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Stent-Related Adverse Events >1 Year After Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND The majority of stent-related major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) are believed to occur within the first year. Very-late (>1-year) stent-related MACE have not been well described.

OBJECTIVES The purpose of this study was to assess the frequency and predictors of very-late stent-related events or MACE by stent type.

METHODS Individual patient data from 19 prospective, randomized metallic stent trials maintained at a leading academic research organization were pooled. Very-late MACE (a composite of cardiac death, myocardial infarction [MI], or ischemia-driven target lesion revascularization [ID-TLR]), and target lesion failure (cardiac death, target-vessel MI, or ID-TLR) were assessed within year 1 and between 1 and 5 years after PCI with bare-metal stents (BMS), first-generation drug-eluting stents (DES1) and second-generation drug-eluting stents (DES2). A network meta-analysis was performed to evaluate direct and indirect comparisons.

RESULTS Among 25,032 total patients, 3,718, 7,934, and 13,380 were treated with BMS, DES1, and DES2, respectively. MACE rates within 1 year after PCI were progressively lower after treatment with BMS versus DES1 versus DES2 (17.9% vs. 8.2% vs. 5.1%, respectively, $p < 0.0001$). Between years 1 and 5, very-late MACE occurred in 9.4% of patients (including 2.9% cardiac death, 3.1% MI, and 5.1% ID-TLR). Very-late MACE occurred in 9.7%, 11.0%, and 8.3% of patients treated with BMS, DES1, and DES2, respectively ($p < 0.0001$), linearly increasing between 1 and 5 years. Similar findings were observed for target lesion failure in 19,578 patients from 12 trials. Findings were confirmed in the network meta-analysis.

CONCLUSIONS In this large-scale, individual patient data pooled study, very-late stent-related events occurred between 1 and 5 years after PCI at a rate of ~2%/year with all stent types, with no plateau evident. New approaches are required to improve long-term outcomes after PCI. (J Am Coll Cardiol 2020;75:590–604) © 2020 by the American College of Cardiology Foundation.

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Contemporary drug-eluting stents (DES) have improved event-free survival in patients undergoing percutaneous coronary intervention (PCI) compared with earlier stent designs (1,2). Although common belief holds that the majority of major adverse cardiovascular events (MACE) after PCI occur within the first year after treatment (3), very-late (>1-year) events may originate from the stented target lesion with all devices (1,2,4–13). Characterizing the frequency and type of these very-late stent-related events is important, as many patients will live for many years with permanently implanted coronary devices. In addition, differences in clinical outcomes between devices present at 1 year do not necessarily predict later events (6,11,12). In this regard, the frequency and predictors of stent-related MACE after the first year have not been comprehensively studied. We thus sought to examine very-late outcomes after PCI from a large individual patient data (IPD) pooled analysis of randomized metallic stent trials.

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METHODS

STUDY PROTOCOL. A PubMed search using the terms "drug-eluting stent" and "drug-eluting stents" returned 284 randomized trials. Pooling all such studies was not feasible (Online Figure 1). We thus pooled all randomized comparative trials of coronary stents with >1-year follow-up maintained at a leading interventional cardiology academic research organization (Cardiovascular Research Foundation, New York, New York). The current analysis includes 19 randomized trials (summarized in Online Table 1): RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), SIRIUS (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), E-SIRIUS (European Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), C-SIRIUS (Canadian Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), TAXUS II (Randomized Study to Assess the Effectiveness of Slow- and Moderate-Release Polymer-Based Paclitaxel-Eluting Stents for Coronary Artery Lesions), TAXUS IV (A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease), TAXUS V (Comparison of a Polymer-Based Paclitaxel-Eluting Stent with a Bare Metal Stent in Patients with Complex Coronary Artery Disease), ENDEAVOR II (Randomized, Double-Blind, Multicenter Study of the Endeavor Zotarolimus-Eluting Phosphorylcholine-Encapsulated Stent for Treatment of Native Coronary Artery Lesions), ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions), ENDEAVOR IV (Randomized Comparison of Zotarolimus-Eluting and Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease), HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction), SPIRIT II (A Randomised Comparison of an Everolimus-Eluting Coronary Stent with a Paclitaxel-Eluting Coronary Stent), SPIRIT III (Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease), SPIRIT IV (Everolimus-Eluting versus Paclitaxel-Eluting Stents in Coronary Artery Disease),

ABBREVIATIONS AND ACRONYMS

BES = biolimus-eluting stents
BMS = bare-metal stents
BVS = bioresorbable vascular scaffolds
CAD = coronary artery disease
DES = drug-eluting stents
DES1 = first-generation drug-eluting stents
DES2 = second-generation drug-eluting stents
EES = everolimus-eluting stents
ID-TLR = ischemia-driven target lesion revascularization
IPD = individual patient data
MACE = major adverse cardiovascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLF = target lesion failure

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TABLE 1 Baseline Clinical Characteristics by Stent Type

	All Patients (N = 25,032)	BMS (n = 3,718)	DES1 (n = 7,934)	DES2 (n = 13,380)	Overall p Value
Age, yrs	62.7 ± 10.9	61.6 ± 10.8	62.4 ± 11.2	63.3 ± 10.7	<0.0001
Male	71.9 (17,984/25,027)	73.2 (2,719/3,715)	72.2 (5,728/7,933)	71.3 (9,537/13,379)	0.05
White	92.9 (13,603/14,644)	93.7 (2,376/2,537)	93.9 (5,647/5,822)	91.6 (5,760/6,285)	<0.0001
BMI, kg/m^2	28.9 ± 5.3	28.6 ± 5.2	29.1 ± 5.5	28.9 ± 5.3	0.002
Diabetes mellitus	23.6 (5,907/25,013)	22.7 (844/3,712)	23.4 (1,857/7,927)	24.0 (3,206/13,374)	0.26
Insulin-treated	6.8 (1,699/25,013)	6.8 (253/3,712)	6.4 (509/7,927)	7.0 (937/13,374)	0.26
Recent smoker	27.6 (6,822/24,753)	30.0 (1,105/3,681)	30.6 (2,398/7,831)	25.1 (3,319/13,241)	<0.0001
Hypertension	64.2 (16,035/24,993)	64.4 (2,382/3,701)	64.4 (5,102/7,921)	64.0 (8,551/13,371)	0.77
Hyperlipidemia	64.6 (16,041/24,846)	65.9 (2,432/3,692)	62.6 (4,934/7,885)	65.4 (8,875/13,269)	<0.0001
Prior MI	23.0 (5,701/24,824)	29.6 (1,097/3,706)	20.3 (1,598/7,868)	22.7 (3,006/13,250)	<0.0001
Prior PCI	19.4 (4,835/24,932)	20.9 (775/3,706)	18.1 (1,433/7,903)	19.7 (2,627/13,323)	0.0007
Prior CABG	6.9 (1,720/25,022)	6.7 (250/3,715)	6.1 (480/7,932)	7.4 (990/13,375)	0.0008
LVEF, %	57.6 ± 11.0	57.1 ± 11.2	57.1 ± 11.3	58.8 ± 10.3	<0.0001
<40%	5.6 (561/10,100)	6.1 (168/2,755)	6.7 (289/4,355)	3.5 (104/3,010)	<0.0001
Clinical presentation					
ACS	52.6 (12,128/23,054)	54.9 (1,847/3,367)	62.2 (4,510/7,255)	46.4 (5,771/12,432)	<0.0001
STEMI	17.6 (4,397/25,029)	20.1 (749/3,718)	31.1 (2,469/7,931)	8.8 (1,179/13,380)	<0.0001
NSTEMI	8.0 (2,003/25,029)	0.0 (0/3,718)	3.0 (235/7,931)	13.2 (1,768/13,380)	<0.0001
Unstable angina	24.8 (5,728/23,054)	32.6 (1,098/3,367)	24.9 (1,806/7,255)	22.7 (2,824/12,432)	<0.0001
SIHD	47.4 (10,926/23,054)	45.1 (1,520/3,367)	37.8 (2,745/7,255)	53.6 (6,661/12,432)	<0.0001

Values are mean ± SD or % (n/N).

ACS = acute coronary syndrome; BMI = body mass index; BMS = bare metal stents; CABG = coronary artery bypass graft; DES1 = first-generation drug-eluting stents; DES2 = second-generation drug-eluting stents; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; STEMI = ST-segment elevation myocardial infarction.

PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions), COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-life Practice), COMPARE II (Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent), TWENTE (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente), and TWENTE II/DUTCH PEERS (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente II/Durable Polymer-Based Stent Challenge of Promus Element versus Resolute Integrity). All trials were approved by their respective individual institutional review committees. Baseline patient and lesion characteristics, procedural details, and event rates were confirmed to be consistent with prior publications. Investigators and sponsors were contacted to clarify definitions and reconcile data inconsistencies. IPD from these trials were pooled to create the master dataset. The present study was performed according to modified PRISMA-IPD guidelines (14) (Online Table 2). The Cochrane tool was used to evaluate the risk of bias (15).

The majority of patients enrolled in these trials presented with stable ischemic heart disease (stable angina or silent ischemia); however, 6 trials included patients presenting with ST-segment elevation myocardial infarction (MI) or non-ST-segment elevation MI. DES platforms included sirolimus-eluting stents (SES) (CYPHER, Cordis, Johnson & Johnson, Miami Lakes, Florida); paclitaxel-eluting stents (PES) (TAXUS, Boston Scientific, Marlborough, Massachusetts); everolimus-eluting stents (EES) (cobalt chromium: XIENCE, Abbott Vascular, Santa Clara, California, and Promus, Boston Scientific; platinum chromium: Promus Element, Boston Scientific); fast-release zotarolimus-eluting stents (ZES) (Endeavor, Medtronic, Santa Rosa, California); slow-release ZES (Resolute, Medtronic); and biolimus-eluting stents (BES) with a bioabsorbable polymer coating (Nobori, Terumo, Tokyo, Japan). For the present study, SES and PES were considered first-generation drug-eluting stents (DES1), whereas all other DES were considered second-generation drug-eluting stents (DES2).

OBJECTIVES AND ENDPOINTS. Our primary objective was to determine the frequency and predictors of very-late stent-related events by stent type (bare-metal stents [BMS] vs. DES1 vs. DES2). Very-late events were defined as those occurring after the first year to the latest follow-up available in each study (ranging from 3 to 5 years). The primary endpoint was

TABLE 2 Angiographic and Procedural Variables by Stent Type

	All Patients (N = 25,032)	BMS (n = 3,718)	DES1 (n = 7,934)	DES2 (n = 13,380)	Overall p Value
Lesion characteristics					
Lesion location					
LAD	46.6 (11,623/24,958)	44.1 (1,630/3,692)	44.6 (3,521/7,896)	48.4 (6,472/13,370)	<0.0001
RCA	37.4 (9,344/24,958)	34.1 (1,258/3,692)	38.5 (3,042/7,896)	37.7 (5,044/13,370)	<0.0001
LCX	27.1 (6,759/24,958)	22.6 (834/3,692)	25.2 (1,987/7,896)	29.5 (3,938/13,370)	<0.0001
LM	0.8 (210/24,958)	0.1 (5/3,692)	0.4 (34/7,896)	1.3 (171/13,370)	<0.0001
Moderate-to-severe tortuosity	7.6 (878/11,623)	7.4 (243/3,304)	5.7 (290/5,104)	10.7 (345/3,215)	<0.0001
Moderate-to-severe calcification	30.5 (7,171/23,513)	26.1 (960/3,680)	30.6 (2,408/7,873)	31.8 (3,803/11,960)	<0.0001
Any occlusion	10.9 (2,679/24,553)	13.7 (470/3,420)	18.7 (1,455/7,765)	5.6 (754/13,368)	<0.0001
ACC lesion class C	37.1 (9,101/24,516)	36.3 (1,241/3,422)	44.5 (3,449/7,752)	33.1 (4,411/13,342)	<0.0001
Baseline QCA (core laboratory)					
Reference vessel diameter, mm	2.8 ± 0.7	2.8 ± 0.5	2.8 ± 0.5	2.8 ± 0.8	0.27
Minimal lumen diameter, mm	0.8 ± 0.5	0.8 ± 0.4	0.7 ± 0.5	0.8 ± 0.4	<0.0001
Diameter stenosis, %	73.9 ± 16.0	71.7 ± 15.1	75.2 ± 16.8	73.7 ± 15.7	<0.0001
Pre-procedure TIMI flow					
0–1	15.8 (3,882/24,537)	14.6 (498/3,419)	22.8 (1,768/7,759)	12.1 (1,616/13,359)	<0.0001
2	8.4 (2,068/24,536)	7.4 (254/3,419)	9.5 (740/7,759)	8.0 (1,074/13,358)	<0.0001
3	80.6 (19,785/24,536)	79.6 (2,721/3,419)	72.6 (5,632/7,759)	85.6 (11,432/13,358)	<0.0001
Lesion length, mm	16.9 ± 11.0	14.7 ± 7.4	16.3 ± 9.9	17.9 ± 12.4	<0.0001
Final QCA (core laboratory)					
Minimal lumen diameter, mm	2.3 ± 0.8	2.3 ± 0.5	2.3 ± 0.5	2.3 ± 1.0	<0.0001
Diameter stenosis, %	17.0 ± 11.0	20.2 ± 10.7	19.3 ± 11.0	14.7 ± 10.5	<0.0001
Post-procedure TIMI flow grade					
0–1	0.4 (108/24,297)	0.3 (11/3,313)	0.8 (62/7,625)	0.3 (35/13,359)	<0.0001
2	2.2 (542/24,296)	2.5 (83/3,313)	4.2 (320/7,625)	1.0 (139/13,358)	<0.0001
3	97.7 (23,739/24,296)	97.3 (3,223/3,313)	95.7 (7,294/7,625)	99.0 (13,222/13,358)	<0.0001
Number of lesions treated	1.2 ± 0.5	1.0 ± 0.2	1.1 ± 0.4	1.3 ± 0.6	<0.0001
1	84.1 (21,001/24,976)	98.2 (3,638/3,705)	88.1 (6,950/7,891)	77.8 (10,413/13,380)	<0.0001
2	13.2 (3,285/24,976)	1.5 (56/3,705)	10.2 (802/7,891)	18.1 (2,427/13,380)	<0.0001
≥3	2.8 (690/24,976)	0.3 (11/3,705)	1.8 (139/7,891)	4.0 (540/13,380)	<0.0001
Total stent length, mm	30.3 ± 21.2	23.8 ± 10.9	28.8 ± 19.1	33.0 ± 23.8	<0.0001

Values are % (n/N) or mean ± SD.

ACC = American College of Cardiology; ACS = acute coronary syndrome; LAD = left anterior descending; LCX = left circumflex; LM = left main; QCA = quantitative coronary angiography; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

very-late MACE, the composite of cardiac death, MI, or ischemia-driven target lesion revascularization (ID-TLR), as this outcome was determined in all trials. The more stent-specific measure of target lesion failure (TLF) (cardiac death, target vessel myocardial infarction [TV-MI], or ID-TLR) was considered a key secondary endpoint, and was available in 12 trials in which TV-MI was adjudicated. Complete description of secondary endpoints can be found in the Online Methods.

STATISTICAL ANALYSIS. All analyses were performed as intention-to-treat. Continuous data are presented as mean ± SD and were compared using Wilcoxon rank sum test or analysis of variance (ANOVA). Categorical variables were compared using the chi-square or Fisher exact test. Event rates were determined as Kaplan-Meier estimates and compared using the log-rank test. Landmark analysis was performed in the 0- to 1-year and 1- to 5-year periods; patients with MACE within 1 year were censored from the 1- to 5-year landmark analysis. Study-adjusted Poisson multivariable regression was performed to determine the independent predictors of MACE, TLF, and stent thrombosis at 1 year and between 1 and 5 years. In addition to stent type (DES1 vs. BMS and DES1 vs. DES2), a number of clinical and core laboratory-assessed angiographic variables were entered into the multivariable models. A p value <0.05 was considered statistically significant; all p values are 2-sided. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

META-ANALYSIS. Fixed and random-effect meta-analysis for very-late MACE were performed. Individual study and pooled MACE were reported as incidence rate ratios with 95% confidence intervals. I^2 values >50% indicated significant heterogeneity. Studies comparing the same generational type of stent to each other were excluded.

TABLE 3 Adverse Clinical Events Through 1-Year Follow-Up by Stent Type

	All Patients (N = 25,032)	BMS (n = 3,718)	DES1 (n = 7,934)	DES2 (n = 13,380)	Overall p Value
Major adverse cardiovascular events	8.0 (1,982)	17.9 (658)	8.2 (643)	5.1 (681)	<0.0001
Target lesion failure*	6.9 (1,342)	17.8 (322)	8.1 (367)	5.0 (653)	<0.0001
POCE	12.1 (3,024)	21.6 (797)	12.9 (1,013)	9.1 (1,214)	<0.0001
All-cause death	1.7 (415)	1.7 (64)	2.0 (161)	1.4 (190)	0.003
Cardiac	1.0 (256)	1.2 (46)	1.2 (97)	0.9 (113)	0.01
Noncardiac	0.6 (159)	0.5 (18)	0.8 (64)	0.6 (77)	0.05
MI	3.1 (776)	4.4 (162)	3.8 (297)	2.4 (317)	<0.0001
Target vessel†	2.7 (521)	3.8 (70)	3.5 (160)	2.2 (291)	<0.0001
Nontarget vessel	0.3 (48)	0.6 (10)	0.3 (15)	0.2 (23)	0.004
Death or MI	4.6 (1,137)	5.7 (211)	5.5 (438)	3.7 (488)	<0.0001
Cardiac death or MI	4.0 (986)	5.3 (196)	4.8 (376)	3.1 (414)	<0.0001
Any revascularization	9.7 (2,254)	18.4 (673)	9.6 (751)	7.1 (830)	<0.0001
Ischemia-driven TVR	6.6 (1,636)	16.7 (608)	6.8 (532)	3.7 (496)	<0.0001
PCI	5.8 (1,434)	15.2 (553)	5.9 (455)	3.2 (426)	<0.0001
CABG	0.8 (205)	1.5 (56)	1.0 (77)	0.5 (72)	<0.0001
Ischemia-driven TLR	5.1 (1,253)	14.7 (537)	4.9 (380)	2.5 (336)	<0.0001
PCI	4.5 (1,115)	13.5 (491)	4.3 (332)	2.2 (292)	<0.0001
CABG	0.6 (140)	1.3 (47)	0.6 (48)	0.3 (45)	<0.0001
NTVR	4.4 (828)	7.3 (96)	5.3 (298)	3.7 (434)	<0.0001
NTLR	6.0 (926)	8.8 (115)	6.3 (350)	5.4 (461)	<0.0001
ST (definite/probable)	1.1 (269)	1.5 (54)	1.6 (128)	0.7 (87)	<0.0001
Definite	0.8 (208)	1.1 (42)	1.3 (105)	0.5 (61)	<0.0001
Probable	0.3 (63)	0.3 (12)	0.3 (25)	0.2 (26)	0.14

Values are Kaplan-Meier estimates and are presented as % (n). *19,578 patients had 1-year target lesion failure data, including 1,830, 4,591, and 13,157 treated with BMS, DES1, and DES2, respectively. †19,574 patients had 1-year target-vessel MI data, including 1,827, 4,591, and 13,156 treated with BMS, DES1, and DES2, respectively.

CABG = coronary artery bypass graft; MI = myocardial infarction; NTLR = non-target lesion revascularization; NTVR = non-target vessel revascularization; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

NETWORK META-ANALYSIS. Network meta-analysis of events occurring between 1 and 5 years was performed using R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) with the GeMTC and rjags packages, which interface with JAGS software, version 3.4.0 (GNU General Public License version 2) (16). Additional methodological details of the network meta-analysis are reported in the Online Methods section.

RESULTS

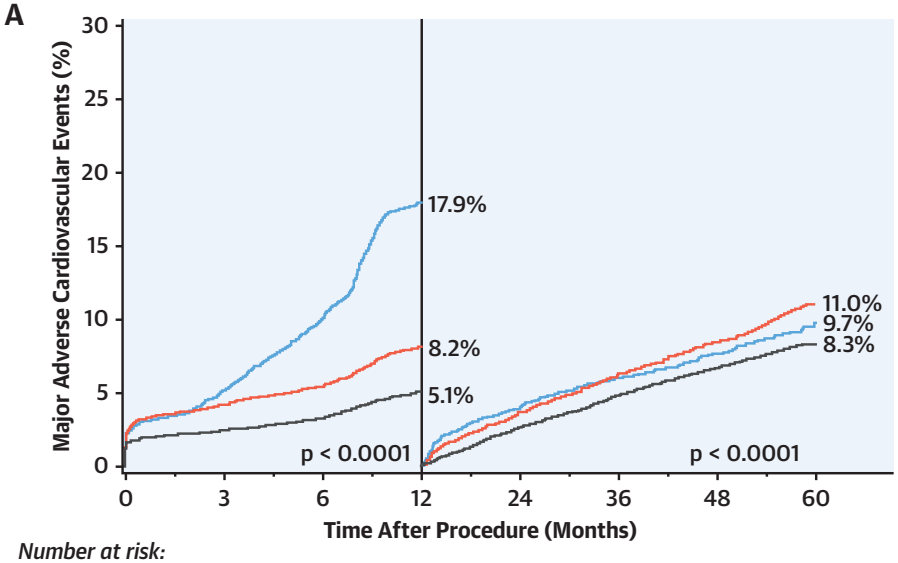
PATIENTS AND STENT TYPES. The IPD dataset consisted of 25,032 patients from 19 trials; 3,718 (14.9%), 7,934 (31.7%), and 13,380 (53.5%) patients were treated with BMS, DES1, and DES2, respectively. In the DES1 group, 6,943 (87.5%) patients were treated with PES and 991 (12.5%) were treated with SES. In the DES2 group, 8,288 (61.9%), 1,694 (12.7%), 1,603 (12.0%), and 1,795 (13.4%) patients were treated with EES, fast-release ZES, slow-release ZES, and BES, respectively.

Baseline clinical, angiographic, and procedural characteristics by stent type appear in Tables 1 and 2. Mean patient age was 62.7 years; 71.9% were men, 23.6% had diabetes mellitus, and 52.6% presented with acute coronary syndromes. The mean number of stented lesions per patient was 1.2 ± 0.5; 3,975 (15.9%) had treatment of >1 lesion. Some differences in clinical and angiographic characteristics between stent types are noted. Select clinical and angiographic characteristics by trial are presented in Online Table 3. The overall risk of bias was low other than bias from lack of blinding of participants and personnel (11 studies) (Online Table 4).

1-YEAR EVENTS. The 1-year outcomes are shown in Table 3, Central Illustration, Figure 1, and Online Figure 2. MACE within 1 year occurred in 1,982 of 25,032 patients (Kaplan-Meier estimate 8.0%). The unadjusted 1-year rate of MACE progressively declined after treatment with BMS, DES1, and DES2 (17.9% vs. 8.2% vs. 5.1%, respectively; $p < 0.0001$). Risk for 1-year MACE was greater for BMS compared with DES1 (relative risk [RR]: 2.27; 95% confidence interval [CI]: 2.03 to 2.53; $p < 0.0001$), and DES1 was associated with higher 1-year rates of MACE compared with DES2 (RR: 1.62; 95% CI: 1.46 to 1.81; $p < 0.0001$). TLF within 1 year occurred in 1,342 of 19,578 patients in the 12 trials with adjudicated TLF data (Kaplan-Meier estimate 6.9%). Similar to MACE, the 1-year rate of TLF fell progressively from BMS to DES1 to DES2 (17.8% vs. 8.1% vs. 5.0%, respectively; $p < 0.0001$). Risk for 1-year TLF was greater with BMS compared with DES1 (RR: 2.29; 95% CI: 1.97 to 2.66; $p < 0.0001$) and DES1 compared with DES2 (RR: 1.64; 95% CI: 1.45 to 1.87; $p < 0.0001$). DES2 had the lowest unadjusted 1-year rates of all-cause death and cardiac death, MI and TV-MI, ischemia-driven target vessel revascularization and ID-TLR, and stent thrombosis.

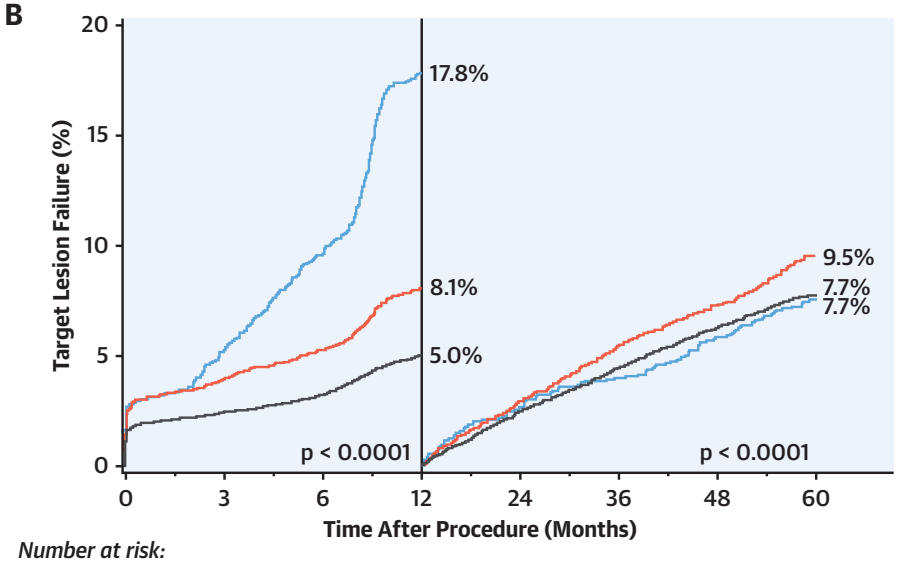
VERY-LATE EVENTS. Median duration of follow-up was 4.1 years (interquartile range [IQR]: 3.0 to 5.0 years), and was longest after BMS (BMS: 4.9 years [IQR: 3.0 to 5.0 years], DES1: 4.1 years [IQR: 3.0 to 5.0 years], and DES2: 3.9 years [IQR: 3.0 to 5.0 years]; $p < 0.001$). Outcomes between 1 and 5 years are shown in Table 4, Central Illustration, Figure 1, Online Figure 2, and Online Table 5. Very-late MACE and TLF in this 4-year period occurred in 9.4% and 8.2% of patients, respectively, with a linearly increasing event rate with all stent types with no plateau evident at 5 years. These rates, along with cardiac death (2.9%), MI (3.1%), ID-TLR (5.1%), and stent thrombosis (1.1%), equaled or exceeded those observed within the first year. DES1 had the highest observed rates of

CENTRAL ILLUSTRATION **Very-Late Stent-Related Cardiovascular Events**



Number at risk:

BMS	3,718	3,506	3,309	2,984	2,811	2,497	2,029	746
DES1	7,934	7,543	7,403	7,112	6,707	5,595	3,688	1,757
DES2	13,380	13,003	12,853	12,502	11,998	11,080	5,848	3,523



Number at risk:

BMS	1,830	1,725	1,636	1,462	1,395	1,335	1,267	479
DES1	4,591	4,384	4,296	4,108	3,916	3,465	2,850	1,470
DES2	13,157	12,792	12,653	12,287	11,819	10,928	5,679	3,446

Bare-Metal Stent (BMS)
First-Generation Drug-Eluting Stent (DES1)
Second-Generation Drug-Eluting Stent (DES2)

Madhavan, M.V. et al. J Am Coll Cardiol. 2020;75(6):590–604.

Principal composite outcomes by stent type within 1 year and in the landmark period of 1 to 5 years. **(A)** Major adverse cardiovascular events; **(B)** target lesion failure. BMS = bare-metal stents; DES = drug-eluting stents; DES1 = first-generation drug-eluting stents; DES2 = second-generation drug-eluting stents.

both very-late MACE (BMS vs. DES1 vs. DES2: 9.7% vs. 11.0% vs. 8.3%; $p < 0.0001$) and TLF (BMS vs. DES1 vs. DES2: 7.7% vs. 9.5% vs. 7.7%; $p = 0.006$). Rates of very-late MACE were higher with DES1 compared with DES2 (RR: 1.33; 95% CI: 1.19 to 1.47; $p < 0.0001$), but were not significantly different between DES1 and BMS (RR: 1.12; 95% CI: 0.97 to 1.30; $p = 0.12$). Rates of TLF were higher with DES1 compared with BMS (RR: 1.27; 95% CI: 1.01 to 1.56; $p = 0.04$) and DES2 (RR: 1.23; 95% CI: 1.08 to 1.40; $p = 0.002$). Of note, stent thrombosis between 1 and 5 years occurred in 0.5% of BMS-treated patients, 1.8% of DES1-treated patients, and 0.9% of DES2-treated patients ($p < 0.0001$). The 1-year and landmarked 1- to 5-year MACE and TLF Kaplan-Meier curves for the 6 DES stent types (plus BMS) are shown in Online Figure 3. All stents demonstrated an ongoing risk of very-late events, with no plateau evident.

META-ANALYSIS. Fixed and random effect meta-analysis data during the landmark period of 1 to 5 years are presented in Online Figure 4. Network meta-analysis outcomes during this period by stent type are presented in **Figure 2**. DES2 was associated with lower rates of very-late MACE compared with DES1 (incidence rate ratio 0.72; 95% credible interval: 0.52 to 0.94; $p = 0.04$). **Table 5** lists incidence rate ratios for stent comparisons for landmarked adverse events between 1 and 5 years for direct, indirect, and network meta-analysis after node split to assess for inconsistency. These data confirm that DES2 were associated with lower rates of very-late MACE, TLF, MI, and stent thrombosis compared with DES1. Similarly, rates of very-late adverse events, including MI, TV-MI, and stent thrombosis, were lower with BMS compared with DES1. There were no significant differences in very-late adverse event rates between DES2 and BMS. Incidence rate ratios (and credible intervals) for MACE determined by network meta-analysis were similar to the risk ratios (and CIs) from the direct comparisons of stent types as presented above and in **Table 4**. Similar trends were also noted for TLF, although no significant difference in TLF rates were found between DES1 and BMS in the network meta-analysis.

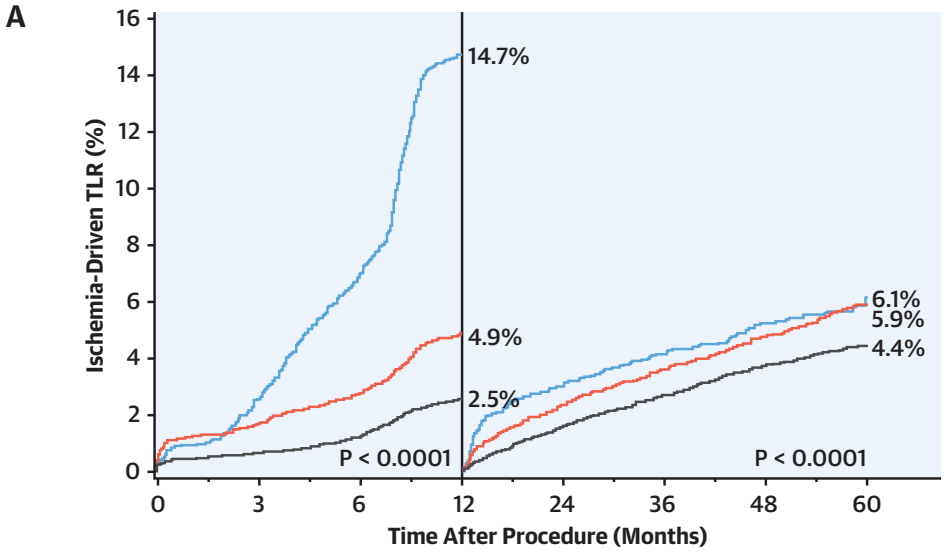
MULTIVARIABLE PREDICTORS OF ADVERSE EVENTS. By Poisson regression analysis (**Table 6**), DES1 had lower 1-year MACE rates compared with BMS (rate ratio: 0.50; 95% CI: 0.43 to 0.59; $p < 0.0001$). DES1 also was an independent predictor of lower 1-year rates of TLF compared with BMS. However, DES1 was associated with higher 1-year rates of MACE (rate ratio: 1.35; 95% CI: 1.09 to 1.67; $p = 0.006$) and TLF compared with DES2. Stent type was not independently associated with stent thrombosis in this period. Between 1 and 5 years, there were no significant differences in the adjusted rate ratios of MACE (rate ratio: 1.00; 95% CI: 0.83 to 1.19; $p = 0.95$) or TLF after treatment with BMS or DES1, although DES1 was an independent predictor of both MACE (rate ratio: 1.30; 95% CI: 1.09 to 1.56; $p = 0.004$) and TLF compared with DES2. Both BMS and DES2 were independently predictive of lower rates of stent thrombosis between 1 and 5 years compared with DES1. Other clinical and angiographic predictors of MACE, TLF, and stent thrombosis are shown in **Table 6**. All other variables included in Poisson regression analysis models are presented in **Table 6**.

Online Figure 5 shows the adjusted Kaplan-Meier curves for very-late MACE across all stent types in the landmark period of 1 to 5 years. **Figure 3** presents the rates of MACE between 1 and 5 years in important clinical and angiographic subgroups. Adverse event rates in the high-risk subgroups of patients with acute coronary syndromes and diabetes mellitus are presented in Online Tables 6 and 7. After controlling for study with Poisson regression analysis, age, diabetes mellitus, and complex coronary artery disease (but not acute coronary syndrome presentation) were significantly associated with very-late MACE.

DISCUSSION

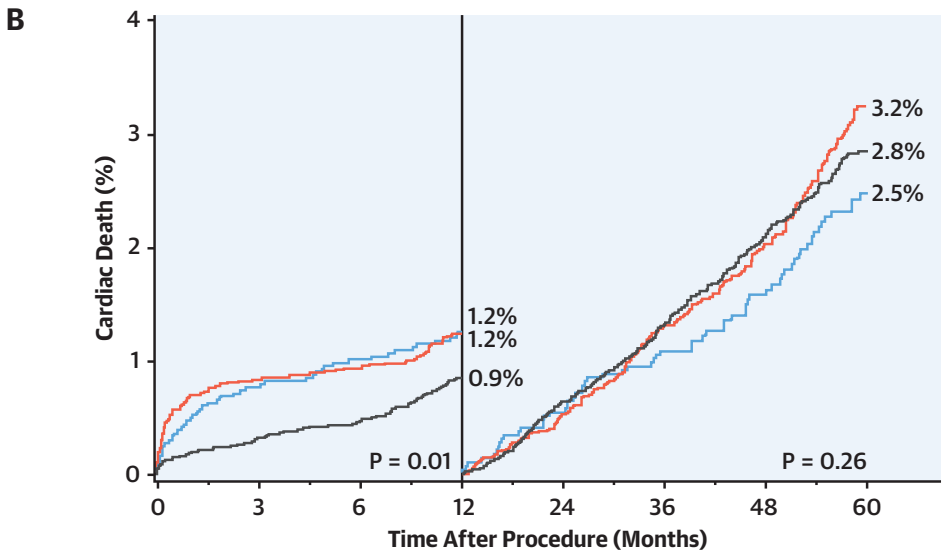
To our knowledge, the present IPD pooled analysis of 25,032 patients from 19 carefully conducted randomized trials is the largest study to date to examine the frequency and predictors of very-late (1- to 5-year) adverse cardiovascular events after coronary stent implantation. The principal findings of this analysis are: 1) as expected, MACE and TLF rates within the first year progressively fell with the evolution from BMS to DES1 to DES2; 2) nonetheless, very-late stent-related ischemic events occurred at a rate of ~2%/year after PCI with all metallic stents, with no plateau evident through 5-year follow-up; 3) in contrast to the 1-year findings, the highest rate of very-late events was observed with DES1, and although this rate was somewhat lower with DES2, very-late stent-related events (including ID-TLR and stent thrombosis) continued to accrue even with contemporary DES at a rate of ~2%/year; 4) the overall rate of very-late stent-related adverse events between 1 and 5 years was equal to or greater than within the first year for most endpoints; and 5) a number of clinical and angiographic variables were identified by multivariable analysis that had a modest

FIGURE 1 Time to First Event Curves by Stent Type Within 1 Year and in the Landmark Period of 1 to 5 Years



Number at risk:

BMS	3,449	3,317	3,145	2,768	2,615	2,316	1,851	663
DES1	7,804	7,556	7,428	6,992	6,648	5,572	3,660	1,758
DES2	13,380	13,206	13,074	12,502	12,059	11,191	5,913	3,580



Number at risk:

BMS	3,718	3,663	3,637	3,019	2,945	2,656	2,167	808
DES1	7,934	7,805	7,755	7,118	6,925	5,893	3,915	1,905
DES2	13,380	13,285	13,227	12,502	12,239	11,485	6,101	3,717

Bare Metal Stent — First-Generation DES — Second-Generation DES

(A) Ischemia-driven target lesion revascularization (TLR); **(B)** cardiac death; **(C)** myocardial infarction; and **(D)** definite/probable stent thrombosis. BMS = bare-metal stents; DES1 = first-generation drug-eluting stents; DES2 = second-generation drug-eluting stents.

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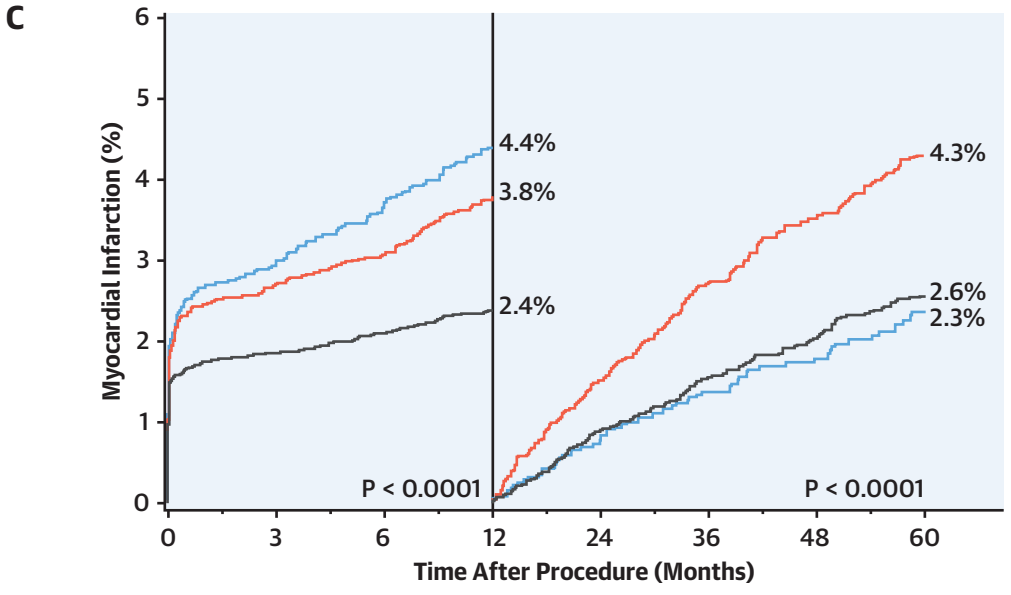
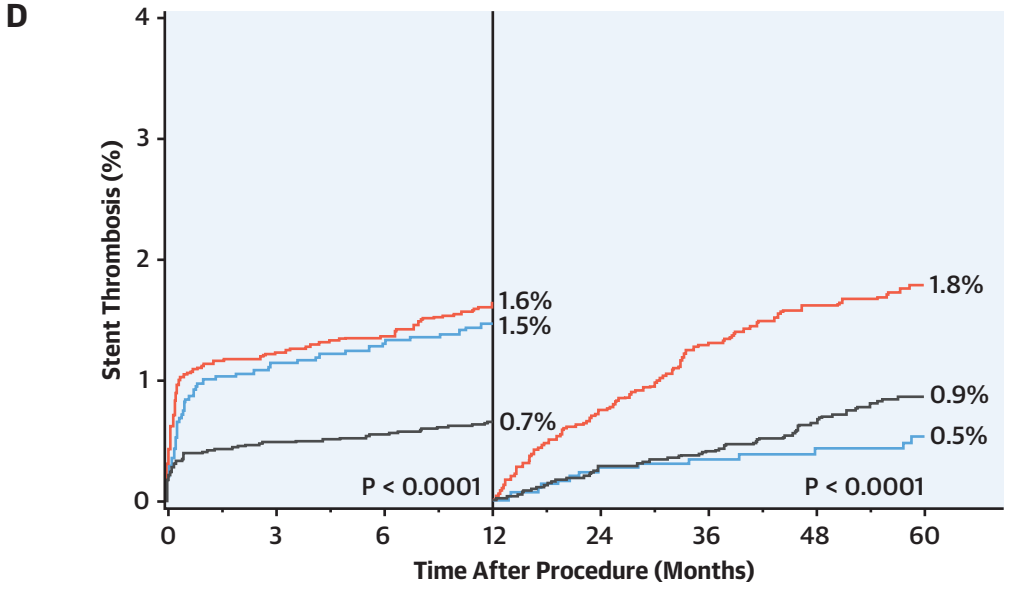
FIGURE 1 Continued



Number at risk:

BMS	3,718	3,563	3,513	3,019	2,925	2,625	2,137	792
DES1	7,934	7,604	7,526	7,118	6,828	5,745	3,796	1,820
DES2	13,380	13,046	12,960	12,502	12,147	11,318	6,005	3,631



Number at risk:

BMS	3,713	3,631	3,600	3,017	2,936	2,647	2,162	804
DES1	7,915	7,716	7,655	7,106	6,868	5,814	3,862	1,870
DES2	13,380	13,232	13,168	12,498	12,209	11,434	6,068	3,684

Bare Metal Stent — First-Generation DES — Second-Generation DES

modifying effect on the risk for very-late target lesion-related adverse events after PCI.

The present report demonstrates that an ongoing risk of very-late events is common to all metallic stents. Indeed, in the present large-scale IPD pooled analysis from 19 randomized trials, the rate of very-late stent-related events between 1 and 5 years equaled or exceed those within 1 year. TLF, which is fairly specific for stent-related events, occurred in 5.0% of patients after DES2 within the first year and in 7.7% of patients between years 1 and 5. Similarly, stent thrombosis and ID-TLR after DES2 occurred in 0.7% and 2.5% of patients, respectively, within the first year, and in 0.9% and 4.4% of patients, respectively, between years 1 and 5. Thus, although contemporary DES have markedly improved 1-year outcomes, the ongoing risk of very-late events arising from BMS and contemporary DES is similar, occurring in ~2% of patients per year with no plateau evident, at least through 5-year follow-up. Given the fact that many patients will survive with permanent coronary stent implants for 20 years or longer, target lesion-related events arising from the stent site may ultimately occur in more than one-half of all patients, assuming that the ongoing 20-year or longer risk of very-late stent-related events that has been reported with BMS (17) generalizes to contemporary DES.

This report confirms and extends selected findings from prior reports regarding very-late adverse events after DES. Regarding DES1, analysis from the TAXUS program previously demonstrated increased 1- to 5-year rates of MI after PES compared with BMS, although the differences in other adverse events did not reach statistical significance (18). Stent thrombosis rates between 30 days and 4 years were observed to be higher with PES compared with both BMS and SES in a network meta-analysis by Stettler et al. (19). Ten-year follow-up of the randomized SIRTAX trial noted comparable very-late rates of MACE (including its components of cardiac death, MI, and ID-TLR) as well as definite stent thrombosis with PES and SES (8).

In contrast to these studies with DES1, the frequency and predictors of very-late events after contemporary DES (DES2) have not been reported in detail. In this regard, among the 25,032 patients in the present IPD, 11,686 (47% of the total patient population) received devices that are used in contemporary practice, including EES (cobalt chromium and platinum chromium), slow-release ZES, and BES. Our results demonstrate a constant slope in the MACE and TLF curves between 1 and 5 years with all stent generations, which although greatest with DES1, were still considerable (and similar) with BMS and DES2. Confirmation of the present results may be observed from a recently published IPD and meta-analysis of long-term outcomes in 26,606 patients from 20 randomized coronary trials of DES2 versus BMS (20). Although the annual rates of very-late events were not reported, substantial rates of cardiac death or MI (~9.3%), target vessel revascularization (~6.3%), and stent thrombosis (~1%) between 1 and 6 years were observed after both DES2 and BMS. Notably, there was no overlap in the studies included in this IPD and our analysis with the exception of ENDEAVOR II. Thus, the present report provides critical data regarding the chronic outcomes of contemporary DES. The persistent and prolonged occurrence of stent-derived adverse events represents a considerable accumulating lifelong risk to the health of patients with coronary artery disease (CAD).

Several mechanisms have been purported to explain the ongoing risk of target lesion-related restenosis and stent thrombosis common to all stent platforms. Stent underexpansion, malapposition, uncovered struts, hypersensitivity reactions, device

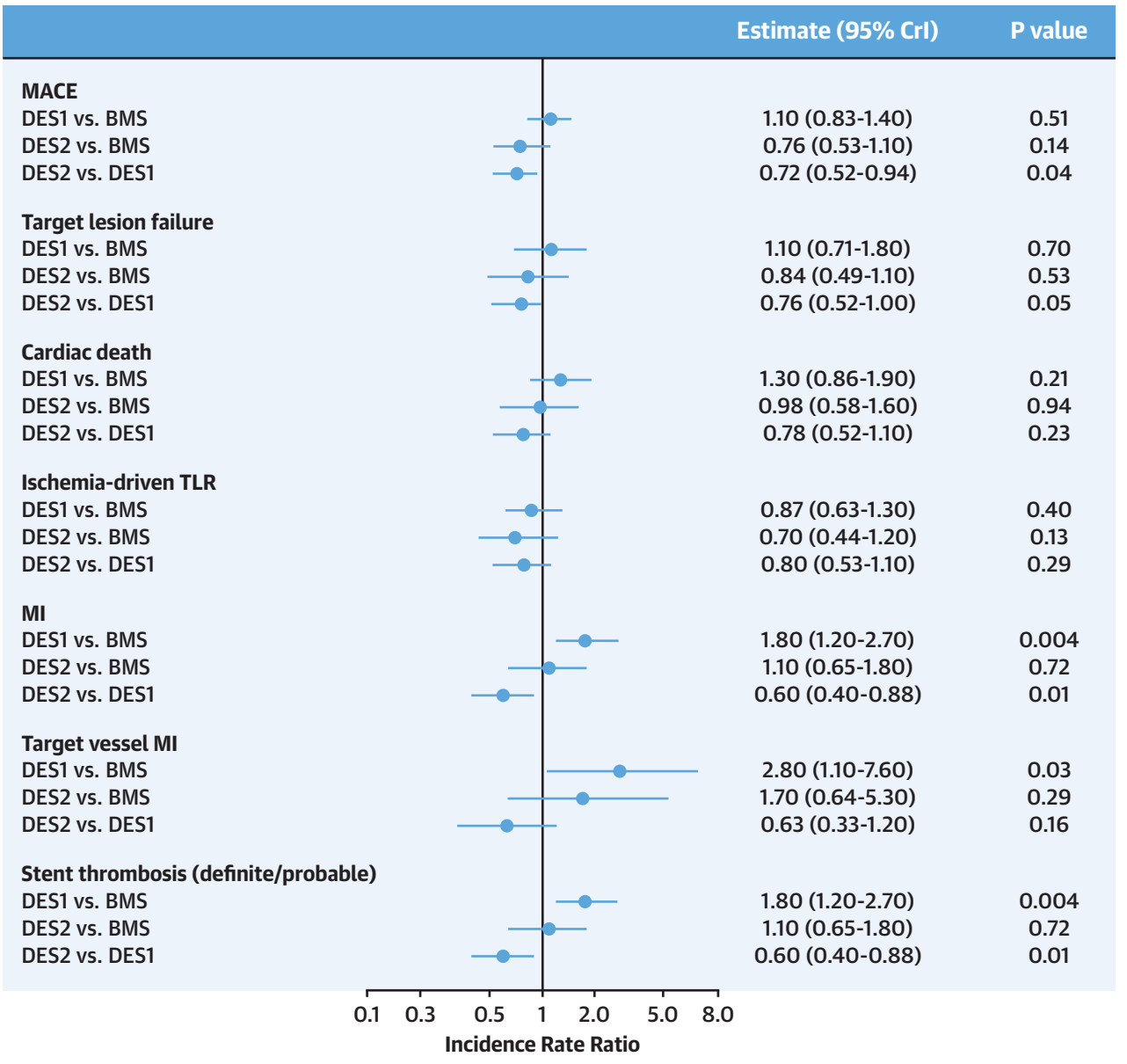
TABLE 4 Landmark Analysis of Adverse Events Between 1 and 5 Years by Stent Type

	All Patients (N = 25,032)	BMS (n = 3,718)	DES1 (n = 7,934)	DES2 (n = 13,380)	Overall p Value
Major adverse cardiovascular events	9.4 (1,688)	9.7 (254)	11.0 (622)	8.3 (812)	<0.0001
Target lesion failure*	8.2 (1,177)	7.7 (105)	9.5 (339)	7.7 (733)	0.006
POCE	18.3 (3,170)	18.2 (462)	21.1 (1,154)	16.6 (1,554)	<0.0001
All-cause death	7.1 (1,188)	6.9 (177)	7.8 (407)	6.8 (604)	0.14
Cardiac	2.9 (482)	2.5 (62)	3.2 (164)	2.8 (256)	0.26
Noncardiac	4.3 (706)	4.6 (115)	4.8 (243)	4.0 (348)	0.13
MI	3.1 (561)	2.3 (61)	4.3 (249)	2.6 (251)	<0.0001
Target vessel*	1.9 (286)	1.0 (13)	2.8 (102)	1.8 (171)	<0.0001
Nontarget vessel	1.0 (131)	1.1 (15)	1.2 (40)	0.8 (76)	0.21
Death or MI	9.5 (1,640)	8.6 (224)	11.2 (615)	8.6 (801)	<0.0001
Cardiac death or MI	5.4 (952)	4.3 (110)	6.9 (381)	4.9 (461)	<0.0001
Any revascularization	12.4 (1,990)	11.7 (296)	13.3 (735)	12.2 (959)	0.02
Ischemia-driven TVR	8.3 (1,474)	9.9 (252)	9.4 (531)	7.2 (691)	<0.0001
PCI	7.1 (1,260)	8.4 (217)	8.2 (461)	6.1 (582)	<0.0001
CABG	1.2 (217)	1.4 (35)	1.2 (70)	1.2 (112))	0.75
Ischemia-driven TLR	5.1 (928)	5.9 (156)	5.8 (335)	4.4 (437)	<0.0001
PCI	4.5 (823)	5.2 (137)	5.3 (307)	3.8 (379)	<0.0001
CABG	0.6 (109)	0.7 (19)	0.5 (28)	0.6 (62)	0.37
NTVR	8.2 (959)	9.7 (75)	9.8 (335)	7.3 (549)	<0.0001
NTLR	10.2 (1,008)	11.0 (89)	10.7 (385)	9.8 (534)	0.02
ST (definite/probable)	1.1 (200)	0.5 (14)	1.8 (109)	0.9 (77)	<0.0001
Definite	0.8 (150)	0.4 (12)	1.3 (82)	0.6 (56)	<0.0001
Probable	0.3 (51)	0.1 (2)	0.5 (28)	0.3 (21)	0.0007

Values are Kaplan-Meier estimates and are presented as % (n). *17,857 patients had data for target lesion failure and target-vessel MI between 1 and 5 years, including 1,462, 4,108, and 12,287 treated with BMS, DES1, and DES2, respectively.

Abbreviations as in Tables 1 and 3.

FIGURE 2 Network Meta-Analysis for Adverse Events by Stent Type Between 1 and 5 Years



Adverse event incidence rate ratios and 95% credible intervals (CrIs) are shown. MACE = major adverse cardiovascular events; MI = myocardial infarction; other abbreviations as in Figure 1.

fracture, and neoatherosclerosis have all been reported in patients experiencing very-late adverse events with metallic coronary stents (13,21).

Moving forward, the development of devices, procedural techniques, and medication regimens to prevent very-late events is necessary to further improve lifelong outcomes in patients undergoing coronary revascularization. Thicker stent strut designs may contribute to higher stent-related event rates after PCI, and outcomes can be improved with ultrathin strut designs, at least within the first year (22). Long-term follow-up is required to determine if this benefit extends to the very-late period. In the present analysis, moderate or severe coronary calcification was significantly associated with very-late adverse event rates. A large-scale randomized trial

(ECLIPSE [Evaluation of Treatment Strategies for Severe CaLcIfic Coronary Arteries: Orbital Atherectomy vs. Conventional Angioplasty Technique Prior to Implantation of Drug-Eluting StEnts]; NCT03108456) is ongoing to determine whether plaque modification with orbital atherectomy can improve long-term outcomes after stent implantation in such lesions. Imaging-guided intervention may also reduce very-late event rates after revascularization (23), and a large-scale randomized trial (ILUMIEN IV; NCT03507777) is evaluating whether optical coherence tomography-guided stenting can improve long-term prognosis. Regarding novel devices, bioresorbable vascular scaffolds (BVS) were specifically developed to improve long-term outcomes after the time of their complete bioresorption (~3 years with poly-L-lactic acid-based devices). Unfortunately, suboptimal mechanical performance of first-generation BVS (thick struts, restricted expansion capability) (24) coupled with suboptimal technique (25) and a novel failure mode (intraluminal scaffold dismantling) (26) resulted in an excessive rate of adverse events prior to this 3-year landmark (27). Further studies are required to determine whether improved BVS devices implanted with optimized technique and imaging guidance may mitigate these events.

Finally, secondary preventive therapies are the foundation to improve the lifelong prognosis of all patients with CAD (28), potentially affecting both stent-related and non-stent-related late events. Diabetes mellitus, recent smoking, prior revascularization, and prior MI were all significant predictors of very-late MACE and TLF in the present analysis. Aggressive treatment of such risk factors may thus enhance long-term outcomes after PCI. Also of note, non-stent-related nontarget lesion revascularization and non-TV-MI occurred in ~10% and ~1% of patients, respectively, between 1 and 5 years in the present study, contributing to the overall patient risk of very-late events. Novel lipid-lowering and anti-inflammatory therapies which reduce revascularization and non-stent-related MI rates (29,30) may also improve prognosis after coronary revascularization with metallic stents.

TABLE 5 Network Meta-Analysis: Direct and Indirect Comparisons Between Stent Types for Landmarked Adverse Events

	DES1 Versus BMS IRR (95% CrI)	DES2 Versus BMS IRR (95% CrI)	DES2 Versus DES1 IRR (95% CrI)
Major adverse cardiovascular events*			
Entire network	1.10 (0.83–1.40)	0.76 (0.53–1.10)	0.72 (0.53–0.93)
Direct	1.10 (0.82–1.50)	0.67 (0.31–1.50)	0.73 (0.52–0.98)
Indirect	0.91 (0.40–2.20)	0.80 (0.51–1.20)	0.62 (0.27–1.40)
p value	0.67	0.68	0.68
Target lesion failure			
Entire network	1.10 (0.70–1.80)	0.84 (0.49–1.40)	0.76 (0.52–1.00)
Direct	1.20 (0.69–2.20)	0.66 (0.27–1.60)	0.79 (0.52–1.10)
Indirect	0.82 (0.34–2.20)	0.96 (0.48–1.90)	0.54 (0.19–1.50)
p value	0.43	0.44	0.43
Cardiac death			
Entire network	1.20 (0.85–1.80)	0.97 (0.58–1.60)	0.78 (0.52–1.10)
Direct	1.30 (0.84–2.00)	0.84 (0.30–2.40)	0.78 (0.49–1.10)
Indirect	1.10 (0.37–3.40)	1.00 (0.52–1.80)	0.65 (0.21–2.00)
p value	0.75	0.77	0.76
Ischemia-driven TLR			
Entire network	0.87 (0.64–1.30)	0.70 (0.45–1.20)	0.80 (0.53–1.10)
Direct	0.93 (0.67–1.50)	0.39 (0.13–1.10)	0.86 (0.56–1.30)
Indirect	0.47 (1.14–1.50)	0.80 (0.49–1.50)	0.42 (0.12–1.30)
p value	0.22	0.21	0.23
MI			
Entire network	1.80 (1.30–2.70)	1.10 (0.67–1.80)	0.60 (0.41–0.87)
Direct	1.80 (1.20–2.90)	1.00 (0.35–3.00)	0.60 (0.38–0.93)
Indirect	1.70 (0.53–5.60)	1.10 (0.60–2.00)	0.55 (0.17–1.80)
p value	0.85	0.85	0.88
Target-vessel MI			
Entire network	2.80 (1.10–7.50)	1.70 (0.65–5.10)	0.63 (0.33–1.20)
Direct	3.10 (0.97–12.00	1.40 (0.22–10.00)	0.65 (0.30–1.50)
Indirect	2.20 (0.28–17.00)	2.00 (0.52–10.00)	0.47 (0.046–4.30)
p value	0.75	0.74	0.75
ST (definite/probable)			
Entire network	2.90 (1.40–7.50)	1.80 (0.69–5.90)	0.60 (0.30–1.20)
Direct	3.00 (1.50–8.60)	0.85 (0.01–49.00)	0.62 (0.30–1.40)
Indirect	1.40 (0.03–83.00)	1.90 (0.69–7.80)	0.29 (0.005–13.00)
p value	0.67	0.67	0.64

*A total of 15 studies were included in this network meta-analysis.
CrI = credible interval; IRR = incidence rate ratio; other abbreviations as in Tables 1 and 3.

STUDY STRENGTHS AND LIMITATIONS. As the largest study to date to examine very-late adverse events after metallic coronary stents, with outcomes based on IPD from 19 randomized trials (and confirmed by direct and indirect data from network meta-analysis), the present study has notable strengths. Comprised of all randomized stent studies with >1-year follow-up maintained at a high-volume academic research organization performed over >2 decades, we believe that the present analysis cohort is a representative sample of the 284 or more randomized stent trials performed to date. Nonetheless, several limitations should be acknowledged. The included trials had variable inclusion and exclusion criteria, resulting in a heterogeneous patient population. The study population included patients with relatively complex coronary anatomy. However, only 5 of 19 studies enrolled all-comers or patients with ST-segment or non-ST-segment elevation MI. Our findings may not apply to individuals with

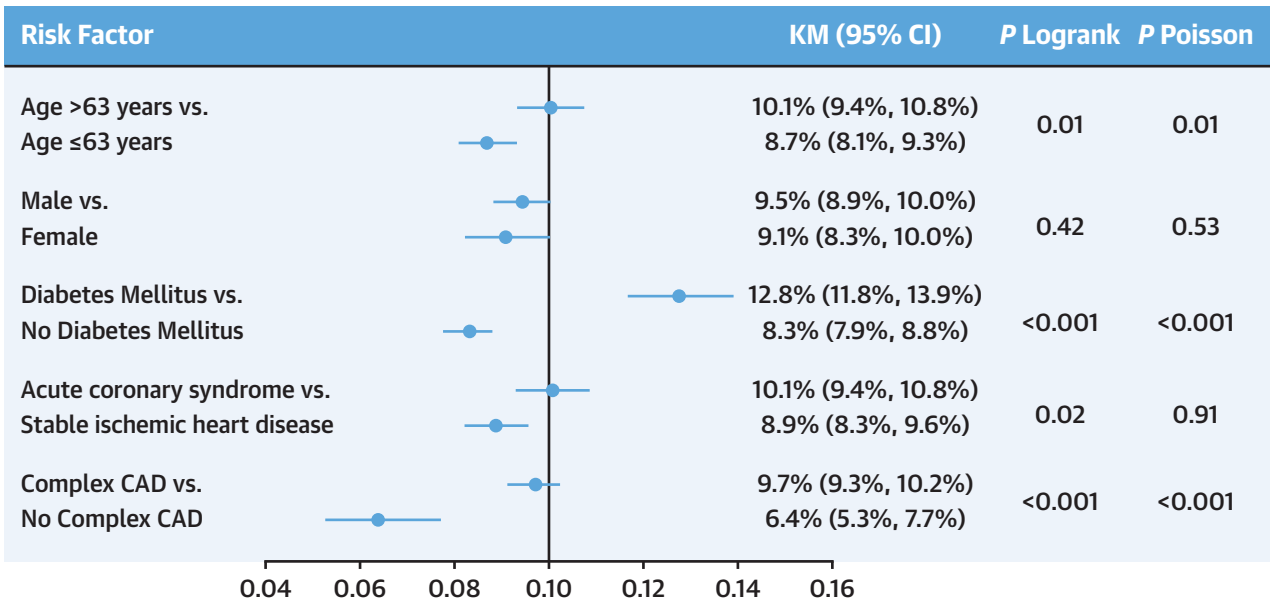
TABLE 6 Multivariable Predictors of Adverse Outcomes by Poisson Regression Analysis

	Major Adverse Cardiovascular Events		Target Lesion Failure		Stent Thrombosis	
	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Through 1 yr						
DES1 (vs. BMS)	0.50 (0.43–0.59)	<0.0001	0.56 (0.45–067)	<0.0001	0.83 (0.56–1.26)	0.43
DES1 (vs. DES2)	1.35 (1.09–1.67)	0.006	1.32 (1.05–1.64)	0.02	1.37 (0.71–2.50)	0.32
Age (per 5 yrs)	1.00 (0.99–1.10)	0.16	1.00 (0.97–1.00)	0.76	0.94 (0.87–1.00)	0.12
Male	0.85 (0.76–0.96)	0.007	0.84 (0.73–0.97)	0.02	0.81 (0.58–1.10)	0.23
Diabetes mellitus	1.40 (1.30–1.60)	<0.0001	1.40 (1.20–1.60)	<0.0001	1.80 (1.30–2.50)	0.0006
Recent smoker	1.10 (0.95–1.20)	0.21	1.00 (0.86–1.20)	0.82	1.70 (1.20–2.40)	0.003
ACS (vs. stable presentation)	1.10 (0.94–1.20)	0.38	0.95 (0.82–1.10)	0.44	0.93 (0.62–1.40)	0.72
Hypertension	1.20 (1.10–1.40)	0.002	1.30 (1.10–1.50)	0.003	1.10 (0.81–1.60)	0.49
Hyperlipidemia	0.95 (0.85–1.10)	0.43	0.93 (0.81–1.10)	0.37	0.90 (0.65–1.30)	0.53
Prior CABG	1.40 (1.20–1.70)	0.0002	1.50 (1.20–1.80)	0.0003	1.00 (0.54–1.90)	0.95
Prior myocardial infarction	1.00 (0.91–1.20)	0.65	0.99 (0.85–1.20)	0.94	1.60 (1.10–2.40)	0.009
Prior PCI	1.00 (0.90–1.20)	0.68	1.00 (0.86–1.20)	0.91	1.40 (0.91–2.00)	0.14
Moderate-severe calcium	1.20 (1.00–1.30)	0.01	1.10 (0.98–1.30)	0.09	1.50 (1.10–2.10)	0.008
LM or LAD disease	1.30 (1.10–1.40)	<0.0001	1.20 (1.10–1.40)	0.0006	1.20 (0.86–1.60)	0.32
>1 treated lesion	1.70 (1.40–2.00)	<0.0001	1.60 (1.30–1.90)	<0.0001	2.30 (1.60–3.40)	<0.0001
Baseline RVD (per 1 mm)	0.75 (0.67–0.83)	<0.0001	0.76 (0.67–0.87)	<0.0001	0.92 (0.69–1.20)	0.57
Pre-procedure DS (per 5%)	1.00 (0.98–1.00)	0.77	1.00 (0.97–1.00)	0.99	1.00 (0.96–1.10)	0.54
Lesion length (per 10 mm)	1.20 (1.10–1.30)	<0.0001	1.20 (1.10–1.30)	<0.0001	1.20 (1.10–1.40)	0.003
Between 1 and 5 yrs						
DES1 (vs. BMS)	1.00 (0.83–1.19)	0.95	1.16 (0.91–1.54)	0.30	2.38 (1.30–4.35)	0.005
DES1 (vs. DES2)	1.30 (1.09–1.56)	0.004	1.25 (1.04–1.51)	0.02	1.96 (1.20–3.22)	0.007
Age (per 5 yrs)	1.00 (1.00–1.10)	0.01	1.10 (1.00–1.10)	0.005	0.92 (0.85–1.00)	0.04
Male	1.10 (0.97–1.20)	0.14	1.10 (0.92–1.20)	0.42	1.40 (0.94–2.10)	0.10
Diabetes mellitus	1.50 (1.30–1.60)	<0.0001	1.50 (1.30–1.70)	<0.0001	1.20 (0.85–1.80)	0.29
Recent smoker	1.40 (1.30–1.60)	<0.0001	1.40 (1.20–1.70)	<0.0001	1.50 (1.10–2.10)	0.02
ACS (vs. stable presentation)	0.99 (0.88–1.10)	0.84	1.10 (0.92–1.20)	0.42	1.10 (0.77–1.60)	0.59
Hypertension	1.10 (0.97–1.20)	0.17	1.00 (0.89–1.20)	0.69	1.10 (0.75–1.50)	0.78
Hyperlipidemia	0.92 (0.82–1.00)	0.18	0.92 (0.80–1.10)	0.27	1.00 (0.72–1.40)	0.98
Previous CABG	1.90 (1.60–2.30)	<0.0001	2.00 (1.70–2.40)	<0.001	1.30 (0.75–2.40)	0.33
Previous myocardial infarction	1.20 (1.00–1.30)	0.04	1.00 (0.89–1.20)	0.62	1.30 (0.92–2.00)	0.13
Previous PCI	1.30 (1.10–1.50)	<0.0001	1.30 (1.10–1.50)	0.004	1.50 (1.00–2.20)	0.04
Moderate-severe calcium	1.10 (0.99–1.30)	0.06	1.20 (1.00–1.30)	0.03	1.10 (0.79–1.60)	0.55
LM or LAD disease	1.10 (0.95–1.20)	0.32	1.10 (0.92–1.20)	0.48	1.00 (0.73–1.40)	0.98
>1 treated lesion	1.30 (1.10–1.50)	0.0008	1.30 (1.10–1.60)	0.001	1.20 (0.80–1.80)	0.38
Baseline RVD (per 1 mm)	0.79 (0.71–0.88)	<0.0001	0.70 (0.62–0.80)	<0.0001	0.81 (0.60–1.10)	0.16
Pre-procedure DS (per 5%)	0.98 (0.96–1.00)	0.07	0.98 (0.96–1.00)	0.21	1.00 (0.95–1.0)	0.88
Lesion length (per 10 mm)	1.10 (1.00–1.10)	0.005	1.10 (0.99–1.10)	0.11	1.20 (1.10–1.30)	0.006

ACS = acute coronary syndrome; CI = confidence interval; DS = diameter stenosis; RR = rate ratio; RVD = reference vessel diameter; other abbreviations as in Tables 1 to 3.

higher-risk or more complex CAD. Very-late stent-related adverse events may be even greater in such patients. We controlled for differences between trials and patient populations with study-level stratified multivariable models. Nonetheless, as a post hoc analysis of prospective, randomized trials, there remains the potential for unmeasured confounders. TV-MI and TLF were not adjudicated in all trials; however, the findings regarding TLF (generally accepted as the most specific composite measure for stent-related events) were consistent with that for the slightly broader definition of MACE (which was available in all studies). Not all studies included in the present analysis had follow-up data available to 5 years, and moreover, none had follow-up beyond 5 years. Thus, whether adverse stent-related events after contemporary DES continue to accrue beyond this time period is unknown (although there is no reason to believe this very-late risk would be different than with BMS or DES1, the risk of which

FIGURE 3 Major Adverse Cardiovascular Events by Subgroups Between 1 and 5 Years



Kaplan-Meier (KM) event rates, 95% confidence intervals (CIs), and p values are shown. Complex coronary artery disease (CAD) was defined as left anterior descending or left main disease, lesion reference vessel diameter ≤ median (2.73 mm), lesion length > median (14 mm), and moderate/severe coronary calcium. The median age was 63 years.

have been demonstrated for ≤20 and 10 years, respectively [10,17]). Detailed data on antiplatelet agent usage was not available. Although most of the trials recommended dual antiplatelet therapy for 1 year, varying regimens and degrees to adherence may have influenced our findings. However, the consistency of the very-late stent-related risk across trials is notable. Last, given the few available trials randomizing BMS versus DES2, we were limited in our ability to directly compare event rates and model for differences between these 2 stent types. Although the network meta-analysis allowed for indirect comparisons between these stent types, not all studies from the 19-trial database were included in this subanalysis.

CONCLUSIONS

Stent-related events continue to accrue at a rate of ~2%/year between 1 and 5 years after PCI with all metallic coronary stents due to events related to stent thrombosis, MI, and restenosis necessitating repeat revascularization. This rate has not meaningfully improved as stent technology has evolved from BMS to contemporary DES, and no plateau in this ongoing risk is evident, signifying a lifelong patient concern. Novel device-based and pharmacological approaches are needed to mitigate the long-term occurrence of stent-related events (as well as progressive atherosclerosis arising from untreated coronary segments) to further improve the prognosis of patients with CAD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Ischemic events may arise from either stented segments or progressive disease elsewhere in the coronary vasculature >1 year after PCI. Late stent-related events occur at a rate of ~2%/year long after implantation, related to patient age, diabetes, and coronary lesion complexity.

TRANSLATIONAL OUTLOOK: Improvements in stent technology, implant technique, and secondary prevention are necessary to improve the prognosis of patients with CAD following PCI.

REFERENCES

1. Stefanini GG, Baber U, Windecker S, et al. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. Lancet 2013;382:1879–88.

2. Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015;65:2496–507.

3. Laham RJ, Carrozza JP, Berger C, Cohen DJ, Kuntz RE, Baim DS. Long-term (4- to 6-year) outcome of Palmaz-Schatz stenting: paucity of late clinical stent-related problems. J Am Coll Cardiol 1996;28:820–6.

4. Cutlip DE, Chhabra AG, Baim DS, et al. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. Circulation 2004;110:1226–30.

5. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393–402.

6. Kandzari DE, Leon MB, Meredith I, et al. Final 5-year outcomes from the Endeavor zotarolimus-eluting stent clinical trial program: comparison of safety and efficacy with first-generation drug-eluting and bare-metal stents. J Am Coll Cardiol Intv 2013;6:504–12.

7. Smits PC, Vlachojannis GJ, McFadden EP, et al. Final 5-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice: the COMPARE Trial (A Trial of Everolimus-Eluting Stents and Paclitaxel Stents for Coronary Revascularization in Daily Practice). J Am Coll Cardiol Intv 2015;8:1157–65.

8. Yamaji K, Raber L, Zanchin T, et al. Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial. Eur Heart J 2016;37:3386–95.

9. Moliterno DJ, Ziada KM. More time to SORT OUT clinical outcomes after first-generation drug-eluting stents: related versus unrelated events. J Am Coll Cardiol 2017;69:625–7.

10. Galløe AM, Kelbaek H, Thuesen L, et al. 10-year clinical outcome after randomization to treatment by sirolimus- or paclitaxel-eluting coronary stents. J Am Coll Cardiol 2017;69:616–24.

11. Maeng M, Tilsted HH, Jensen LO, et al. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. Lancet 2014;383:2047–56.

12. Wijns W, Steg PG, Mauri L, et al. Endeavour zotarolimus-eluting stent reduces stent thrombosis and improves clinical outcomes compared with cypher sirolimus-eluting stent: 4-year results of the PROTECT randomized trial. Eur Heart J 2014;35:2812–20.

13. Mori H, Atmakuri DR, Torii S, et al. Very late pathological responses to cobalt-chromium everolimus-eluting, stainless steel sirolimus-eluting, and cobalt-chromium bare metal stents in humans. J Am Heart Assoc 2017;6:e007244.

14. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657–65.

15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

16. Panagiotou OA. Network meta-analysis: evidence synthesis with mixed treatment comparison edited by Giuseppe Biondi-Zoccai. Am J Epidemiol 2015;181:288–9.

17. Yamaji K, Kimura T, Morimoto T, et al. Very long-term (15 to 20 years) clinical and angiographic outcome after coronary bare metal stent implantation. Circ Cardiovasc Interv 2010;3:468–75.

18. Stone GW, Ellis SG, Colombo A, et al. Long-term safety and efficacy of paclitaxel-eluting stents final 5-year analysis from the TAXUS Clinical Trial Program. J Am Coll Cardiol Intv 2011;4:530–42.

19. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.

20. Piccolo R, Bonaa KH, Efthimiou O, et al. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2019;393:2503–10.

21. Nakamura D, Attizzani GF, Toma C, et al. Failure mechanisms and neoatherosclerosis patterns in very late drug-eluting and bare-metal stent thrombosis. Circ Cardiovasc Interv 2016;9:e003785.

22. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer-generation ultrathin strut drug-eluting stents versus older second-generation thicker strut drug-eluting stents for coronary artery disease. Circulation 2018;138:2216–26.

23. Bavishi C, Sardar P, Chatterjee S, et al. Intravascular ultrasound-guided vs angiography-guided drug-eluting stent implantation in complex coronary lesions: Meta-analysis of randomized trials. Am Heart J 2017;185:26–34.

24. Kereiakes DJ, Onuma Y, Serruys PW, Stone GW. Bioresorbable vascular scaffolds for coronary revascularization. Circulation 2016;134:168–82.

25. Stone GW, Abizaid A, Onuma Y, et al. Effect of technique on outcomes following bioresorbable vascular scaffold implantation: analysis from the ABSORB trials. J Am Coll Cardiol 2017;70:2863–74.

26. Stone GW, Granada JF. Very late thrombosis after bioresorbable scaffolds: cause for concern? J Am Coll Cardiol 2015;66:1915–7.

27. Ali ZA, Gao R, Kimura T, et al. Three-year outcomes with the absorb bioresorbable scaffold: individual-patient-data meta-analysis from the ABSORB randomized trials. Circulation 2018;137:464–79.

28. Smith SC Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol 2011;58:2432–46.

29. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

30. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

KEY WORDS clinical trials, late events, major adverse cardiovascular events, PCI, stents

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.