Stent Thrombosis in New-Generation Drug-Eluting Stents in Patients With STEMI Undergoing Primary PCI

A Report From SCAAR

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ABSTRACT

BACKGROUND Some concerns still have not been resolved about the long-term safety of drug-eluting stents (DES) in patients with acute STEMI.

OBJECTIVES The aim of this study was to evaluate the stent thrombosis (ST) rate up to 3 years in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI) with new-generation drug-eluting stents (n-DES) compared with bare-metal stents (BMS) and old-generation drug-eluting stents (o-DES) enrolled in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry).

METHODS From January 2007 to January 2013, 34,147 patients with STEMI were treated by PCI with n-DES (n = 4,811), o-DES (n = 4,271), or BMS (n = 25,065). The risks of early/late (up to 1 year) and very late definite ST (after 1 year) were estimated.

RESULTS Cox regression landmark analysis showed a significantly lower risk of early/late ST in patients treated with n-DES (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.43 to 0.99; p = 0.04) and o-DES (HR: 0.60; 95% CI: 0.41 to 0.89; p = 0.01) compared with the BMS group. The risk of very late ST was similar between the n-DES and BMS groups (HR: 1.52; 95% CI: 0.78 to 2.98; p = 0.21), whereas a higher risk of very late ST was observed with o-DES compared with BMS (HR: 2.88; 95% CI: 1.70 to 4.89; p < 0.01).

CONCLUSIONS Patients treated with n-DES have a lower risk of early/late ST than patients treated with BMS. The risk of very late ST is low and comparable between n-DES and BMS up to 3 years of follow-up, whereas o-DES treatment is associated with an increased risk of very late ST. The current STEMI guidelines might require an update in light of the results of this and other recent studies. (J Am Coll Cardiol 2014;64:16–24) © 2014 by the American College of Cardiology Foundation.

Drug-eluting stents (DES) have been shown to significantly reduce the rate of restenosis and target lesion revascularization (1,2), and consequently, their use has been commonly extended to complex lesions and acute clinical settings (3-6). Concerns have been raised and still not resolved about the long-term safety of DES in patients with acute ST-segment elevation myocardial infarction (STEMI).

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Platelet activation is increased in patients with STEMI (7,8). Moreover, a delay in arterial healing has been recognized at the culprit site in patients with STEMI compared with patients treated for stable angina (9). Percutaneous coronary intervention (PCI) in STEMI patients is therefore associated with a higher risk of stent thrombosis (ST) (10-12).

Comparisons of new-generation DES (n-DES) and bare-metal stents (BMS) in the STEMI setting (13-15) are limited. The available data on the outcome of PCI in STEMI patients are mainly based on comparisons of old-generation DES (o-DES) and BMS (16-22).

The objective of this study was to evaluate the ST rate up to 3 years in patients with STEMI treated by PCI with n-DES compared with BMS and o-DES documented in a national registry with complete consecutive enrollment, the SCAAR (Swedish Coronary Angiography and Angioplasty Registry).

METHODS

All consecutive patients in Sweden with STEMI undergoing primary PCI from January 2007 to January 2013 were included. The n-DES group included the Endeavor Resolute (Medtronic Inc., Minneapolis, Minnesota); Xience V and Xience Prime (Abbott Vascular, Santa Clara, California); Promus and Promus Element (Boston Scientific, Natick, Massachusetts). The o-DES group included the Cypher and Cypher Select (Cordis Corporation, Miami, Florida), Taxus Express and Taxus Liberté (Boston Scientific), and Endeavor (Medtronic). The BMS group included the Multilink Vision, Multilink MiniVision, Multilink 8, and Multilink Flexmaster (Abbott Vascular); Driver, Micro Driver coronary, and Integrity (Medtronic); Liberté (Boston Scientific); Braun Coroflex Blue (B. Braun, Melsungen, Germany); and Chrono stent (CID, Saluggia, Italy). The choice of stent type was at the operator's discretion.

Definite ST was defined according to the Academic Research Consortium definition (23).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD and discrete variables
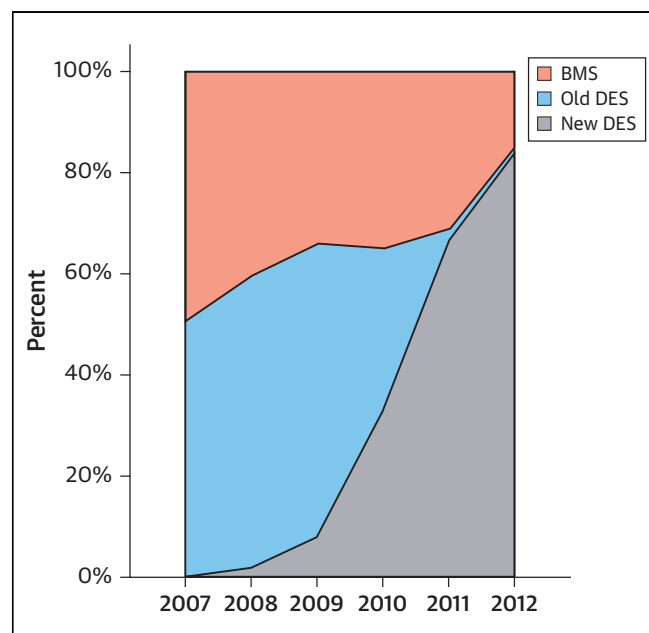
as percentages. Differences in means among groups were analyzed by a 2-sided *t* test or by 1-way analysis of variance using a Tukey-Kramer test to compare all pairs. Categorical variables are expressed as absolute numbers and percentages. Differences in categorical variables were analyzed by the chi-square test.

The predefined primary endpoint was to evaluate the ST rate after the implantation of n-DES, o-DES, and BMS in STEMI patients. The log-minus-log test was used to assess the proportional hazard assumption. Analyses were based on the first recorded procedure during the inclusion period to avoid duplicate entries. For patients receiving several stents during the same procedure, only 1 stent was randomly selected and followed over time. Patients with cardiogenic shock were excluded.

The cumulative adjusted hazard risk (HR) of ST up to 3 years was calculated using Cox proportional hazard method. The Cox analysis models were censored up to 3 years. Propensity score analysis was used to compensate for the nonrandomized nature of this study. The propensity score models were defined as the conditional probability of receiving a

FIGURE 1 Distribution of the Use of n-DES, o-DES, and BMS During the Study Period

The use of new-generation drug-eluting stents (n-DES) increased from 10% in 2009 to 85% in 2012. The use of bare-metal stents (BMS) decreased from 50% in 2007 to 15% in 2012. The use of old-generation drug-eluting stents (o-DES) decreased from 50% in 2007 to 0.1% in 2012.

TABLE 1 Baseline Characteristics (N = 34,147)

Variable	n-DES* (n = 4,811)	o-DES† (n = 4,271)	BMS (n = 25,065)
Women	1,295 (26.9)	1,119 (26.2)	7,183 (28.7)
Body mass index, kg/m^2	27.1 ± 4.5	27.08 ± 4.3	26.7 ± 5.2
Age, yrs	65.8 ± 10.9	66.1 ± 11.2	67.3 ± 12.1
Hypertension	2,181 (45.3)	1,968 (46.1)	9,994 (39.9)
Diabetes mellitus	862 (18.0)	879 (20.6)	2,979 (11.5)
Insulin treatment	406 (8.4)	395 (9.2)	1,176 (4.7)
Noninsulin treatment	451 (9.4)	483 (11.3)	1,668 (10.3)
Unknown treatment	57 (1.2)	43 (1.0)	370 (1.5)
Hypercholesterolemia	1,270 (26.4)	1,211 (28.4)	4,744 (18.6)
Smoking status			
Former smoker	1,329 (27.6)	1,237 (29.0)	6,313 (25.2)
Current smoker	1,393 (29.0)	1,189 (27.8)	7,171 (28.6)
Previous MI	817 (17.0)	834 (19.5)	3,072 (12.3)
Previous CABG	204 (4.2)	198 (4.6)	764 (3.0)

Values are n (%) or mean ± SD. *p value for n-DES versus o-DES <0.05 for diabetes mellitus, smoking status, previous MI. †p value for o-DES versus BMS <0.05 for all variables.

BMS = bare-metal stent(s); CABG = coronary artery bypass grafting; MI = myocardial infarction; n-DES = new-generation drug-eluting stent(s); o-DES = old-generation drug-eluting stent(s).

TABLE 2 Procedural Characteristics (N = 34,147)

Variable	n-DES* (n = 4,811)	o-DES† (N = 4,271)	BMS (n = 25,065)
No. of stents per procedure	1.96 ± 1.10	1.96 ± 1.08	1.78 ± 0.99
Stent diameter, mm	2.96 ± 0.46	3.01 ± 0.50	3.16 ± 0.49
Total stent length, mm	20.08 ± 7.37	20.10 ± 7.19	17.85 ± 5.78
Treated vessel			
RCA	1,551 (32.2)	1,435 (33.6)	11,051 (44.1)
Left main	73 (1.5)	91 (2.1)	154 (0.6)
LAD	2,406 (47.8)	2,041 (47.8)	10,002 (39.9)
LCX	699 (14.5)	621 (14.5)	3,544 (14.1)
CABG	82 (1.7)	83 (1.9)	314 (1.2)
Bifurcation lesions	616 (12.8)	494 (11.6)	1,941 (7.8)
3-vessel disease	859 (17.9)	763 (17.9)	4,750 (19)
Procedural success	4,741 (98.5)	4,174 (97.7)	24,591 (98.1)
Medications before PCI			
ASA	4,203 (87.4)	3,702 (86.7)	21,394 (85.4)
Clopidogrel	3,010 (62.6)	2,393 (56.0)	18,134 (72.3)
Ticagrelor	493 (17.7)	874 (37.4)	797 (12.4)
Bivalirudin	36 (0.7)	22 (0.5)	88 (0.4)
GP IIb/IIIa	111 (2.3)	131 (3.1)	1,237 (4.9)
Heparin	6,858 (27.4)	1,552 (36.3)	1,960 (40.7)
LMWH	136 (2.8)	170 (4.0)	2,128 (8.5)
Medications during PCI			
ASA	514 (10.7)	515 (12.0)	3,233 (12.9)
Clopidogrel	1,115 (23.2)	983 (23.0)	5,727 (22.8)
Ticagrelor	363 (13.8)	434 (20.2)	513 (11.7)
Bivalirudin	3,168 (65.8)	2,583 (60.5)	11,296 (45.1)
GP IIb/IIIa	1,170 (24.3)	1,332 (31.2)	10,878 (43.4)
Heparin	2,599 (54.0)	2,322 (54.4)	14,616 (58.3)
LMWH	188 (3.9)	188 (4.4)	1,265 (5.0)

Values are mean ± SD or n (%). *p value for n-DES versus o-DES: <0.05 for clopidogrel, ticagrelor, heparin, LMWH before PCI, ticagrelor, bivalirudin, GP IIb/IIIa during PCI. †p value for o-DES versus BMS: <0.05 for all variables unless bivalirudin before PCI.

ASA = acetylsalicylic acid; GP = glycoprotein; LAD = left anterior descending artery; LCX = left circumflex artery; LMWH = low molecular weight heparin; PCI = percutaneous coronary intervention; RCA = right coronary artery.

DES (n-DES or o-DES) or a BMS on the basis of available variables and were estimated with a multiple logistic regression model. The pre-specified variables included in the 3 propensity score models for the different comparisons were age, sex, diabetes, hypertension, dyslipidemia, smoking status, use of acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, and/or P2Y$_{12}$ receptor inhibitors at the index procedure, treated vessel, previous myocardial infarction, previous coronary artery bypass grafting, previous PCI, year of the index procedure, enrolling center, lesion type, bifurcation lesions, and 3-vessel/left main disease.

The C-index for the ability of propensity score to differentiate o-DES and n-DES from BMS and o-DES from n-DES was 0.92, 0.91, and 0.87, respectively.

Adjusted relative risks in the n-DES, o-DES, and BMS groups were estimated with the use of Cox regression models in which the propensity score and the stent group were entered as covariates.

All reported p values are 2-sided. All analyses were performed with the use of SPSS statistical software (version 19.0, SPSS Inc., Chicago, Illinois).

RESULTS

During the study period, 34,147 patients with STEMI were treated by PCI with n-DES (n = 4,811), o-DES (n = 4,271), or BMS (n = 25,065). The relative distribution of n-DES, o-DES, and BMS during the study period is described in **Figure 1**.

Baseline characteristics are listed in **Table 1**. The clinical risk profile was higher in the DES groups compared with the BMS group with no relevant differences between the n-DES and o-DES groups.

Procedural characteristics are shown in **Table 2**. Ticagrelor was more often used in the o-DES group, whereas lower use of bivalirudin was observed in the BMS group. Also, glycoprotein IIb/IIIa inhibitors were more often used with BMS.

The assumption of proportionality of the hazards for ST during the 3-year follow-up period was not met (p = 0.07). Therefore, we performed a landmark analysis with a pre-specified landmark set at 1 year to provide separate descriptions of the early/late (up to 1 year) and very late risks of ST (>1 year) events. The total number of events of definite ST up to 3 years was 544. The cumulative rates of ST up to 3 years in the n-DES, o-DES, and BMS groups are shown in **Figure 2**.

EARLY/LATE ST. Cox regression landmark analysis adjusted by propensity score showed a significantly lower risk of early/late ST in the n-DES and o-DES groups compared with the BMS group. There was no
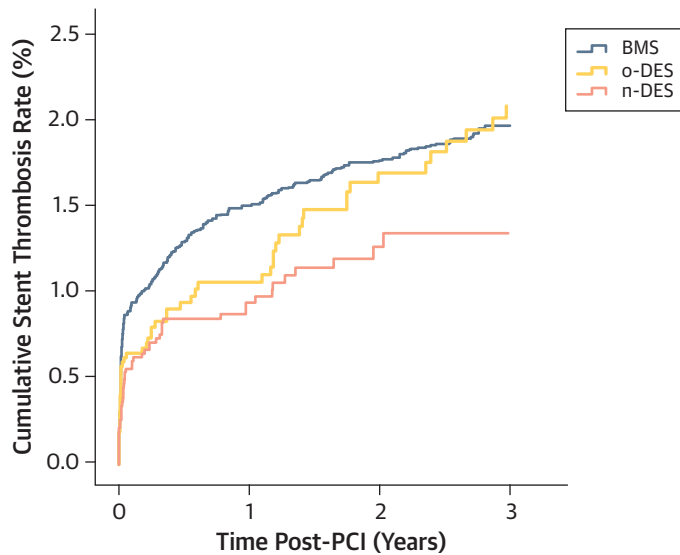
N patients at risk. (event rate %)	0 months	30 days	1 year	2 years	3 years
BMS	25065	24851 (0.9%)	21962 (1.5%)	19336 (1.8%)	15882 (2.0%)
o-DES	4271	4137 (0.6%)	3869 (1.1%)	2154 (1.7%)	1661 (2.1%)
n-DES	4811	4649 (0.5%)	4497 (0.9%)	2751 (1.2%)	1235 (1.3%)

FIGURE 2 Cumulative Rates of Definite Stent Thrombosis Up to 3 Years in the n-DES, o-DES, and BMS Groups

The curves showing the cumulative rates of stent thrombosis in the n-DES and o-DES groups start to diverge before 6 months post-percutaneous coronary intervention (PCI) with a further step-up in the o-DES group after 1 year. The rates of stent thrombosis in the BMS group increased constantly up to 3 years. Abbreviations as in **Figure 1**.

significant difference between n-DES and o-DES in the risk of early/late ST (**Fig. 3**, **Table 3**).

Cox regression analysis showed no statistically significant impact of bivalirudin use (HR: 1.17; 95% confidence interval [CI]: 0.93 to 1.46), glycoprotein IIb/IIIa inhibitors (HR: 0.95; 95% CI: 0.74 to 1.22), and ticagrelor (HR: 1.09; 95% CI: 0.49 to 2.39) on the early ST risk up to 30 days.

VERY LATE ST. There was no significant difference in the risk of very late ST between the n-DES group and the BMS group, whereas a higher risk of very late ST was observed in the o-DES group compared with the BMS group. There was no significant difference between the n-DES and o-DES groups in the risk of very late ST (**Fig. 3**, **Table 3**).

ALL-CAUSE MORTALITY. The total number of events of death up to 3 years was 3,579. The cumulative rates of death up to 3 years in the n-DES, o-DES, and BMS groups are shown in **Figure 4**.

The risk of death was significantly and constantly lower in the n-DES (adjusted HR: 0.55; 95% CI: 0.48

to 0.62) and o-DES (adjusted HR: 0.58; 95% CI: 0.52 to 0.65) groups compared with the BMS group. No significant differences were observed between the n-DES and o-DES groups (adjusted HR: 1.05; 95% CI: 0.89 to 1.24).

DISCUSSION

The main findings of this study were as follows: 1) a significant lower risk of ST during the first year after PCI with both n-DES and o-DES compared with BMS, but a higher risk of very late ST up to 3 years in the o-DES group compared with the BMS group; and 2) a similar risk of very late ST in the n-DES and BMS groups.

Differently from the previously published results of an unselected all-comers population of the SCAAR (24), in this population of STEMI patients enrolled consecutively in the SCAAR, a significantly lower risk of ST in both the n-DES and o-DES groups was observed only during the first year after PCI, with an ST rate at 1 year of 0.9% in the n-DES group versus
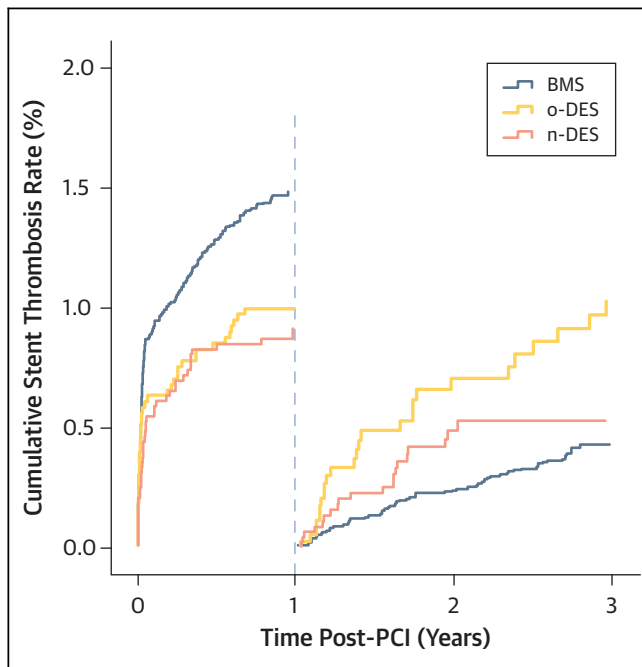
FIGURE 3   Landmark Analysis of Definite Stent Thrombosis in n-DES, o-DES, and BMS

The curves showing the cumulative rates of very late stent thrombosis are similar in n-DES and BMS. Very late stent thrombosis rate is significantly higher with o-DES compared with BMS. Although the rate of very late stent thrombosis up to 3 years is lower in n-DES compared with o-DES, no significant difference between n-DES and o-DES was observed. Abbreviations as in **Figure 1**.

significant decrease in in-stent restenosis, whereas no differences in ST were observed in up to 2 years follow-up. Other smaller randomized, first-generation DES/BMS studies (16,20,21,27) found similar results, with reduced rates of repeat revascularization in first-generation DES and no difference between first-generation DES and BMS in the risk of ST up to 4 and 5 years. However, in the TYPHOON (Trial to Assess the Use of the CYPHer Sirolimus-Eluting Coronary Stent in Acute Myocardial Infarction Treated With BallOON Angioplasty) study (16), although the overall rate of ST up to 4 years was similar between the sirolimus-eluting stent (SES) group and the BMS group (3.6% vs. 4.0%, respectively), the rate of very late ST was numerically higher in the SES group (2.0% vs. 0.8%) without reaching statistical significance. Similarly, in the PAS-SION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) study (28), the rates of late/very late ST were 3.2% in patients treated with PES versus 1.1% in the BMS group (p = 0.09). Data from a single-center registry of 1,738 patients with STEMI (29) also showed a very late ST rate of 2.7% in a group of patients treated with SESs compared with 0.9% in patients treated with PES, whereas no cases of ST were observed in the BMS group at a median follow-up of 3 years.

Consistent with these findings, a recent meta-analysis on 6,270 patients with STEMI from 11 randomized studies (30) also found a higher rate of very late ST in patients treated with o-DES compared with patients treated with BMS.

Our finding of a higher risk of very late ST in the o-DES group compared with the BMS group confirms concerns about the use of o-DES in the STEMI setting, which have led to a Class IIA recommendation for the use of DES in the current STEMI guidelines (31).

Looking at **Figure 1**, the ST rates deviate after the first days of follow-up with an early ST rate (up to 30 days) of 0.5% and 0.6% in the n-DES and o-DES groups, respectively, versus 0.9% in the BMS group. As a multifactorial event, ST is difficult to differentiate between patient characteristics, lesion, and procedural precipitating factors and features associated with the device.

Our finding of a lower risk of ST in patients treated with o-DES during the first year of follow-up and a

1.1% in the o-DES group and 1.5% in the BMS group. The ST rate in the o-DES group increased by 0.6% during the second year and by 0.4% during the third year of follow-up. The very late ST risk up to 3 years was more than doubled in the o-DES group compared with the BMS group.

Most previous randomized studies (19,22,25,26) failed to show any significant difference in the ST risk between DES and BMS, and this could be related to the limited statistical power inadequate to detect a small but statistically significant difference in low-frequency events such as ST.

In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study (22), the use of paclitaxel-eluting stents (PES) was associated with a statistically

TABLE 3   Adjusted Risks of Definite Stent Thrombosis

	n-DES vs. BMS	o-DES vs. BMS	n-DES vs. o-DES
Early/late ST	HR: 0.65; 95% CI: 0.43–0.99; p = 0.04	HR: 0.60; 95% CI: 0.41–0.89; p = 0.01	HR: 0.73; 95% CI: 0.44–1.21; p = 0.22
Very late ST	HR: 1.52; 95% CI: 0.78–2.98; p = 0.21	HR: 2.88; 95% CI: 1.70–4.89; p < 0.01	HR: 0.77; 95% CI: 0.23–1.47; p = 0.35

CI = confidence interval; HR = hazard ratio; ST = stent thrombosis; other abbreviations as in **Table 1**.

N patients at risk	0 months	30 days	1 year	2 years	3 years
BMS	25065	23893 (4.8%)	22757 (8.0%)	20322 (11.0%)	16954 (12.8%)
o-DES	4271	4148 (3.8%)	3912 (5.0%)	2228 (8.0%)	1754 (10.3%)
n-DES	4811	4657 (3.7%)	4520 (5.0%)	2793 (8.0%)	1266 (10.6%)

FIGURE 4 **Cumulative Rates of All-Cause Mortality Up to 3 Years in the n-DES, o-DES, and BMS Groups**

The curves showing the cumulative rates of all-cause mortality show a higher mortality rate with BMS compared with n-DES and o-DES. No significant differences were observed between n-DES and o-DES. DAPT = dual-antiplatelet therapy; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in **Figure 1**.
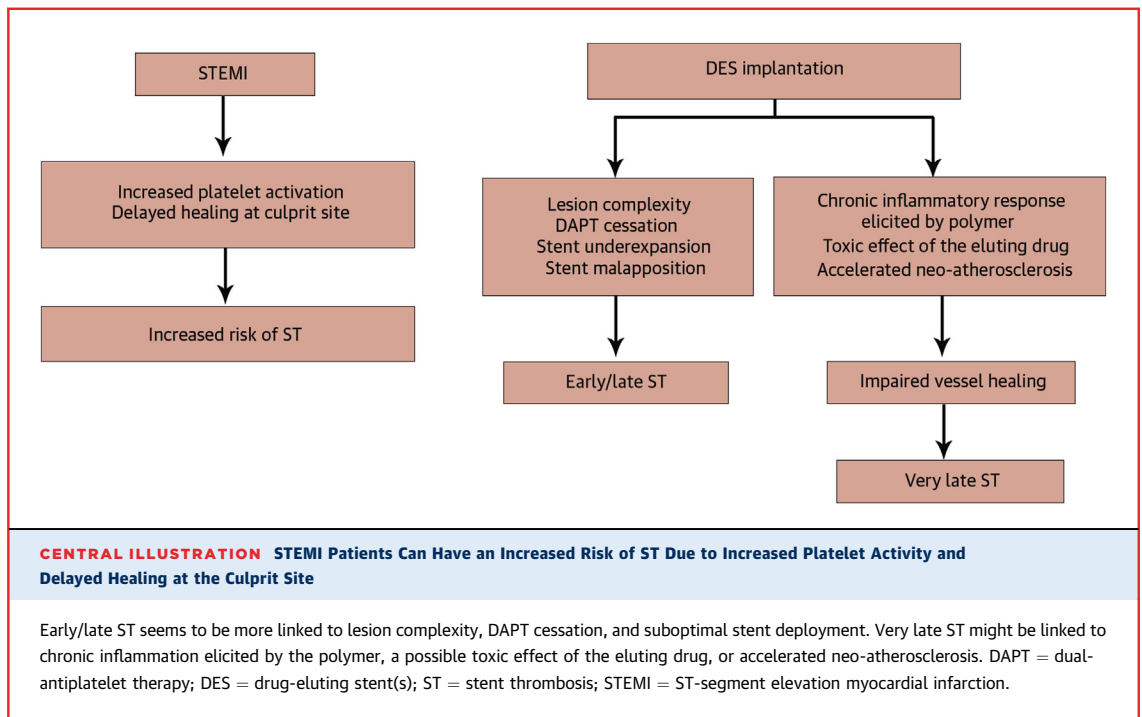
higher risk of very late ST compared with patients treated with BMS align with a previous meta-analysis (32) from 15 randomized, controlled trials (n = 7,867) comparing first-generation U.S. Food and Drug Administration–approved DES with BMS in patients with STEMI. In this meta-analysis, the early benefits of first-generation DES in reducing repeat revascularization and ST were offset by an increase in very late ST, and the authors suggest time-dependent effects of first-generation DES for ST. These findings support the hypothesis of 2 opposite, time-dependent effects that have been described for polymers used in DES technology—an early protective effect against ST and a late proinflammatory and prothrombotic effect. Recent studies on biodegradable polymers used in newer-generation DES (15) suggest the possibility of obtaining the early advantages of polymers while avoiding the very late hazards, which may be especially useful in patients with STEMI.

Unfortunately, we continue to lack data on the long-term duration of the dual-antiplatelet therapy (DAPT). In STEMI patients, the standard recommendation for DAPT was 1 year in both the DES and the BMS groups. However, it is unlikely that the DAPT duration has affected the results of very late ST. The early cessation of DAPT and other procedural factors, such as stent underexpansion, malapposition, and lesion complexity, are known to contribute mainly to the development of early and late ST (33). Very late ST seems more likely linked to impaired vessel healing (34,35), secondary to a chronic inflammatory response elicited by the permanent polymer and/or to accelerated neo-atherosclerosis (36,37) (**Central Illustration**).

In the current study, n-DES were associated with a lower risk of ST at 1 year and the risk of very late ST up to 3 years was similar to BMS. A similar risk of overall and very late ST between everolimus-eluting stents and BMS up to 2 years of follow-up was reported in a recent meta-analysis on 14,740 patients with STEMI from 28 randomized, controlled trials (38). In contrast, we found no statistically significant difference in the risk of ST between patients

CENTRAL ILLUSTRATION   STEMI Patients Can Have an Increased Risk of ST Due to Increased Platelet Activity and Delayed Healing at the Culprit Site

Early/late ST seems to be more linked to lesion complexity, DAPT cessation, and suboptimal stent deployment. Very late ST might be linked to chronic inflammation elicited by the polymer, a possible toxic effect of the eluting drug, or accelerated neo-atherosclerosis. DAPT = dual-antiplatelet therapy; DES = drug-eluting stent(s); ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction.

treated with n-DES or o-DES. Most likely, this could relate to a smaller number of patients treated with o-DES and n-DES during the study period, and the sample size might still be inadequate to determine a significant difference due to the low frequency of the event.

Although BMS have been proved to be safe in STEMI patients (39,40) and the improvements of the new stent platforms have reduced restenosis rates, DES are superior in terms of a decrease in restenosis occurrence. Our study shows that n-DES are associated with a low risk of ST even on long-term follow-up.

The advantages of o-DES over BMS at 1 year of follow-up in terms of ST are counterbalanced by a higher risk of very late ST.

The constantly significant higher mortality during the 3-year follow-up in the BMS group compared with the n-DES and o-DES groups cannot be simply explained by our ST findings.

STUDY LIMITATIONS. There are intrinsic limitations to registry data, such as differences in baseline characteristics and/or selection bias, which might not have been recorded, as well as time-dependent changes in outcome.

The definition of hypercholesterolemia, hypertension, and diabetes in the SCAAR is "medically treated" hypercholesterolemia, hypertension, and diabetes. Therefore, the actual incidence of these factors might have been underestimated.

Although we used a propensity score analysis to take into account possible factors related to patient and procedural characteristics and time, we cannot rule out the presence of selection bias and other unknown patient/procedure-related factors that could affect the outcome in this population. ST is a low-frequency event that can significantly affect the individual outcome (41,42), but it is less probable to affect the overall mortality in a large population.

Another limitation of the present study is the lack of information about the medical therapy during the follow-up and the duration and doses of $P2Y_{12}$ receptor inhibition treatment in individual patients.

CONCLUSIONS

This study shows that the use of new-generation DES in STEMI patients undergoing PCI is safe in short- and long-term follow-up, with a lower risk of early/late ST and a low risk of very late ST, similar to BMS. The current guidelines on STEMI might require an update in light of the results of this and other recent studies (13-15,38).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1:
The use of new-generation DES in patients with STEMI undergoing percutaneous coronary intervention is safe on short- and long-term follow-up with a lower risk of early/ late stent thrombosis and a low risk of very late stent thrombosis, similar to BMS.

COMPETENCY IN MEDICAL KNOWLEDGE 2:
Our finding of a higher risk of very late stent thrombosis

in the older-generation DES group compared with the BMS group confirms concerns about the use of older- generation DES in the STEMI setting that have led to a Class IIA recommendation for the use of DES in the current STEMI guidelines.

TRANSLATIONAL OUTLOOK: The current guidelines on STEMI might require an update in light of the results of this and other recent studies.

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