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CLINICAL RESEARCH

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Correlates and Outcomes of Late and Very Late Drug-Eluting Stent Thrombosis

Results From DESERT (International Drug-Eluting Stent Event Registry of Thrombosis)

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ABSTRACT

OBJECTIVES The aim of this study was to identify clinical, procedural, and angiographic correlates of late/very late drug-eluting stent (DES) thrombosis as well as to determine the clinical outcomes of these events.

BACKGROUND Late/very late DES thromboses are a poorly studied phenomenon, partly due to the relative infrequency of these events, even in large cohort studies.

METHODS In the DESERT (International Drug-Eluting Stent Event Registry of Thrombosis), a retrospective, case-control registry, 492 cases of late/very late definite DES thrombosis from 21 international sites were matched in a 1:1 fashion with controls without stent thrombosis (ST). Controls were matched according to 2 criteria: same enrolling institution and date of initial DES implantation. Baseline and procedural variables were collected, and clinical follow-up was obtained for patients with ST as long as 1 year after the event. Offline quantitative coronary angiography was performed for a subset of 378 case-control pairs.

RESULTS The majority of ST events occurred after 1 year (75%) and continued to occur for as long as 7.3 years. The clinical presentation of late/very late ST events was mainly myocardial infarction (66.7% ST-segment elevation myocardial infarction and 22.0% non-ST-segment elevation myocardial infarction); in-hospital mortality was 3.8%. A minority of patients (30%) with ST were receiving dual-antiplatelet therapy at the time of the event. Independent clinical correlates of late/very late ST were younger age, African-American race, current smoking, multivessel disease, longer stented length, overlapping stents, and percutaneous coronary intervention of vein graft lesions. Independent angiographic correlates for late/very late ST were lesions within the left anterior descending artery or a bypass graft, thrombus, and a larger residual diameter stenosis after the initial DES implantation. Despite the large sample of ST cases, all identified correlates of late/very late ST had weak associations with subsequent ST (all odds ratios <2.5).

CONCLUSIONS Despite a large sample of ST cases and use of limited matching to maximize the identification of predictive factors associated with late/very late ST, the variables associated with the development of late/very late ST were only weakly predictive of subsequent events. Additionally, a relatively low observed mortality rate of ST in this series may reflect a different pathophysiology of these late/very late events compared with acute/subacute ST. (Drug Eluting Stent Registry of Thrombosis [DESERT]; NCT00812552) (J Am Coll Cardiol Intv 2014;7:1093–102)
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

IQR = interquartile range

LAD = left anterior descending

MI = myocardial infarction

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

ST = stent thrombosis

STEMI = ST-elevation myocardial infarction

SVG = saphenous vein graft

TIMI = Thrombolysis In Myocardial Infarction

Since the introduction of bare metal stents (BMS), stent thrombosis (ST) has been a major concern due to significant morbidity and mortality (1–3). The widespread adoption of dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor antagonist (4) and improved percutaneous coronary intervention (PCI) techniques (5) have decreased the risk of thrombosis to an acceptable level (<~1%), although the incidence of ST remained higher when stents were placed in more complex subjects and lesions (2,6). Drug-eluting stents (DES) held the promise of mitigating, if not abolishing, restenosis and the need for repeat revascularization procedures (7,8). Nonetheless, reports of late ST events (beyond 30 days) with DES, including data that demonstrated a constant hazard of ST of 0.6%/year after DES implantation, led to continued concerns regarding the safety of DES (9–15).

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Although the phenomenon of subacute ST has been well described in the BMS era and still constitutes the majority of ST events with DES, the predictors and outcomes of late ST (30 days to 12 months) and very late ST (beyond 12 months) with DES have been less well understood, in part because of the low frequency of these events. Previous reports have been limited to small cohorts or case series (16–22). Furthermore, the optimal duration of DAPT for patients undergoing DES implantation and the relationship between the duration of DAPT and the occurrence of late/very late DES thrombosis remains unclear. The aim of this prospective case-control study was to identify clinical, procedural, and angiographic correlates of late/very late DES thrombosis, as well as to determine the clinical outcomes of these events.

METHODS

STUDY POPULATION. The DESERT (International Drug-Eluting Stent Event Registry of Thrombosis) was a retrospectively designed, multicenter, observational, case-control study with an original aim to enroll as many as 500 patients with definite late/very late DES thrombosis and 500 matched control patients (**Figure 1**). Patients with definite ST of a U.S. Food and Drug Administration–approved DES after April 2003 were included in the study. Included patients were 18 years of age and older and presented with late/very late definite ST (per the Academic Research Consortium definition) (23) confirmed by angiography or autopsy. Sites reported, to the best of their knowledge, consecutive cases of late/very late definite ST patients. A site was included if it 1) had an internal systematic reporting mechanism to identify stent thrombosis patients (i.e., databases) or 2) was able to develop queries within its billing system to identify readmission for ST presentations. Limited matching was used: 492 cases of late/very late definite DES thrombosis from 21 international sites were matched in a 1:1 fashion with controls without ST. Controls were matched according to 2 criteria: same enrolling institution and date of initial DES implantation. Control patients were eligible if they had no known history of ST until the time of matching. In the event that more than 1 control was eligible for a case, the sites were instructed to randomly assign a control. The rationale for limited matching was to maximize identification of covariates potentially associated with late/very late ST (had more extensive matching been used, this would have virtually eliminated the identification of an association between the matched covariates and the outcome of interest). The baseline, clinical, procedural, and angiographic characteristics at the time of initial DES implantation and additional data regarding the ST presentation and treatment procedure were collected using electronic case report forms.

There was no treatment modality specified in this protocol, and the registry did not require the treating physicians to alter therapeutic strategies for either initial stent implantation or ST episode. A subset of case patients was followed after the thrombotic event for as long as 12 months. The appropriate Health

¶Wake Forest School of Medicine, Winston-Salem, North Carolina; #Lahey Clinic Medical Center, Burlington, Massachusetts; and **The Miriam Hospital, Providence, Rhode Island. The study was partially funded by Medtronic Vascular. A complete listing of the investigators participating in the DESERT Study appears in the Online Appendix. Dr. Waksman is on the Speakers' Bureau of Boston Scientific, Medtronic, AstraZeneca, Biotronik, and Abbott Vascular (<$10,000); has received nonroyalty payments from Biotronik, research grants from Boston Scientific, Medtronic, Volcano, Lilly-Daiichi Sankyo, AstraZeneca, and Abbott Vascular; and is a consultant for Biotronik, Boston Scientific, Abbott Vascular, and Volcano. Dr. Cohen has received research grants from Medtronic, Abbott Vascular, Eli Lilly, Daiichi-Sankyo, AstraZeneca, and Boston Scientific; is on the Advisory Boards of Eli Lilly, Medtronic, and AstraZeneca; and is on the Speakers' Bureaus of AstraZeneca and Eli Lilly. Dr. Applegate is a consultant for and has received a research grant from Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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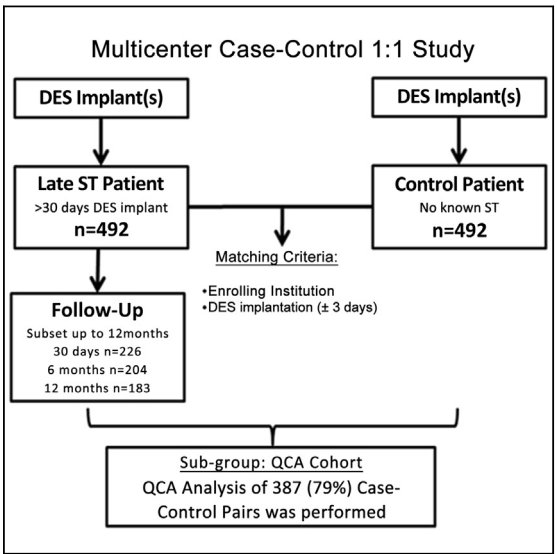

FIGURE 1 The DESERT Study Design

The DESERT study design was case-control with patients matched to the same enrolling institution and within 3 days of the thrombosed stent implantation. Two subgroups were identified with a cohort of stent thrombosis (ST) patients undergoing long-term follow-up after the ST presentation and 387 patient pairs undergoing offline quantitative coronary angiography (QCA) analysis of the drug-eluting stent (DES) implantation procedure and the ST angiograms of the case.

Insurance Portability and Accountability Act waiver/authorization or the appropriate informed consent documentation requirement was obtained per institutional policy for the collection of data.

STUDY ENDPOINTS AND DEFINITIONS. Definite ST had to meet the Academic Research Consortium definition criteria (23): ST in the setting of an acute coronary syndrome (ACS) confirmed by angiography or autopsy. Major adverse cardiac events were defined as the composite of all-cause death, Q-wave myocardial infarction (MI), and target lesion revascularization. Additionally, in-hospital stroke was tracked and classified as either ischemic or hemorrhagic. Data on follow-up target vessel revascularization and recurrent thrombosis were also collected.

A random subgroup of 387 case-control pairs (79%) underwent offline quantitative coronary angiography (QCA) analysis. For these patients, QCA analysis was performed of the original DES implantation procedures for both the ST patients (cases) and the control patients, as well as of the angiogram obtained at the time of the ST presentation for the cases. All QCAs were performed by an independent core laboratory (Cardiovascular Research Foundation Angiographic Core Laboratory, New York, New York), and all quantitative and qualitative definitions were established before analyses commenced.

STATISTICAL ANALYSIS. Categorical variables are reported as number and frequency, and continuous variables are reported as mean ± SD and median with interquartile range where applicable. Because of the matching process, comparison statistics were done with the McNemar test for categorical data and the paired *t* test or Wilcoxon signed rank test for continuous data as appropriate. Potential predictors of late/very late ST were identified independently based on clinical and QCA (if available) data. Multivariable conditional logistic regression was used to identify covariates independently associated with late/very late ST. Candidate covariates either associated with ST in previous reports or associated with ST in this study were considered for these analyses, such as clinical risk factors, lesion characteristics, and previous stent details.

RESULTS

CHARACTERISTICS AT THE TIME OF INDEX DES IMPLANTATION. In the DESERT, a total of 984 patients (492 paired cases and controls) were enrolled from 21 sites in the United States, Canada, Italy, and Switzerland. Patients' baseline demographic characteristics and clinical presentation are displayed in Tables 1 and 2. By design, there was minimal matching of baseline characteristics (to identify correlates of

TABLE 1 Baseline Demographic Factors at the Time of Drug-Eluting Stent Implantation

	ST (n = 492)	Control (n = 492)	p Value
Age, yrs	58.0 ± 12.6	63.2 ± 11.4	<0.001
Men, %	77.0	73.6	0.18
African American, %	10.2	6.3	0.02
Diabetes, %	25.8	29.3	0.22
Hypertension, %	66.3	73.3	0.02
Current smoker, %	45.9	27.3	<0.001
Previous cerebrovascular accident/transient ischemic attack, %	7.6	9.0	0.43
History of peripheral vascular disease, %	9.6	9.8	0.91
History of chronic renal insufficiency, %	6.7	7.4	0.70
Dialysis, %	1.8	1.8	0.99
History of congestive heart failure, %	6.5	4.7	0.20
Current class (III/IV), %	1.2	1.8	0.44
Previous coronary artery bypass graft surgery, %	11.4	12.8	0.49
Previous percutaneous coronary intervention, %	34.4	26.1	0.005
Previous myocardial infarction, %	28.2	20.8	0.008
Previous ST (any), %	2.4	–	–

Values are mean ± SD.
ST = stent thrombosis.

TABLE 2 Presentation at the Time of Drug-Eluting Stent Implantation

	ST (n = 492)	Control (n = 492)	p Value
ST-segment elevation myocardial infarction, %	20.2	13.6	0.004
Acute coronary syndrome/non-ST-segment elevation myocardial infarction, %	25.5	21.1	0.11
Unstable angina, %	30.5	31.9	0.62
Stable angina, %	14.7	18.5	0.08
Positive functional test, %	15.7	19.3	0.13
Cardiogenic shock, %	0	1.0	–
Staged percutaneous coronary intervention, %	1.4	0.6	0.16
Other clinical presentation, %	4.9	7.5	0.07
Single-vessel disease, %	39.5	50.6	<0.001
2-vessel disease, %	35.0	28.5	
3-vessel disease, %	25.5	20.9	
Body mass index, kg/m^2, %	28.8 ± 5.9	29.8 ± 6.8	0.02
Left ventricular ejection fraction, %	51 ± 12	54 ± 11	<0.001

Values are mean ± SD.
ST = stent thrombosis.

ST using a case-control design); as such, there were several differences between case and control patients. At the time of initial DES implantation, patients with subsequent ST were younger, more often smokers, and more frequently African American and more frequently had a history of hypertension, MI, and PCI. At the time of initial DES implantation, case patients more frequently presented with ST-segment elevation myocardial infarction (STEMI) and multivessel disease and additionally had lower left ventricular ejection fractions. The DES type distribution was similar between groups, with one-half of the lesions receiving sirolimus-eluting (50.2%), paclitaxel-eluting (40.3%), everolimus-eluting (7%), and zotarolimus-eluting (1.8%) stents.

Lesion characteristics at the time of DES implantation are displayed in Table 3. Overall, there were more saphenous vein graft (SVG) lesions, left anterior descending (LAD) locations, complex B2/C lesions, and in-stent restenosis lesions in the ST group. QCA was completed in 393 lesions with ST and in 432 lesions from the control group. The baseline angiographic characteristics and the post-procedural angiographic outcomes of index lesions are displayed in Table 4. Lesions with subsequent ST had more thrombi and a higher rate of Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 at the time of baseline DES implantation. Final procedural angiographic analysis demonstrated larger in-stent diameter stenoses and longer stented segments in the ST group.

OCCURRENCE OF LATE/VERY LATE ST. The time distribution from DES implantation to ST is displayed in Figure 2. The majority of late/very late ST events occurred after 1 year (75%) and continued to occur as long as 7.3 years. The median time from DES implantation to ST was 764 (IQR: 376 to 1,338) days. The clinical presentation of late/very late ST was predominantly MI (66.7% STEMI and 22.0% non-STEMI); among those patients, 4.7% presented with cardiogenic shock. At the time of ST, visual thrombus was documented in 98.8% and TIMI flow grade 0 was observed in 74.6% of the patients. Of the lesions that underwent repeat PCI at the time of ST presentation, 9.9% underwent pre-intervention intravascular ultrasound. The rates of stent malapposition (per investigator determination) confirmed by angiography was 5.9% (26 lesions) and by intravascular ultrasound was 4.7% (21 lesions). Of the thrombotic lesions that underwent offline QCA, the thrombus characteristics were total occlusion in 73%, diffuse thrombosis throughout the stent and lesion in 14.1%, focal thrombosis in 9.2%, and stent edge thrombosis in 3.2% of the lesions.

DUAL-ANTIPLATELET THERAPY AND LATE/VERY LATE ST. DAPT adherence rates at the time of the event are shown in Table 5. Overall, 30.2% of patients were receiving DAPT at the time of late/very late ST; 11% stopped the DAPT within 5 days before the thrombosis. As anticipated, there was a stark difference between the rate of DAPT cessation at the time of ST presentation between the patients presenting at 30 days to 1 year and beyond 1 year (49.1% vs. 78.3%, $p < 0.001$, respectively). In those patients who had events within the first year after the DES implantation, 51.8% were receiving DAPT, and for those who had the ST after 1 year, 23.1% were receiving DAPT at the time of event.

LATE/VERY LATE ST TREATMENT AND OUTCOMES. Thrombus aspiration was performed in 47% of the patients who presented with late ST and balloon angioplasty in 78.1%; DES reimplantation was performed in 30.8% of the lesions and BMS in 20.6% of the lesions. Admission to the intensive care unit was required in 72.4% of the patients. The median duration in the ICU was 5 (IQR: 1 to 2) days, and total length of stay was 3 (IQR: 2 to 5) days. The late ST in-hospital mortality rate was 3.7%, reinfarction (STEMI) rate was 0.8%, coronary artery bypass graft rate was 2.9%, repeat PCI rate was 2.2%, acute renal failure rate was 4.1%, stroke (either ischemic or hemorrhagic) rate was 0.4%, and recurrent ST within the same hospitalization rate was 0.6%. All-cause, out-of-hospital mortality rate at 12 months after ST presentation was 2.87%, and the overall major adverse cardiac event rate was 16.4%.

UNIVARIATE AND MULTIVARIATE CORRELATES OF LATE/VERY LATE ST. The univariable clinical and

angiographic correlates and the combined clinical and angiographic correlates for late/very late ST are shown in Table 6. Younger patients, African Americans, patients who smoked at the time of initial DES implantation, patients with multivessel disease, those treated with overlapping stents, those with longer total stented length, and patients with SVG lesions were among the most important univariable clinical correlates, whereas LAD location, the presence of thrombus, final in-stent diameter stenosis, and SVG lesion location were among the most important angiographic univariable correlates. When combining the clinical and angiographic correlates into 1 model, the independent correlates for development of late ST were younger patients, smokers at the time of initial DES implantation, STEMI or the presence of thrombus by QCA at the time of initial DES implantation, the number of diseased vessels, type C lesions, longer total stented length, and overlapping stents.

TABLE 3 Lesion Data at Time of Drug-Eluting Stent Implantation

	ST (n = 531)	Control (n = 658)	p Value
Left main, %	0.4	1.1	0.31
Right coronary artery, %	35.8	36.0	0.933
Left anterior descending artery, %	41.8	36.5	0.06
Left circumflex, %	17.1	24.9	0.001
Saphenous vein graft, %	4.7	1.4	<0.001
Arterial graft, %	0	0.2	1
Lesion location, %			
Ostial	5.5	3.8	0.17
Proximal	42.0	39.8	0.45
Bifurcation	9.1	7.2	0.23
Lesion classification (visual), %			<0.001
A	11.1	17.8	
B1/B2	44.8	54.1	
C	44.1	28.1	
Pre-diameter stenosis visual, %	87.0 ± 11.3	85.4 ± 11.2	0.015
Lesion length visual, mm	20.79 ± 13.2	17.2 ± 10.1	<0.001
Reference vessel diameter visual, mm	3.0 ± 0.4	3.0 ± 0.5	0.27
Visual thrombus, %	20.8	14.1	0.003
Pre-TIMI flow, %			<0.001
3	66.5	80.5	
2	13.0	9.2	
1	4.0	2.3	
0	16.4	8.0	
In-stent restenosis (any stent type), %	10.4	4.7	<0.001
In-stent restenosis (drug-eluting stent), %	4.5	1.7	0.004
Chronic total occlusion, %	2.8	2.9	0.95
Moderate/severe calcium (visual), %	15.9	13.6	0.71
Stent type, %			
Sirolimus-eluting stent	50.8	49.8	0.74
Paclitaxel-eluting stent	41.6	39.3	0.43
Zotarolimus-eluting stent	2.3	1.4	0.27
Everolimus-eluting stent	5.7	8.1	0.12
Other	0.2	0.6	0.39
Stent diameter, mm	2.9 ± 0.4	3.0 ± 0.4	0.007
Total stented length, mm	27.8 ± 16.7	23.3 ± 12.6	<0.001
Maximal deployment pressure, atm	14.1 ± 3.1	14.0 ± 3.2	0.64
No. of stents per lesion	1.3 ± 0.6	1.2 ± 0.5	<0.001
Stent overlap, %	37.4	23.9	<0.001

Values are mean ± SD.
ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

The DESERT is the largest case-control study of late/very late thrombosis of DES. The main findings of this analysis were that the majority of late ST occurred after 1 year and continued to occur >7 years after the initial DES implantation. Approximately 30% of the patients with late ST were receiving DAPT at the time of the event, and although the clinical presentation of late ST was mainly MI, the overall outcome, including mortality rates, is lower compared with acute or subacute ST.

Independent clinical predictors of the occurrence of late ST were younger age, smoking at the time of initial DES implantation, multivessel disease, type C lesions, longer stent length, and overlapping stents. Independent angiographic predictors as assessed by QCA were LAD or a bypass graft, a larger residual diameter stenosis after DES implantation, and the presence of thrombus. The in-hospital and long-term morbidity and mortality rates with late ST were lower compared with historically reported rates of acute and subacute ST.

Subacute DES thrombosis is a devastating event associated with high mortality and morbidity rates (6,11,15). This phenomenon is subject to ongoing investigations to better understand the pathophysiology and to develop measures for its prevention. So far mechanical, biological, and/or patient-related factors have been identified as etiologies. Among the mechanistic etiologies are stent strut fractures (24), lack of full stent expansion, incomplete stent apposition to the vessel wall related to inadequate lesion preparation, and lack of post-dilation (25). Biological etiologies are mainly related to delayed or incomplete healing, incomplete re-endothelialization, inflammation, and late restenosis (26,27). Among the patient-related factors associated with ST are noncompliance with DAPT and nonresponsiveness to DAPT; specifically genomic mutations and polymorphisms have been identified as strong correlates for ST (28–32). However, these etiologies are mainly related to acute and subacute ST (33,34). Although several studies have examined correlates of ST as long as 1 year from the time of DES implantation, to date, no study has focused exclusively on correlates of late and very late

TABLE 4 Angiographic Lesion Characteristics by Quantitative Coronary Angiography

	ST, % (n = 393)	Control, % (n = 432)	p Value
Thrombus, %	40.1	29.4	0.001
Tortuosity (moderate/severe), %	2.3	1.6	0.65
Calcification (moderate/severe), %	14.8	12.6	0.43
Aneurysm, %	0.3	0	0.48
Pre-TIMI flow, %			<0.001
3	65.4	78.2	
2	13.0	6.7	
1	3.3	3.7	
0	18.3	11.3	
Angulation >45°	9.4	12.7	0.13
Reference vessel diameter, mm	2.76 ± 0.43	2.71 ± 0.45	0.09
Lesion length, mm	19.77 ± 12.14	16.86 ± 10.05	<0.001
Pre-minimal lumen diameter, mm	0.67 ± 0.47	0.74 ± 0.46	0.03
Pre-diameter stenosis, %	75.93 ± 16.35	72.79 ± 15.80	0.005
Final reference vessel diameter, mm	2.83 ± 0.44	2.77 ± 0.45	0.08
Final TIMI flow, %			0.70
0	0.5	0.5	
1	0.3	0.5	
2	3.1	1.9	
3	96.2	97.2	
Final in-segment minimal lumen diameter, mm	2.27 ± 0.42	2.26 ± 0.45	0.70
Final in-stent minimal lumen diameter, mm	2.56 ± 0.41	2.60 ± 0.46	0.275
Final in-segment diameter stenosis, %	19.66 ± 8.22	18.66 ± 8.54	0.09
Final in-stent diameter stenosis, %	9.04 ± 9.09	6.20 ± 9.29	<0.001
Final in-segment acute gain, mm	1.60 ± 0.53	1.52 ± 0.56	0.03
Final in-stent acute gain, mm	1.89 ± 0.53	1.86 ± 0.54	0.31
Final stented segment length, mm	28.44 ± 15.64	22.97 ± 12.47	<0.001
Dissection, %	0.3	0.2	1.00

Values are mean ± SD. Only those lesions where ST subsequently occurred were included for the case patients. Abbreviations as in Table 3.

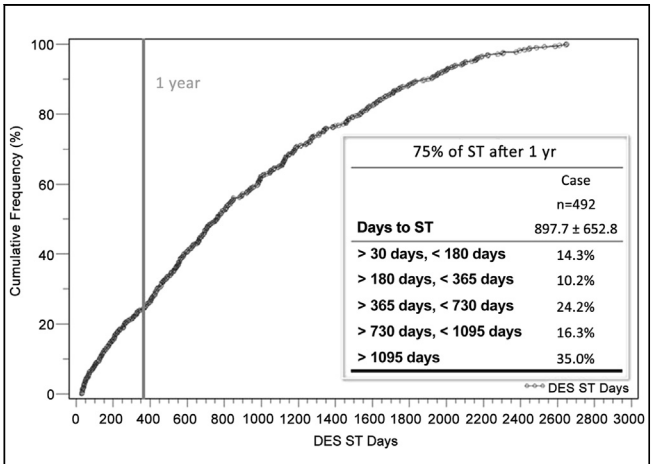

FIGURE 2 Time From DES Implantation to ST Event

A majority of the late/very late ST presentations were beyond 1 year from the DES implantation, with 35% presenting >3 years after the DES implantation. Abbreviations as in Figure 1.

DES thrombosis mainly due to the low frequency of late ST events beyond 1 year (<1%).

The low ST rate per study limits the simultaneous assessment of multiple risk factors. For example, a study of 5,000 patients would have only ~100 late ST events, with the ability to reliably assess only 5 to 10 correlates. By using a case-control design with limited matching (only for site and time to thrombosis), our study allowed the simultaneous assessment of a broad range of associations between clinical and angiographic predictors and late ST.

During the conduction of the present study, 492 patients with definite late/very late ST were identified. Interestingly, the majority of the ST events in this study (~75%) occurred after 1 year from the DES implantation and continued to occur as long as 7.3 years. The Bern Rotterdam group reported a continued hazard ratio of the DES thrombosis up to 5 years with a rate as high as 0.6% per year (35). This continued hazard ratio of late ST was not previously described with BMS, and although the rate of late ST has decreased with second-generation DES, there are no data to ensure patients that they are no longer at risk of the development of ST at any time point after DES implantation. Therefore, identifying these at-risk groups is critical in potentially reducing the incidence of the late/very late DES thrombosis phenomenon.

CLINICAL CORRELATES. Among the clinical correlates of late/very late ST detected in the DESERT were a number of factors associated with more aggressive and extensive coronary disease. These factors, although not overwhelmingly strong, included younger age, active smoking, multivessel disease, overlapping stents, and previous bypass surgery. Of note, this analysis did not independently identify ACS presentation (including STEMI) as a correlate of late/very late ST. This finding is intriguing and may reflect a fundamentally different pathogenesis for the majority of late/very late events compared with subacute ST (for which the presence of ACS is one of the most predictive risk factors). Active smoking, which is usually common in younger populations, was detected as a strong correlate of ST, which can be explained by the increase in platelet reactivity with tobacco use. Despite the previously published "smoking paradox" with clopidogrel, it is important to emphasize that active smoking was associated with an increase in ST in our study, which is in accordance with other trials, such as the PLATO (PLATelet inhibition and patient Outcomes) study (36,37).

Interestingly, the African-American study group was found to be at a higher risk of the development of

late ST, which could be explained by the higher complexity of the disease in this group and/or the potential for higher platelet reactivity on clopidogrel, a phenomenon previously reported in this group (38,39). It is also know that this population has higher rate of CYP2C19*2 and CYP2C9*3 polymorphism (40). Although our analysis did not detect the presence of ACS including STEMI as a clinical correlate for ST, the presence of thrombus at the time of the DES implantation was a predictor of late ST. This may differentiate ACS with and without the presence of a thrombus and corroborate previous reports of the impact of the presence of thrombus and thrombus size on late outcome (41,42).

ANGIOGRAPHIC CORRELATES. Among the cohort of patients with core laboratory–assessed angiographic data, greater residual in-stent diameter stenosis post-implantation, the presence of thrombus, and LAD or vein graft lesions were the main angiographic correlates of late/very late ST. Interestingly, bifurcation and in-stent restenosis lesions, both of which have previously been reported as correlates of DES thrombosis, were not detected as independent correlates of late/very late ST in the DESERT cohort. This may be explained by the fact that the previous studies focused on correlates of ST as long as 1 year (including acute and subacute ST), whereas in the DESERT registry, nearly 75% of the events occurred beyond 1 year after DES implantation. It is possible that the correlates for DES thrombosis beyond 1 year are different from those correlates for early time points of ST. Of note, combining both clinical and angiographic correlates into a combined multivariable model identified younger age, current smoker, multivessel disease, type C lesions, longer total stent length, and overlapping stents as the strongest correlates in this combined model.

ANTIPLATELET THERAPY. The most powerful predictor of DES thrombosis is early cessation of DAPT, especially within the first 30 days of stent implantation (31,32,39). By design, the DESERT focused exclusively on patients who had the event beyond 30 days, so discontinuation of DAPT at that early time was not applicable for this registry. In the DESERT, in patients who had ST within the first year, half were receiving DAPT at the time of the event, and after the first year, nearly one-fourth of the patients who had very late ST were receiving DAPT. These findings suggest that taking DAPT is not a magic bullet for preventing late ST, and other non-antiplatelet-related mechanisms may contribute to the late ST phenomenon. Among these potential mechanisms are late restenosis with progression or narrowing of the stent lumen and neoatherosclerosis as a result of local inflammation of the polymer that may result in rupture of a new form of atherosclerotic plaque (43,44). Neither mechanism is related to incomplete healing or is known to be protected by DAPT. Although the guidelines recommend at least 12 months of DAPT (45,46), the optimal duration of

TABLE 5 Antiplatelet Therapy Adherence

ST (n = 492)	DES Implant Discharge	Receiving at ST	Not Receiving at ST	If Not, Stopped Within 5 Days of ST	Unknown at ST
Aspirin, %	99.2	74.8	24.5	18.1	3.5
Clopidogrel, %	98.6	32.4	65.5	15.3	4.3
Ticlopidine, %	1.2	0.4	1.2	0	1.2
Prasugrel, %	0.4	0.4	0	–	–
Dual-antiplatelet therapy, %	99.2	30.2	71.1	11.0	2.0

	ST ≤1 Year (n = 120)		ST >1 Year (n = 371)		
	On	Off	On	Off	p Value
Aspirin, %	77.4	20.9	74.0	25.7	0.356
Clopidogrel, %	54.8	43.5	25.1	72.6	<0.001
Ticlopidine, %	0.8	0	0.3	1.6	0.344
Prasugrel, %	0.8	0	0.3	0	–
Dual-antiplatelet therapy, %	51.8	49.1	23.1	78.3	<0.001

DES = drug-eluting stent(s); ST = stent thrombosis.

TABLE 6 Clinical and Angiographic Correlates of Late/Very Late Stent Thrombosis

Variable	Clinical, OR (95% CI)	Angiographic	Combined, OR (95% CI)
Age	**0.964 (0.95–0.98)**	*	**0.793 (0.96–0.99)**
Hypertension	0.757 (0.51–1.12)	*	0.863 (0.56–1.34)
Body mass index	0.979 (0.95–1.01)	*	0.981 (0.95–1.01)
ACS/NSTEMI	1.084 (0.70–1.67)	*	0.831 (0.54–1.28)
Left anterior descending lesion	1.107 (0.77–1.59)	**1.671 (1.21–2.32)**	1.302 (0.87–1.96)
Current smoker	**1.890 (1.26–2.85)**	*	**1.633 (1.05–2.53)**
STEMI or thrombus (QCA)	1.059 (0.62–1.80)	**1.486 (1.03, 2.14)**	1.062 (0.66–1.71)
African American	**2.346 (1.21–4.54)**	*	1.612 (0.65–3.99)
Diabetes	0.915 (0.60–1.40)	*	1.021 (0.65–1.60)
Renal insufficiency	1.019 (0.50–2.09)	*	*
No. of diseased vessels	**1.313 (1.05–1.65)**	*	**1.712 (1.32–2.22)**
Type C lesion (QCA)	*	0.939 (0.54–1.63)	**2.188 (1.38–3.47)**
Final reference vessel diameter, mm	*	1.190 (0.77–1.85)	1.436 (0.84–2.44)
Acute gain, mm	*	0.982 (0.64–1.51)	1.013 (0.64–1.61)
Final in-stent diameter stenosis	*	**1.021 (1.00–1.04)**	1.014 (0.99–1.04)
Total stented length	**1.015 (1.00–1.03)**	1.022 (1.00–1.05)	**0.977 (0.97–0.99)**
Bypass graft lesion	**3.306 (1.18–9.27)**	**3.900 (1.55–9.84)**	1.997 (0.60–6.70)
Lesion length (QCA)	*	0.999 (0.97–1.03)	*
Overlapping stents	**1.757 (1.18–2.61)**	*	**2.220 (1.34–3.69)**

Each of the 3 models (clinical, angiographic, and combined) were run independently. *Variable not included in this particular model. Significant correlates are indicated in **bold**.

ACS/NSTEMI = acute coronary syndrome/non-ST-segment elevation myocardial infarction; CI = confidence interval; OR = odds ratio; QCA = quantitative coronary angiography; STEMI = ST-segment elevation myocardial infarction.

DAPT post-DES implantation remains controversial: some suggest 3 to 6 months, whereas others suggest ≥24 to 36 months for this high-risk population. The DESERT does not support the idea that a longer duration of DAPT beyond 1 year will further reduce very late ST. Perhaps the focus should be broadened to include not only DAPT duration but also recognize the other associated correlates as detected in the DESERT.

CLINICAL PRESENTATION AND OUTCOME. Although the main presentation of the patients with late/very late DES thrombosis was MI, and nearly 75% of these patients presented with TIMI flow grade 0 on angiography, the clinical outcome of late/very late ST was favorable in terms of in-hospital and 1-year mortality compared with historical series of patients with acute and subacute DES thrombosis.

van Werkhum et al. (22) reported on a cohort of 437 ST patients initially treated with BMS and DES and observed an in-hospital mortality rate of 6% and a 1-year mortality rate of 10.7%, which is 3 times higher than what we observed. This substantial difference in mortality can be explained by the time interval between the first DES implantation to the ST event that allows the patient to recover from the first event. Only 26% of ST patients presented with late ST in the Dutch registry, whereas only patients with late ST were included in our registry. Another explanation could be related to the mechanism for late/very late ST. In the case of late restenosis or neoatherosclerosis within the stent, the event is not as abrupt as with subacute DES thrombosis, and the patient may experience preconditioning ischemia, or collaterals may even develop that mitigate the adverse clinical outcome of the ST event.

Early-generation DES, compared with BMS, were associated with an increased risk of very late ST; however, mortality rates did not differ. Our observation of low mortality after late/very late ST explains at least in part why differences in ST did not translate into an increased mortality with DES. Conversely, newer generation DES have been associated with a decrease in both early and late/very late ST (47,48) compared with BMS. Whether this will translate into a mortality benefit in favor of newer generation DES remains to be seen.

Despite the modest presentation of late/very late DES thrombosis compared with acute and subacute ST, it is not a benign phenomenon and continues to be unpredictable in its occurrence for patients undergoing DES implantation (49). Once the mechanisms of the phenomenon are better understood, this phenomenon may be prevented or eliminated. It would be interesting to follow newer generation DES, particularly with biodegradable polymers and scaffolds, to determine whether changes in the device can minimize its incidence. Meanwhile, a focus on modifiable risk factors, such as smoking, should be emphasized for patients undergoing stent implantation.

STUDY LIMITATIONS. The DESERT has several limitations. First, as a case-control study, we were unable to provide direct insight into the incidence of late/very late ST in the study population. In addition, in the DESERT, 90% of the patients in both groups had first-generation DES and different correlates may apply for second-generation DES. Finally, because we wanted to use a highly specific definition of ST, virtually all of the ST cases in our series are patients who survived to coronary angiography. As a result, we may have underestimated the prognostic impact of late/very late DES thrombosis (by excluding patients whose initial presentation was sudden cardiac death. Nevertheless, the DESERT registry is the largest report of patients who presented with late/very late ST, and given the millions of patients who are living with DES, the results of the study can be used to alert physicians and patients to the potential late risk of this phenomenon.

CONCLUSIONS

Patients with first-generation DES continue to be at risk of late ST beyond 7 years. Younger patients, smokers at the time of initial DES implantation, patients with multivessel disease, bypass grafts, or thrombus are at higher risk of the development of late ST and should therefore be considered for alternative treatments. The lower mortality rates seen with late ST compared with historically reported acute and subacute ST suggest a different pathological mechanism for this phenomenon (late restenosis and/or neoatherosclerosis). The role of antiplatelet therapy to prevent late ST is not proven to be beneficial, and further improvement in the technology of DES is required to minimize the phenomenon of late ST. Meanwhile, we hope that knowing the correlates of late DES thrombosis as they are identified in the DESERT may be useful to minimize this troubling phenomenon.

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APPENDIX For a list of the investigators, please see the online version of this article.