) | 16 (27.6) | 1086 (20.4) | 0.17 |
| Type B2/C lesions[§] , n(%) | 3952 (73.3) | 47 (81.0) | 3905 (73.3) | 0.18 |
| Calcification, n (%) | 739 (13.7) | 9 (15.5) | 730 (13.7) | 0.68 |
| In-stent restenosis, n (%) | 859 (15.9) | 13 (22.4) | 846 (15.9) | 0.17 |
| Total occlusion, n (%) | 537 (9.8) | 5 (8.6) | 532 (10.0) | 0.73 |
| Rotational atherectomy, n (%) | 50 (0.9) | 1 (1.7) | 49 (0.9) | 0.52 |
| Procedural characteristics | | | | |
| Maximum balloon diameter, mm | 3.0±0.6 | 3.1±0.4) | 3.0±0.6 | 0.6 |
| Maximum balloon inflation, atm | 15.7±3.4 | 15.5±4.0 | 15.7±3.4 | 0.79 |
| Stent length for lesion, mm | 27.9±13.7 | 30.7±13.1 | 27.9±13.7 | 0.13 |
| Stents for lesion, n | 1.18±0.8 | 1.3±0.5 | 1.2±0.8 | 0.13 |

| | | | | |
|---|---|---|---|---|
| Quantitative coronary angiography | | | | |
| Pre-intervention | | | | |
| Reference vessel diameter, mm | 2.72±0.6 | 2.74±0.63 | 2.72±0.62 | 0.84 |
| Minimal lumen diameter, mm | 0.86±0.5 | 0.88±0.48 | 0.86±0.51 | 0.82 |
| Diameter stenosis, % | 68.7±17.8 | 68.4±17.1 | 68.7±17.8 | 0.92 |
| Lesion length, mm | 15.1±9.7 | 16.6±9.6 | 15.1±9.7 | 0.34 |
| Post-intervention | | | | |
| Minimal lumen diameter, mm | 2.78±0.5 | 2.84±0.58 | 2.78±0.55 | 0.50 |
| Diameter stenosis, % | 11.3±8.8 | 10.1±9.5 | 11.3±8.8 | 0.38 |

Abbreviations: ST, stent thrombosis.

†Total lesions treated in these patients = 88. §Based on American College of Cardiology/American Heart Association Classification.

**TABLE 3. Clinical Characteristics of Patients with Stent Thrombosis According to Thienopyridine Therapy and Time of Occurrence (Before and After 6 months)**

| | ST on thieno-pyridine (n = 43) | ST not on thieno-pyridine (n = 15) | P value | ST within first 6 months (n = 42) | ST after 6 months (n = 16) | P value |
|---|---|---|---|---|---|---|
| Age, years | 65.6±14.6 | 65.0±14.9 | 0.90 | 68.2±10.9 | 58.2±19.9 | 0.02 |
| Male gender, n (%) | 33 (76.7) | 14 (93.3) | 0.60 | 31 (73.8) | 16 (100) | 0.02 |
| Hypertension, n (%) | 28 (65.1) | 8 (53.3) | 0.41 | 30 (71.4) | 6 (37.5) | 0.02 |
| Diabetes mellitus, n (%) | 14 (32.6) | 5 (33.3) | 0.95 | 16 (38.1) | 3 (18.8) | 0.16 |
| Hypercholesterolemia, n (%) | 30 (69.8) | 11 (73.3) | 0.79 | 30 (71.4) | 11 (68.8) | 0.84 |
| Brachytherapy | 3 (7.0) | 0 | 0.29 | 1 (2.4) | 2 (12.5) | 0.12 |
| Family history of CAD, n (%) | 8 (18.6) | 4 (26.7) | 0.50 | 8 (19.0) | 4 (25.0) | 0.61 |
| Current smoker, n (%) | 6 (14) | 2 (13.3) | 0.95 | 5 (11.9) | 3 (18.8) | 0.5 |
| Unstable angina, n (%) | 12 (27.9) | 5 (33.3) | 0.69 | 12 (28.6) | 5 (31.3) | 0.84 |
| Previous MI , n(%) | 20 (46.5) | 4 (26.7) | 0.17 | 19 (45.2) | 5 (31.3) | 0.33 |
| Previous bypass surgery, n (%) | 10 (23.3) | 3 (20) | 0.79 | 10 (23.8) | 3 (18.8) | 0.7 |
| Previous PCI, n (%) | 19 (44.2) | 4 (26.7) | 0.23 | 13 (31.0) | 10 (62.5) | 0.03 |
| Chronic renal failure, n (%) | 6 (14.0) | 1 (7.1) | 0.31 | 6 (14.3) | 1 (6.3) | 0.66 |
| Intra-aortic balloon pump, | 6 (14.0 | 1 (6.7) | 0.45 | 7 (16.7) | 0 | 0.08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| n (%) | | | | | | |
| Glycoprotein IIb/IIIa inhibitor use, n (%) | 13 (30.2) | 4 (26.7) | 0.79 | 15 (35.7) | 2 (12.5) | 0.08 |
| Bifurcation, n (%) | 14 (32.6) | 5 (33.3) | 0.78 | 16 (38.1) | 3 (18.8) | 0.16 |
| Stent length, mm | 35.0±28.3 | 38.6±24.0 | 0.02 | 36.9±28.3 | 33.3±24.0 | 0.64 |
| LVEF <30%, n (%) | 5 (12.2) | 0 | 0.31 | 4 (10) | 1 (6.3) | 0.65 |

Abbreviations: ST, stent thrombosis; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

**TABLE 4. Clinical Outcomes at 30-day and 18-Months Follow-Up**

| | Overall (n = 3021) | ST (n = 58) | No ST (n = 2963) | P value |
|---|---|---|---|---|
| **30 days** | | | | |
| Death, n (%) | 18 (0.6) | 12 (20.7) | 6 (0.2) | <0.001 |
| Non Q-wave MI, n (%) | 83 (2.7) | 7 (12.1) | 76 (2.6) | <0.001 |
| Q-wave MI, n (%) | 7 (0.2) | 3 (5.2) | 4 (0.1) | <0.001 |
| CABG, n (%) | 1 (0.03) | 0 | 1 (0.03) | 0.89 |
| **31days to 18-month follow-up** | | | | |
| Death, n (%) | 94 (3.1) | 11 (19.0) | 83 (2.8) | <0.001 |
| Non Q-wave MI, n (%) | 51 (1.7) | 23 (39.7) | 28 (0.9) | <0.001 |
| Q-wave MI, n (%) | 20 (0.7) | 13 (22.4) | 7 (0.2) | <0.001 |
| CABG, n (%) | 36 (1.2) | 3 (5.2) | 33 (1.1) | 0.005 |
| TVR, n (%) | 434 (14.4) | 32 (55.2) | 402 (13.6) | <0.001 |
| TLR, n (%) | 342 (11.3) | 30 (51.7) | 312 (10.5) | <0.001 |
| **Cumulative MACE** | | | | |
| Death, n (%) | 112 (3.7) | 23 (39.7) | 89 (3.0) | <0.001 |
| Non Q-wave MI, n (%) | 134 (4.4) | 30 (51.7) | 104 (3.5) | <0.001 |
| Q-wave MI, n (%) | 27 (0.9) | 16 (27.5) | 11 (0.4) | <0.001 |
| CABG, n (%) | 37 (1.2) | 3 (5.2) | 34 (1.1) | 0.006 |
| TVR, n (%) | 434 (14.4) | 32 (55.2) | 402 (13.6) | <0.001 |
| TLR, n (%) | 342 (11.3) | 30 (51.7) | 312 (10.5) | <0.001 |

Abbreviations: ST, stent thrombosis; MI, myocardial infarction; CABG, coronary artery bypass graft; TVR, target vessel revascularization; TLR, target lesion revascularization; MACE, major adverse cardiac event.

**TABLE 5. Univariate Cox Regression Analysis for the Occurrence of Stent Thrombosis**

| Parameter | Hazard Ratio | 95% Lower Confidence Limit for Hazard Ratio | 95% Upper Confidence Limit for Hazard Ratio | Pr > Chi-Square | Bootstrap Selection |
|---|---|---|---|---|---|
| Stent length | 2.918 | 1.613 | 5.282 | 0.0004 | 89% |
| Brachytherapy | 8.196 | 2.367 | 28.374 | 0.0009 | 76% |
| Final atm stent implantation | 0.402 | 0.176 | 0.919 | 0.0308 | 72% |
| Reference vessel diameter - pre | 0.146 | 0.038 | 0.553 | 0.0046 | 63% |
| LVEF | 3.154 | 1.248 | 7.974 | 0.0152 | 58% |
| Eccentric lesion | 2.018 | 1.047 | 3.891 | 0.0360 | 50% |
| Left main coronary artery | 1.848 | 0.832 | 4.107 | 0.1317 | 44% |
| Thrombus in lesion | 1.987 | 0.695 | 5.683 | 0.2005 | 39% |
| Renal failure | 1.691 | 0.658 | 4.345 | 0.2753 | 39% |
| Ostial lesion | 1.434 | 0.719 | 2.863 | 0.3065 | 34% |
| Lesion length | 0.900 | 0.729 | 1.113 | 0.3312 | 29% |
| Statin therapy | 2.070 | 0.727 | 5.890 | 0.1728 | 27% |
| Diabetes mellitus | 1.439 | 0.807 | 2.564 | 0.2174 | 24% |
| Unstable angina | 1.591 | 0.843 | 3.001 | 0.1518 | 21% |
| TIMI 3 flow at baseline | 1.436 | 0.661 | 3.119 | 0.3601 | 20% |
| Current smoker | 1.627 | 0.741 | 3.577 | 0.2254 | 20% |
| Bifurcation | 1.683 | 0.927 | 3.055 | 0.0873 | 17% |

| Parameter | Hazard Ratio | 95% Lower Confidence Limit for Hazard Ratio | 95% Upper Confidence Limit for Hazard Ratio | Pr > Chi-Square | Bootstrap Selection |
|---|---|---|---|---|---|
| Previous CABG | 1.434 | 0.785 | 2.617 | 0.2410 | 12% |
| Male gender | 0.863 | 0.431 | 1.731 | 0.6785 | 10% |
| Diameter stenosis – post | 0.968 | 0.766 | 1.225 | 0.7885 | 10% |
| Minimal lumen diameter –pre | 1.326 | 0.617 | 2.851 | 0.4700 | 9% |
| Dyslipidemia | 1.278 | 0.705 | 2.317 | 0.4187 | 8% |
| Calcification | 1.172 | 0.570 | 2.412 | 0.6663 | 7% |
| Type B2/C lesions[§] | 1.233 | 0.614 | 2.478 | 0.5563 | 7% |
| Minimal lumen diameter –post | 0.346 | 0.065 | 1.831 | 0.2120 | 7% |
| Number of diseased vessels | 1.330 | 0.489 | 3.620 | 0.5766 | 6% |
| Previous PCI | 1.121 | 0.640 | 1.963 | 0.6894 | 6% |
| Reference vessel diameter – post | 0.423 | 0.070 | 2.550 | 0.3480 | 6% |
| Diameter stenosis – pre | 0.850 | 0.670 | 1.078 | 0.1796 | 5% |
| Previous MI | 1.247 | 0.720 | 2.160 | 0.4312 | 5% |
| Hypertension | 0.987 | 0.558 | 1.746 | 0.9643 | 5% |
| Number of vessels treated | 1.363 | 0.465 | 3.994 | 0.5721 | 3% |
| Minimal lumen diameter –post | 1.066 | 0.276 | 4.115 | 0.9265 | 2% |
| Total occlusion | 0.911 | 0.374 | 2.221 | 0.8381 | 2% |

Abbreviations: LVEF, left ventricular ejection fraction; TIMI, Thrombolysis In Myocardial Infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction.

§Based on American College of Cardiology/American Heart Association Classification

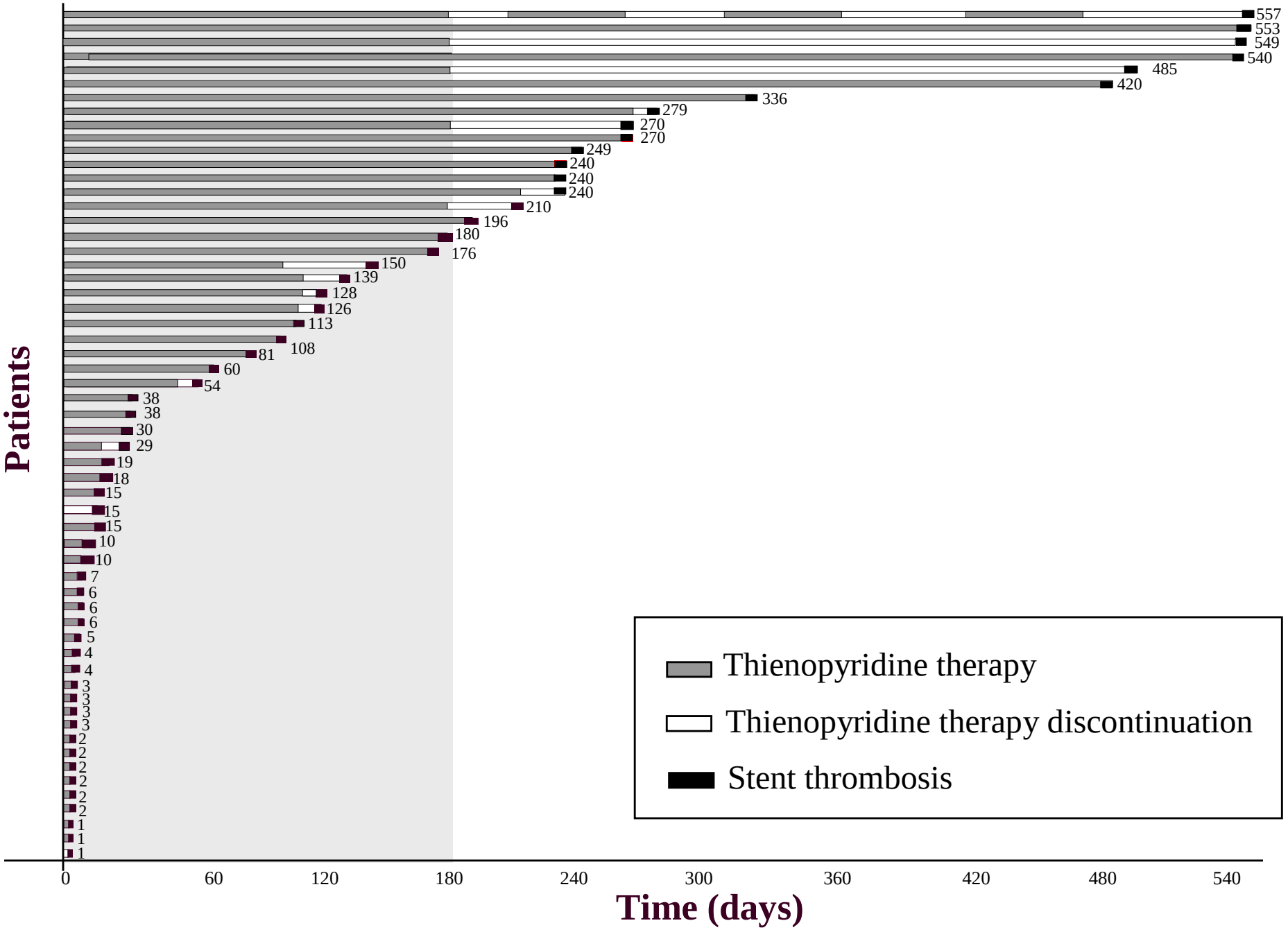
**TABLE 6. Multivariable Analysis for the Predictors of Stent Thrombosis**

| Variable | No. of Patients | Hazard Ratio | 95% Lower Confidence Limit for Hazard Ratio | 95% Upper Confidence Limit for Hazard Ratio | Pr > Chi-Square |
|---|---|---|---|---|---|
| Discontinuation of thienopyridine(0-6 months)† | 583 | 13.74 | 4.04 | 46.68 | <0.001 |
| Discontinuation of thienopyridine (6-18 months)† | 1737 | 0.94 | 0.30 | 2.98 | 0.92 |
| LVEF (≤30%) | 96 | 3.72 | 1.50 | 9.27 | 0.005 |
| Prior brachytherapy | 31 | 9.70 | 2.99 | 31.44 | <0.001 |
| Reference vessel diameter (per 1 mm)‡ | - | 0.27 | 0.06 | 1.13 | 0.07 |
| Final atm stent implantation (per 1 atm)‡ | - | 0.39 | 0.18 | 0.85 | 0.02 |
| Stent length (per 10 mm) ‡ | - | 2.75 | 1.55 | 4.88 | <0.001 |

†Stratified for Center, Stent type (Taxus or Cypher), Baseline risk status (defined as patients with use of an intra-aortic balloon pump and/or treatment with glycoprotein IIb/IIIa inhibitors and/or family history of coronary artery disease), and Age (≤60, 60-75, >75).

‡Square-Root transformed

Abbreviations: atm, atmosphere; LVEF, left ventricular ejection fraction.


Patients
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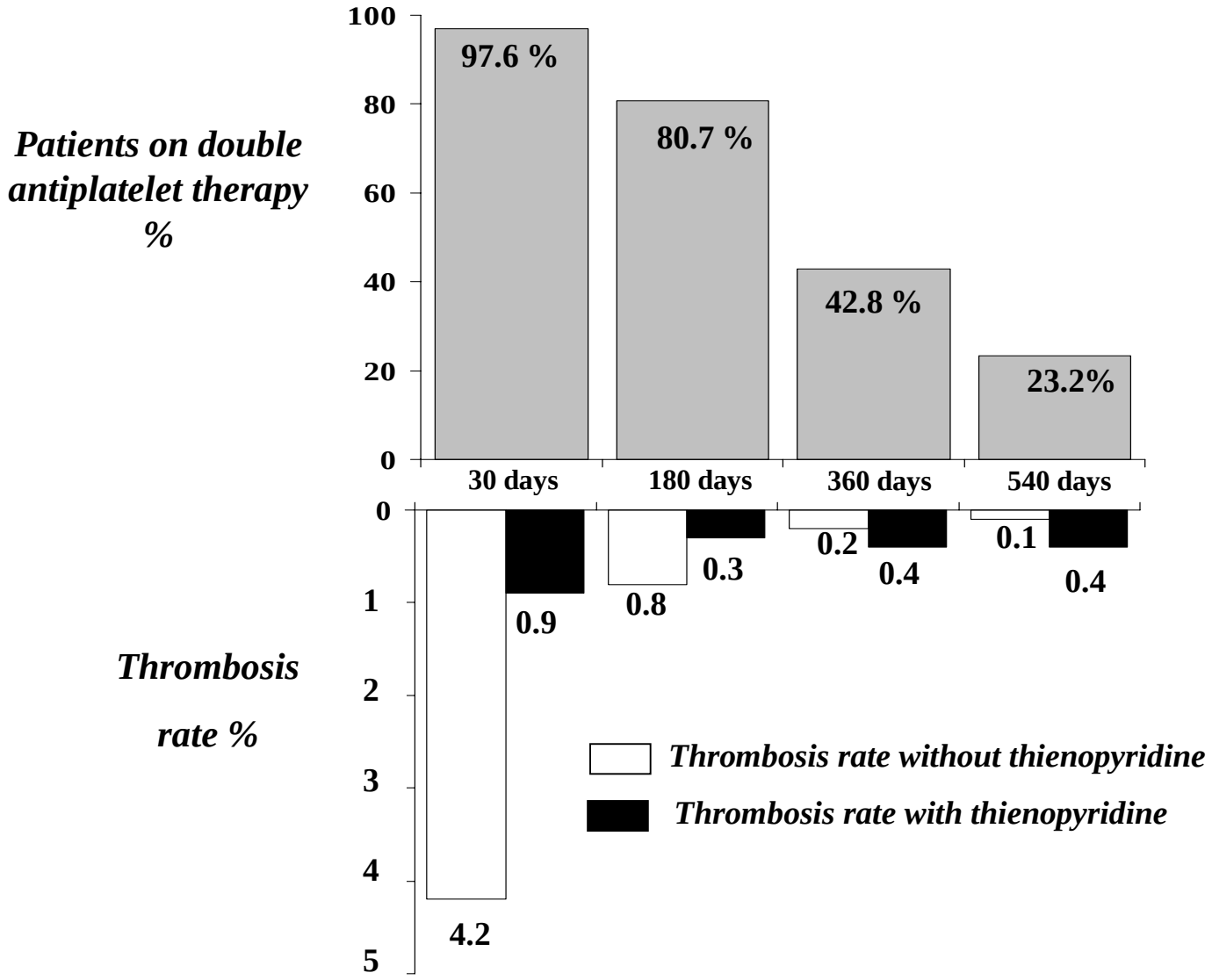
Time (days)
Thienopyridine therapy
Thienopyridine therapy discontinuation
Stent thrombosis


Patients on double antiplatelet therapy %
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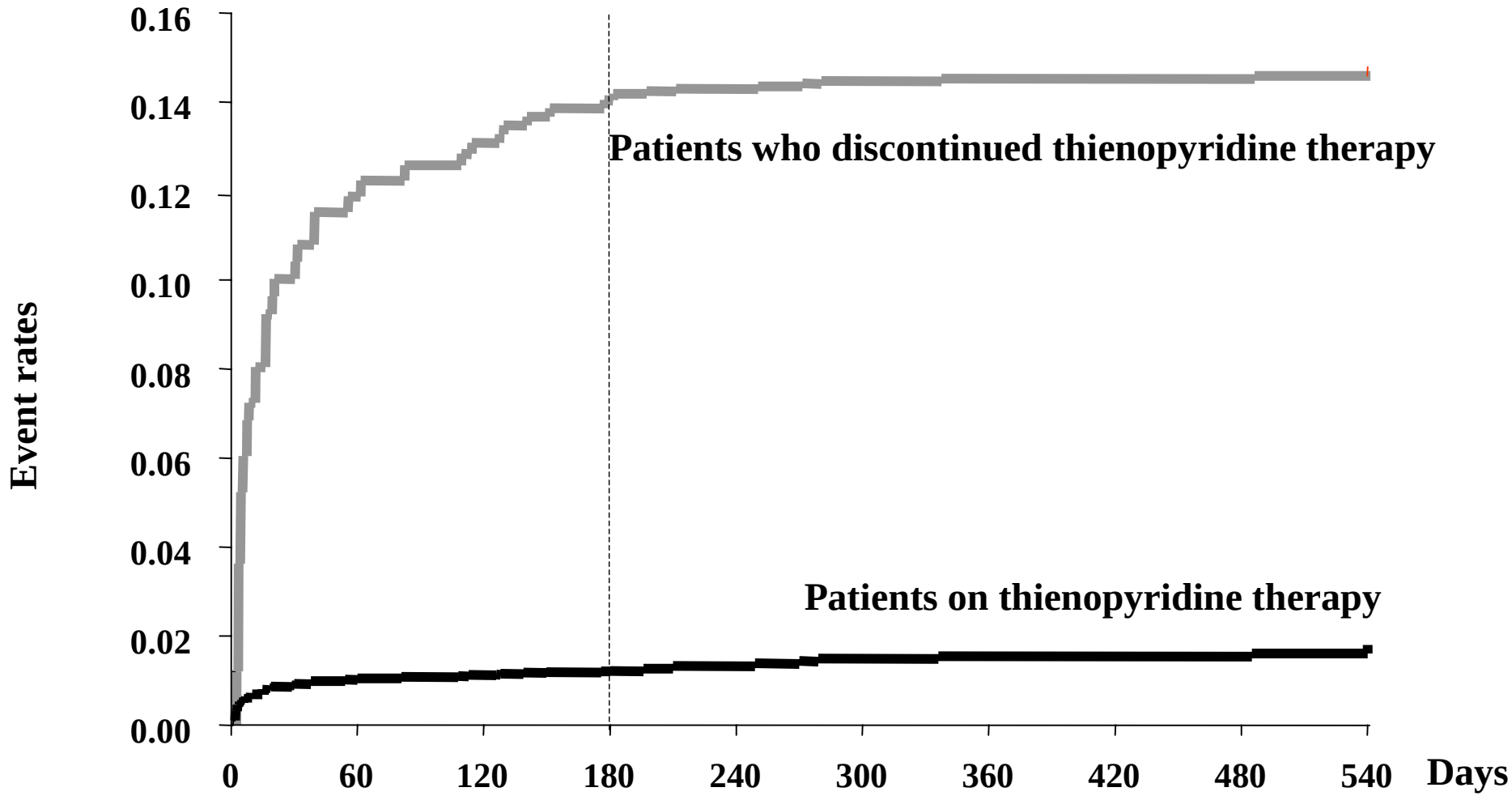
80
60
40
20
0
97.6 %
80.7 %
42.8 %
23.2%
30 days
180 days
360 days
540 days
Thrombosis rate %
0
1
2
3
4
5
4.2
0.9
0.8
0.3
0.2
0.4
0.1
0.4
Thrombosis rate without thienopyridine
Thrombosis rate with thienopyridine




**No. of Patients**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Discontinued thienopyridine | 258 | 422 | 560 | 1128 | 1180 | 1680 | 2044 | 2138 | 2251 |
| On thienopyridine | 2750 | 2576 | 2411 | 1829 | 1771 | 1245 | 865 | 756 | 634 |