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Effect of Increasing Stent Length on 3-Year Clinical Outcomes in Women Undergoing Percutaneous Coronary Intervention With New-Generation Drug-Eluting Stents

Patient-Level Pooled Analysis of Randomized Trials From the WIN-DES Initiative

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ABSTRACT

OBJECTIVES The aim of this study was to examine whether stent length per patient and stent length per lesion are negative markers for 3-year outcomes in women following percutaneous coronary intervention (PCI) with new-generation drug-eluting stents (DES).

BACKGROUND In the era of advanced stent technologies, whether stent length remains a correlate of adverse outcomes is unclear.

METHODS Women treated with new-generation DES in 14 randomized trials from the WIN-DES (Women in Innovation and Drug-Eluting Stents) pooled database were evaluated. Total stent length per patient, which was available in 5,403 women (quartile 1, 8 to 18 mm; quartile 2, 18 to 24 mm; quartile 3, 24 to 36 mm; quartile 4, ≥36 mm), and stent length per lesion, which was available in 5,232 women (quartile 1, 8 to 18 mm; quartile 2, 18 to 20 mm; quartile 3, 20 to 27 mm; quartile 4, ≥27 mm) were analyzed in quartiles. The primary endpoint was 3-year major adverse cardiovascular events (MACE), defined as a composite of all-cause death, myocardial infarction, or target lesion revascularization.

RESULTS In the per-patient analysis, a stepwise increase was observed with increasing stent length in the adjusted risk for 3-year MACE (p for trend <0.0001), myocardial infarction (p for trend <0.001), cardiac death (p for trend = 0.038), and target lesion revascularization (p for trend = 0.011) but not definite or probable stent thrombosis (p for trend = 0.673). In the per-lesion analysis, an increase was observed in the adjusted risk for 3-year MACE (p for trend = 0.002) and myocardial infarction (p for trend <0.0001) but not other individual endpoints. On landmark analysis for late event rates between 1 and 3 years, stent length per patient demonstrated weak associations with target lesion revascularization (p = 0.0131) and MACE (p = 0.0499), whereas stent length per lesion was not associated with higher risk for any late events, suggesting that risk was established early within the first year after PCI.

CONCLUSIONS In this pooled analysis of women undergoing PCI with new-generation DES, increasing stent length per patient and per lesion were independent predictors of 3-year MACE but were not associated with definite or probable stent thrombosis. (J Am Coll Cardiol Intv 2018;11:53–65) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

MACE = major adverse cardiovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

TLR = target lesion revascularization

Stent length has previously been determined to be a significant predictor of short- and long-term adverse cardiovascular outcomes with bare-metal stents, particularly target lesion revascularization (TLR) (1,2). Longer stent length is a correlate of extensive atherosclerotic disease, complex anatomic features, and high-risk systemic factors including increased platelet reactivity (3–6). Both increasing stent length per lesion and stent length per patient have been shown to be associated with greater TLR with sirolimus-eluting stents (2). Furthermore, Suh et al. (7) found stent length per lesion >31.5 mm to be associated with greater stent thrombosis (ST) with sirolimus- and paclitaxel-eluting stents. In contemporary percutaneous coronary intervention (PCI), improvements in stent design have resulted in longer and more easily deliverable stents, allowing greater lesion lengths to be successfully treated (8,9). Although very late ST rates with everolimus-eluting and zotarolimus-eluting stents are significantly lower than with first-generation stents (10), few data have systematically investigated the effect of stent length with second-generation drug-eluting stents (DES) (11–14).

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Moreover, these prior studies have included mostly male patients, with <25% enrolled women. Despite fewer adverse angiographic characteristics, women tend to experience higher ischemic event rates following PCI compared with men (15–17). The WIN-DES (Women in Innovation and Drug-Eluting Stents) collaboration is a pooled patient-level dataset of 11,557 women treated with coronary stents from 26 randomized controlled trials, allowing comprehensive evaluation of outcomes in women undergoing PCI (18). To investigate the long-term impact of increasing stent length in women treated with new-generation DES, we analyzed stent length per patient and stent length per lesion in quartiles.

METHODS

STUDY POPULATION. A total of 11,557 women participating in 26 randomized DES trials from 2000 to

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2013 were included in the main pooled patient-level analysis conceived during the Gender Data Forum in September 2012 and sponsored by the WIN initiative of the Society for Cardiovascular Angiography and Interventions. The full methods are explained in detail in the main report (18). Each trial had different inclusion criteria, and stable and urgent PCI were equally represented. We included only patients receiving new-generation DES in this analysis (**Figure 1**).

New-generation DES were defined as the Xience (Abbott Vascular, Santa Clara, California) and Promus (Boston Scientific, Natick, Massachusetts) everolimus-eluting stents, the Endeavor zotarolimus-eluting stent (Medtronic, Minneapolis, Minnesota), the biolimus-eluting Biomatrix (Biosensors, Newport Beach, California) and Nobori (Terumo, Tokyo, Japan) stents with biodegradable polymer coating, and the polymer-free sirolimus-eluting Yukon stent (Translumina, Hechingen, Germany).

In the present analysis, we evaluated 5,403 women treated with new-generation DES in 14 randomized trials from the WIN-DES pooled database. All trials included in our analysis complied with the provisions of the Declaration of Helsinki, and the study protocols were approved by the Institutional Review Board at each study center. All patients provided written informed consent for participation in each study.

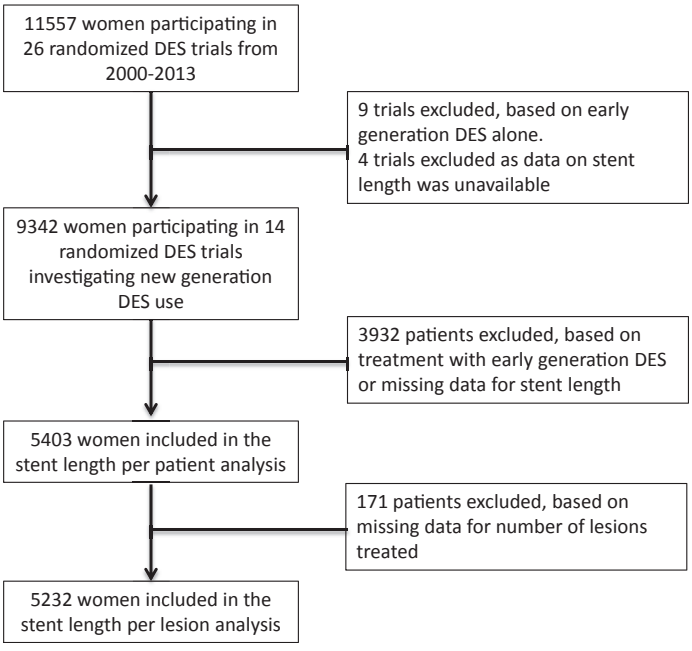
Online Table 1 lists the trials included in this analysis with the mean implanted stent length: ENDEAVOR II (19), ENDEAVOR III (20), ENDEAVOR IV (21), SPIRIT II (22), SPIRIT III (23), BASKET-PROVE (24), COMPARE (25), COMPARE II (26), EXCELLENT (27), RESET (28), TWENTE (29), ISAR-TEST 4 (30), PRODIGY (31), and PROTECT (32).

ENDPOINTS. The primary endpoint of the present patient-level analysis was major adverse cardiovascular events (MACE), defined as a composite of all-cause death, myocardial infarction (MI), or TLR. The key safety endpoint was defined as a composite of atherothrombotic events: all-cause death, MI, or definite or probable ST. Individual secondary endpoints included MI, definite or probable ST, all-cause death, cardiac death, and TLR.

DEFINITIONS. ST was defined per the Academic Research Consortium definition in all trials. The definition of MI differed among the trials. TLR and death were uniformly defined, although the BASKET-PROVE (24) and PRODIGY (33) trials only defined target vessel revascularization, which was used as a proxy for TLR.

STATISTICAL ANALYSIS. Groups were compared in quartiles of total stent length per patient (quartile 1, 8 to 18 mm; quartile 2, 18 to 24 mm; quartile 3, 24 to 36 mm; quartile 4, ≥36 mm) and total stent length per lesion (quartile 1, 8 to 18 mm; quartile 2, 18 to 20 mm; quartile 3, 20 to 27 mm; quartile 4, ≥27 mm). Categorical data were compared using the chi-square test, and continuous variables were compared using the Student *t* test. Events were estimated in a time-to-event manner using Kaplan-Meier methods and compared using the log-rank test. Adjusted hazard ratios were generated using Cox proportional hazards regression including these covariates: age, hypertension, diabetes, smoking, prior PCI, prior MI, indication for PCI, and American College of Cardiology/American Heart Association (ACC/AHA) lesion type. The models also included a frailty term to assess for random effects of the individual trials and unmeasured factors that might influence baseline patient risk in the trials. All analyses were carried out using SAS version 9.4 (SAS, Cary, North Carolina) or Stata version 14.0 (StataCorp, College Station, Texas). A p value of <0.05 was considered to indicate statistical significance.

FIGURE 1 Study Flow



DES = drug-eluting stent(s).

RESULTS

The study sample comprised 5,403 women treated with new-generation DES for whom information on stent length was available. **Table 1** presents the

TABLE 1 Baseline Characteristics for Quartiles of Total Stent Length per Patient

	Quartile 1 (8-18 mm)	Quartile 2 (18-24 mm)	Quartile 3 (24-36 mm)	Quartile 4 (≥36 mm)	
	n = 782 (14.0%)	n = 1,706 (32.0%)	n = 1,329 (25.0%)	n = 1,586 (29.0%)	p Value
Age (yrs)	67.41 ± 10.43	66.22 ± 10.86	67.06 ± 10.43	67.98 ± 10.30	<0.0001
BMI (kg/m^2)	27.51 ± 5.14	28.51 ± 6.32	27.99 ± 5.58	27.84 ± 5.56	0.0004
Diabetes mellitus	221 (28.3%)	549 (32.2%)	403 (30.3%)	546 (34.4%)	0.0117
Insulin-requiring diabetes mellitus	60 (27.1%)	192 (35.0%)	126 (31.3%)	156 (28.6%)	0.0691
Hypertension	544 (69.6%)	1,303 (76.4%)	1,011 (76.1%)	1,199 (75.6%)	0.0017
Hypercholesterolemia	517 (66.2%)	1,188 (69.8%)	912 (68.9%)	1,054 (66.7%)	0.1550
Serum creatinine (mg/dl)	0.94 ± 0.88	0.93 ± 0.84	0.90 ± 0.50	0.96 ± 0.84	0.4193
Smoking	219 (28.1%)	466 (27.4%)	377 (28.5%)	434 (27.5%)	0.9072
Previous MI	131 (16.8%)	272 (16.0%)	238 (18.0%)	297 (18.8%)	0.1772
Previous PCI	168 (21.5%)	356 (20.9%)	244 (18.4%)	297 (18.8%)	0.1389
Previous CABG	43 (5.5%)	90 (5.3%)	57 (4.3%)	78 (4.9%)	0.5466
Left ventricular ejection fraction (%)	52.78 ± 21.86	56.49 ± 17.26	52.41 ± 20.79	47.43 ± 24.86	<0.0001
ACS	366 (47.1%)	674 (40.4%)	551 (42.5%)	690 (43.8%)	0.0143
Type of stent implanted					
Biomatrix/Nobori	459 (8.5%)	86 (11.0%)	79 (4.6%)	112 (8.4%)	182 (11.5%)
Endeavor	1,616 (29.9%)	290 (37.1%)	449 (26.3%)	529 (39.8%)	348 (21.9%)
Resolute	192 (3.6%)	30 (3.8%)	31 (1.8%)	48 (3.6%)	83 (5.2%)
Xience	2,816 (52.1%)	331 (42.3%)	1,047 (61.4%)	571 (43.0%)	867 (54.7%)
Yukon Choice	320 (5.9%)	45 (5.8%)	100 (5.9%)	69 (5.2%)	106 (6.7%)
Multivessel disease	108 (15.6%)	360 (23.7%)	319 (26.8%)	792 (58.1%)	<0.0001
Number of lesions treated	1.01 ± 0.12	1.02 ± 0.15	1.15 ± 0.37	1.86 ± 0.84	<0.0001
Number of stents implanted	1.03 ± 0.20	1.05 ± 0.26	1.36 ± 0.61	2.75 ± 1.07	<0.0001
Mean stent diameter (mm)	3.02 ± 0.43	3.01 ± 0.42	2.99 ± 0.38	2.93 ± 0.32	<0.0001
Total stent length (mm)	12.82 ± 2.31	18.85 ± 1.84	27.70 ± 2.96	54.99 ± 21.42	<0.0001
Total stent length per lesion (mm)	12.71 ± 2.40	18.61 ± 2.10	25.48 ± 5.12	33.60 ± 15.78	<0.0001
At least 1 type B2/C lesion	241 (33.3%)	802 (48.9%)	919 (71.4%)	1,315 (85.9%)	<0.0001
At least 1 lesion with moderate/severe calcifications	117 (18.6%)	190 (18.7%)	248 (25.1%)	384 (34.6%)	<0.0001
At least 1 bifurcation lesion	41 (10.6%)	215 (20.7%)	123 (19.2%)	214 (21.9%)	<0.0001

Values are mean ± SD or n (%).

ACS = acute coronary syndrome(s); BMI = body mass index; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention.

baseline characteristics for quartiles of total stent length per patient. Patients in quartile 4 were older, with a greater prevalence of diabetes mellitus and lower left ventricular ejection fraction than others. There were no differences among groups in the prevalence of other cardiovascular risk factors. Angiographically, patients in quartile 4 had significantly higher burden of multivessel, complex (ACC/AHA lesion type B2/C), and moderate or severely calcific disease. They had a greater number of lesions treated and a greater number of stents implanted, with smaller mean stent diameter.

Analogously, 5,232 patients had available data for total stent length per lesion. Compared with others, patients in quartile 4 had lower left ventricular ejection fractions and a greater prevalence of adverse angiographic characteristics but a lower prevalence of acute coronary syndrome presentation (Table 2).

Median follow-up in the study was 745 days. At 1 year, follow-up was complete in 98.1% of patients. The 3-year clinical outcomes for the per-patient analysis are presented in Table 3 and Figure 2. At 3 years, increasing stent length per patient was associated with higher rates of MACE, MI, cardiac death, TLR, and the key safety endpoint, but not ST. After adjustment for potential confounders and compared with quartile 1, an increasing gradient of 3-year risk was observed with increasing stent length. The incidence of 3-year MACE was 9.2% in quartile 1, 11.1% in quartile 2 (hazard ratio [HR]: 1.13; 95% confidence interval [CI]: 0.82 to 1.56), 14.4% in quartile 3 (HR: 1.49; 95% CI: 1.08 to 2.04), and 19.6%

TABLE 2 Baseline Characteristics for Quartiles of Total Stent Length per Lesion

	Quartile 1 (8-18 mm) n = 1,014 (19.0%)	Quartile 2 (18-20 mm) n = 1,601 (31.0%)	Quartile 3 (20-27 mm) n = 1,143 (22.0%)	Quartile 4 (≥27 mm) n = 1,474 (28.0%)	p Value
Age (yrs)	68.07 ± 10.20	66.28 ± 10.82	67.22 ± 10.68	67.49 ± 10.30	0.0002
BMI (kg/m^2)	27.53 ± 5.11	29.20 ± 6.46	27.49 ± 5.30	27.50 ± 5.65	<0.0001
Diabetes mellitus	295 (29.1%)	527 (32.9%)	371 (32.5%)	484 (32.8%)	0.1625
Insulin-requiring diabetes mellitus	87 (29.5%)	181 (34.3%)	121 (32.6%)	136 (28.1%)	0.1495
Hypertension	734 (72.4%)	1,243 (77.6%)	871 (76.2%)	1,112 (75.4%)	0.0230
Hypercholesterolemia	678 (66.9%)	1,116 (69.9%)	776 (68.1%)	996 (67.8%)	0.4118
Serum creatinine (mg/dl)	0.93 ± 0.78	0.92 ± 0.74	0.90 ± 0.57	0.98 ± 0.94	0.2830
Smoking	284 (28.1%)	438 (27.4%)	327 (28.7%)	403 (27.5%)	0.8724
Previous MI	178 (17.6%)	272 (17.1%)	189 (16.6%)	273 (18.7%)	0.5257
Previous PCI	214 (21.1%)	333 (20.8%)	202 (17.7%)	295 (20.0%)	0.1501
Previous CABG	59 (5.8%)	87 (5.4%)	50 (4.4%)	65 (4.4%)	0.2520
Left ventricular ejection fraction (%)	50.95 ± 23.50	56.66 ± 17.04	52.69 ± 20.62	48.90 ± 23.69	<0.0001
ACS	478 (47.5%)	596 (38.1%)	538 (47.8%)	573 (39.5%)	<0.0001
Type of stent implanted					<0.0001
Biomatrix/Nobori	125 (12.3%)	80 (5.0%)	77 (6.7%)	177 (12.0%)	
Endeavor	372 (36.7%)	491 (30.7%)	410 (35.9%)	343 (23.3%)	
Resolute	46 (4.5%)	31 (1.9%)	48 (4.2%)	67 (4.5%)	
Xience	418 (41.2%)	907 (56.7%)	505 (44.2%)	815 (55.3%)	
Yukon Choice	53 (5.2%)	92 (5.7%)	103 (9.0%)	72 (4.9%)	
Multivessel disease	270 (28.7%)	435 (29.3%)	435 (43.1%)	439 (32.9%)	<0.0001
Number of lesions treated	1.33 ± 0.63	1.16 ± 0.43	1.53 ± 0.83	1.24 ± 0.53	<0.0001
Number of stents implanted	1.33 ± 0.65	1.18 ± 0.47	1.81 ± 1.10	2.09 ± 1.17	<0.0001
Mean stent diameter (mm)	3.00 ± 0.41	3.00 ± 0.41	2.98 ± 0.37	2.95 ± 0.36	0.0125
Total stent length (mm)	17.77 ± 10.32	21.04 ± 8.11	35.97 ± 19.63	45.88 ± 23.05	<0.0001
Total stent length per lesion (mm)	13.13 ± 2.49	18.04 ± 0.21	23.62 ± 1.69	37.58 ± 13.10	<0.0001
At least 1 type B2/C lesion	389 (41.5%)	755 (48.9%)	796 (72.8%)	1,201 (83.8%)	<0.0001
At least 1 lesion with moderate/severe calcifications	174 (20.8%)	177 (20.0%)	240 (25.4%)	348 (32.2%)	<0.0001
At least 1 bifurcation lesion	66 (12.2%)	213 (22.0%)	104 (18.2%)	210 (22.0%)	<0.0001

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

in quartile 4 (HR: 1.82; 95% CI: 1.34 to 2.48). Similarly, the incidence of the key safety endpoint was 6.2% in quartile 1, 6.7% in quartile 2 (HR: 1.15; 95% CI: 0.77 to 1.70), 9.8% in quartile 3 (HR: 1.59; 95% CI: 1.08 to 2.33), and 12.7% in quartile 4 (HR: 1.82; 95% CI: 1.25 to 2.64).

The 3-year clinical outcomes for the per-lesion analysis are presented in Table 4 and Figure 3. At 3 years, increasing stent length per lesion was associated with greater incidence of MACE, MI, and the key safety endpoint, but not cardiac death, ST, or TLR. After adjustment, increasing risk for 3-year MACE and the key safety endpoint was observed in quartile 4 compared with quartile 1. The incidence of 3-year MACE was 12.0% in quartile 1, 11.7% in quartile 2 (HR: 0.95; 95% CI: 0.72 to 1.25), 13.9% in quartile 3 (HR: 0.99; 95% CI: 0.75 to 1.31), and 18.2% in quartile 4 (HR: 1.38; 95% CI: 1.07 to 1.78). Similarly, the incidence of the key safety endpoint was 8.2% in quartile 1, 7.1% in quartile 2 (HR: 0.98; 95% CI: 0.70 to 1.37), 8.5% in quartile 3 (HR: 0.96; 95% CI: 0.69 to 1.35), and 12.3% in quartile 4 (HR: 1.48; 95% CI: 1.09 to 2.01).

In landmark analyses, between 1 and 3 years, increasing stent length per patient showed only a weak association with MACE (p = 0.0449), driven by TLR (p = 0.0131) (Table 5). Conversely, increasing stent length per lesion was not associated with higher risk for any adverse outcome between 1 and 3 years, demonstrating that risk was established early, within the first year after PCI (Table 6). Adjusted risks across the stent length quartiles in the

TABLE 3 Unadjusted and Adjusted Risk for 3-Year Clinical Outcomes Across Quartiles of Total Stent Length per Patient

	n (KM %)	Log-Rank p Value	Adjusted*		p Value for Trend
			HR (95% CI)	p Value	
MACE		<0.0001			<0.0001
Quartile 1	60 (9.2%)		Reference		
Quartile 2	158 (11.1%)		1.13 (0.82–1.56)	0.446	
Quartile 3	167 (14.4%)		1.49 (1.08–2.04)	0.014	
Quartile 4	260 (19.6%)		1.82 (1.34–2.48)	<0.001	
Key safety endpoint		<0.0001			<0.001
Quartile 1	41 (6.2%)		Reference		
Quartile 2	95 (6.7%)		1.15 (0.77–1.70)	0.495	
Quartile 3	114 (9.8%)		1.59 (1.08–2.33)	0.018	
Quartile 4	173 (12.7%)		1.82 (1.25–2.64)	0.002	
All-cause death		0.0062			0.122
Quartile 1	24 (3.8%)		Reference		
Quartile 2	57 (4.2%)		1.17 (0.71–1.94)	0.538	
Quartile 3	65 (6.1%)		1.65 (1.00–2.71)	0.049	
Quartile 4	78 (6.4%)		1.40 (0.85–2.31)	0.182	
Cardiac death		0.0146			0.038
Quartile 1	12 (2.0%)		Reference		
Quartile 2	26 (2.8%)		1.24 (0.60–2.57)	0.557	
Quartile 3	37 (4.2%)		2.10 (1.05–4.23)	0.037	
Quartile 4	46 (4.6%)		1.85 (0.92–3.72)	0.086	
Myocardial infarction		<0.0001			<0.001
Quartile 1	15 (2.1%)		Reference		
Quartile 2	43 (2.9%)		1.47 (0.78–2.78)	0.237	
Quartile 3	60 (4.8%)		2.31 (1.24–4.28)	0.008	
Quartile 4	108 (7.4%)		3.12 (1.71–5.70)	<0.001	
Definite or probable ST†		0.7393			0.673
Quartile 1	5 (0.7%)		Reference		
Quartile 2	18 (1.2%)		1.17 (0.41–3.34)	0.773	
Quartile 3	15 (1.2%)		1.21 (0.42–3.50)	0.728	
Quartile 4	15 (1.1%)		0.89 (0.30–2.63)	0.839	
TLR		0.0001			0.011
Quartile 1	27 (4.1%)		Reference		
Quartile 2	80 (5.5%)		1.00 (0.63–1.59)	0.495	
Quartile 3	68 (6.0%)		1.13 (0.70–1.82)	0.616	
Quartile 4	113 (9.1%)		1.51 (0.96–2.39)	0.077	

The key safety endpoint was defined as a composite of all-cause death, myocardial infarction, or definite or probable ST. MACE was defined as a composite of all-cause death, myocardial infarction, or TLR. *Adjusted for the following variables using a frailty model: age, hypertension, diabetes, smoking, prior PCI, prior myocardial infarction, PCI indication, and American College of Cardiology/American Heart Association lesion type B2/C. †Adjusted for the above variables with trial included as an additional covariate.

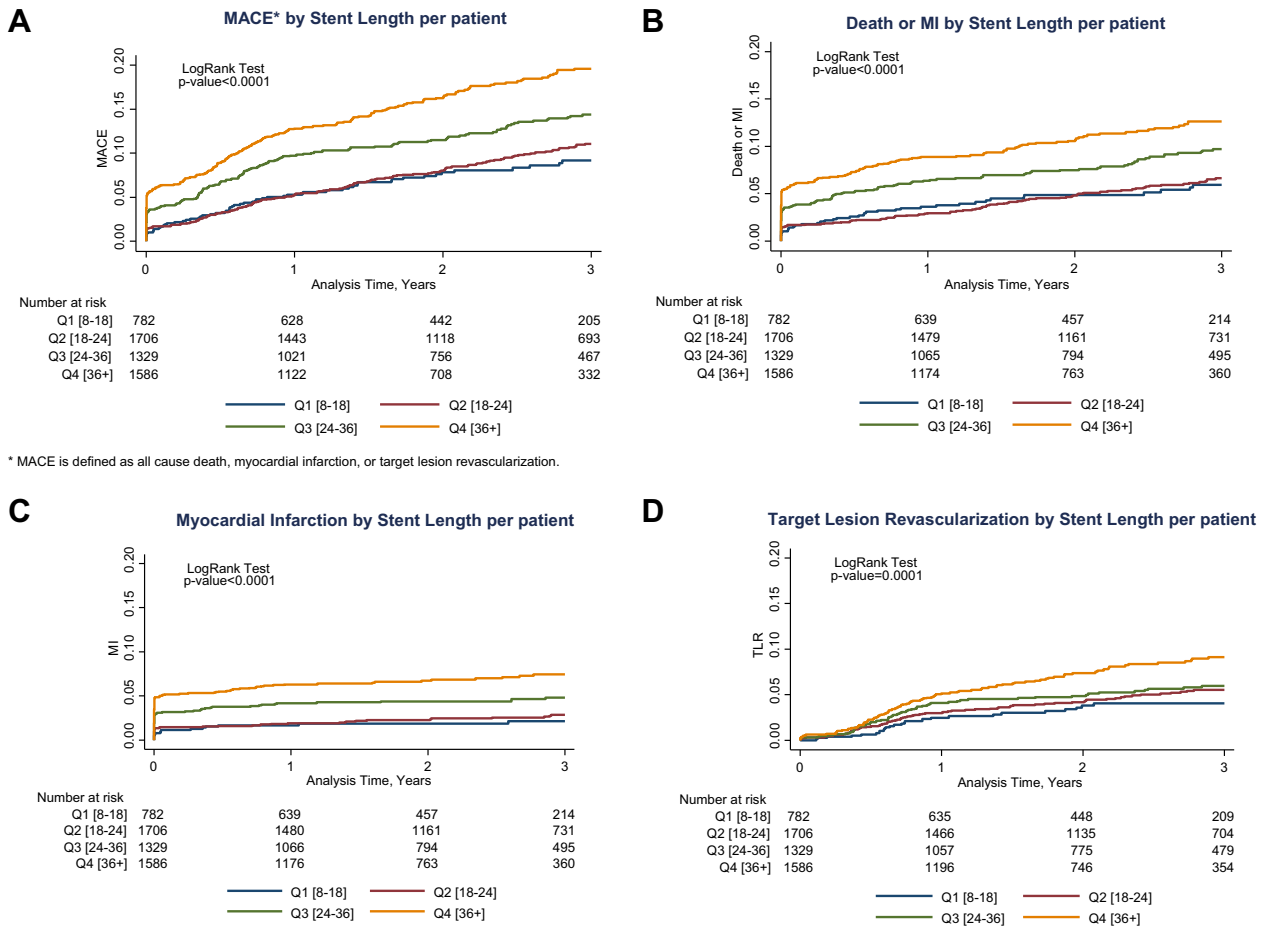
CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; MACE = major adverse cardiovascular event; PCI = percutaneous coronary intervention; ST = stent thrombosis; TLR = target lesion revascularization.

early (0 to 1 year) and late (1 to 3 years) periods are shown in Online Tables 2 and 3.

DISCUSSION

In this study, we examined the effect of increasing stent length among women treated with new-generation DES, pooled from 14 randomized controlled trials. The main findings are as follows. 1) In both unadjusted and adjusted analyses, increasing stent length per patient was associated with greater risk for 3-year MACE, MI, cardiac death, TLR, and the key safety endpoint. On landmark analyses, the greatest risk was noted within the first year, and between 1 and 3 years, only weak associations were noted for MACE and TLR. 2) Similarly, increasing stent length per lesion was associated with greater risk for 3-year MACE, MI, and the key safety

FIGURE 2 **Cumulative Incidence of Major Adverse Cardiovascular Events, All-Cause Death or Myocardial Infarction, Myocardial Infarction, and Target Lesion Revascularization in Quartiles of Total Stent Length per Patient**



(A) Cumulative incidence of MACE during 3-year follow-up by quartiles of stent length per patient. **(B)** Cumulative incidence of all-cause death or MI during 3-year follow-up by quartiles of stent length per patient. **(C)** Cumulative incidence of MI during 3-year follow-up by quartiles of stent length per patient. **(D)** Cumulative incidence of TLR during 3-year follow-up by quartiles of stent length per patient. MACE = major adverse cardiovascular event(s); MI = myocardial infarction; Q = quartile; TLR = target lesion revascularization.

endpoint. On landmark analysis, there was no association between stent length and increased risk for events between 1 and 3 years. 3) In both per-patient and per-lesion analyses, increasing stent length had no impact on ST up to 3 years.

The WIN-DES initiative is the largest patient-level collaboration of female patients treated with coronary stents in randomized controlled trials, allowing several important analyses to study the effect of DES in women. In general, women undergoing PCI tend to be older than men, with less extensive angiographic disease, yet they manifest several systemic risk factors and greater risk for recurrent events (15-17). In the current registry, women in the longest stent length quartiles had greater prevalence of diabetes mellitus and lower left ventricular ejection fraction. Procedurally, they demonstrated multivessel and complex disease, resulting in smaller implanted stent diameter, all well-known correlates of post-PCI adverse events (1,34,35).

Despite such a worse baseline profile, some prior studies have suggested that longer stent length with new-generation DES is not associated with increased risk for ST, TLR, or MACE (13,14). In particular, total stent length >32 mm has been associated with greater adverse outcomes with first-generation but not second-generation DES (13,14). However, only under a quarter of the included

TABLE 4 Unadjusted and Adjusted Risk for 3-Year Clinical Outcomes Across Quartiles of Total Stent Length per Lesion

	n (KM %)	Log-Rank p Value	Adjusted* HR (95% CI)	Adjusted* p Value	p Value for Trend
MACE		<0.0001			0.002
Quartile 1	99 (12.0%)		Reference		
Quartile 2	165 (11.7%)		0.95 (0.72–1.25)	0.708	
Quartile 3	136 (13.9%)		0.99 (0.75–1.31)	0.953	
Quartile 4	229 (18.2%)		1.38 (1.07–1.78)	0.014	
Key safety endpoint		<0.0001			0.004
Quartile 1	68 (8.2%)		Reference		
Quartile 2	99 (7.1%)		0.98 (0.70–1.37)	0.896	
Quartile 3	84 (8.5%)		0.96 (0.69–1.35)	0.953	
Quartile 4	158 (12.3%)		1.48 (1.09–2.01)	0.013	
All-cause death		<0.0001			0.558
Quartile 1	39 (5.1%)		Reference		
Quartile 2	58 (4.3%)		0.97 (0.63–1.50)	0.896	
Quartile 3	84 (8.5%)		1.08 (0.70–1.68)	0.718	
Quartile 4	68 (6.1%)		1.09 (0.72–1.67)	0.677	
Cardiac death		<0.0001			0.376
Quartile 1	21 (2.7%)		Reference		
Quartile 2	25 (3.1%)		0.94 (0.51–1.74)	0.852	
Quartile 3	35 (4.0%)		1.44 (0.81–2.56)	0.209	
Quartile 4	34 (4.4%)		1.17 (0.66–2.08)	0.598	
Myocardial infarction		<0.0001			<0.0001
Quartile 1	30 (3.4%)		Reference		
Quartile 2	49 (3.4%)		1.16 (0.71–1.90)	0.553	
Quartile 3	41 (3.8%)		1.08 (0.66–1.77)	0.770	
Quartile 4	99 (7.1%)		2.05 (1.32–3.20)	0.001	
Definite or probable ST†		<0.0001			0.944
Quartile 1	10 (1.1%)		Reference		
Quartile 2	18 (1.2%)		0.79 (0.33–1.89)	0.602	
Quartile 3	4 (0.4%)		0.27 (0.08–0.88)	0.030	
Quartile 4	20 (1.5%)		1.00 (0.44–2.28)	0.998	
TLR		<0.0001			0.366
Quartile 1	44 (5.2%)		Reference		
Quartile 2	86 (6.1%)		0.86 (0.57–1.27)	0.442	
Quartile 3	58 (6.2%)		0.83 (0.55–1.27)	0.396	
Quartile 4	96 (8.1%)		1.10 (0.74–1.62)	0.641	

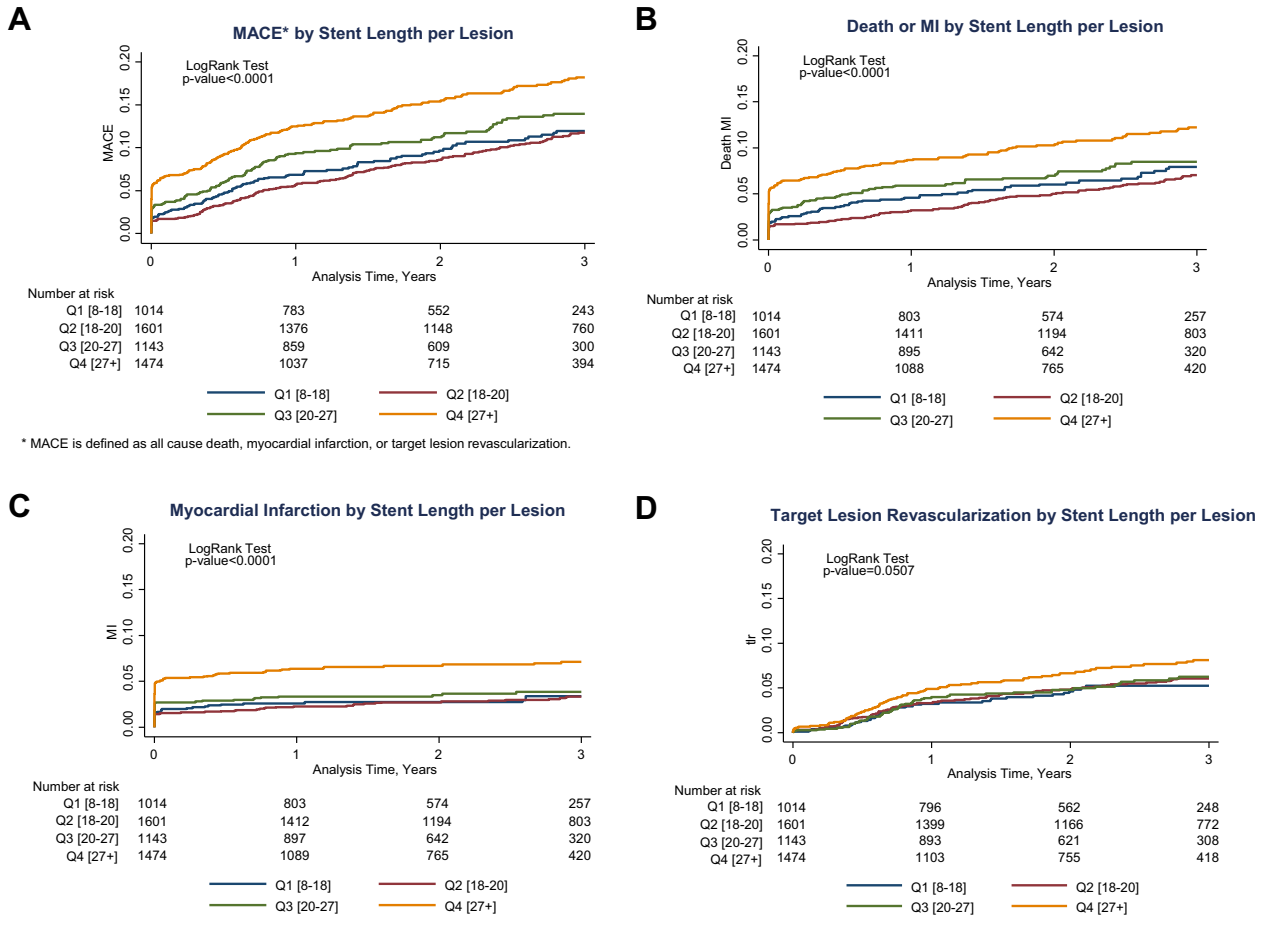
The key safety endpoint was defined as a composite of all-cause death, myocardial infarction, or definite or probable ST. MACE was defined as a composite of all-cause death, myocardial infarction, or TLR. *Adjusted for the following variables using a frailty model: age, hypertension, diabetes, smoking, prior PCI, prior myocardial infarction, PCI indication, and American College of Cardiology/American Heart Association lesion type B2/C. †Adjusted for the above variables with trial included as an additional covariate.

Abbreviations as in Table 3.

population in these studies comprised women. In our pooled analysis of only women participating in randomized trials, we observed that despite treatment with new-generation stents, increasing total stent length per patient was associated with greater adjusted risk for long-term MACE, driven by MI and TLR. Notwithstanding, risk was greatest within the first year after PCI. Furthermore, the higher adjusted risk for MI was not associated with a parallel increase in ST. This allows us to infer that not all MI events were stent related and may therefore be amenable to pharmacotherapy and secondary prevention of systemic risks. Certainly, novel stents with biocompatible polymers or polymer-free designs have demonstrated better healing scores and endothelialization rates associated with very low long-term ST rates (36–39).

Risk for stent failure with longer stent length may be a function of technical factors such as stent sizing, underexpansion, and malapposition, which

FIGURE 3 **Cumulative Incidence of Major Adverse Cardiovascular Events, All-Cause Death or Myocardial Infarction, Myocardial Infarction, and Target Lesion Revascularization in Quartiles of Total Stent Length per Lesion**



(A) Cumulative incidence of MACE during 3-year follow-up by quartiles of stent length per lesion. **(B)** Cumulative incidence of all-cause death or MI during 3-year follow-up by quartiles of stent length per lesion. **(C)** Cumulative incidence of MI during 3-year follow-up by quartiles of stent length per lesion. **(D)** Cumulative incidence of TLR during 3-year follow-up by quartiles of stent length per lesion. MACE = major adverse cardiovascular event(s); MI = myocardial infarction; Q = quartile; TLR = target lesion revascularization.

may be influenced by the use of intravascular imaging and post-dilation as well as the extent of lesion calcification. Although more than one-third of patients in our analysis had moderate or severe lesion calcification, we did not have detailed information on intravascular imaging use or post-dilation, which were not mandated by study design in the included studies. Where available, information regarding these procedural issues is indicated in Online Table 1. Notably, 2 recent observational studies found total stent length up to 46 and 50 mm to be reasonably safe for long-term outcomes with new-generation DES (11,12). However, the rate of imaging-guided stent implantation in these studies was high, with 96% use of intravascular ultrasound in the latter study. Nevertheless, consistent with our analysis, these studies also showed higher risk for TLR among patients receiving the greatest stents lengths per patient (>46 and >50 mm) (11,12), calling for closer attention to meticulous assessment of stent optimization in contemporary PCI. These observations also allow speculation regarding the potential use of bioresorbable scaffolds in long lesions and multilesion stenting.

Additional clinical parameters such as dual-antiplatelet therapy (DAPT) potency, nonresponsiveness, duration, and temporary or premature

TABLE 5 Cumulative Incidence of Clinical Outcomes by Quartiles of Total Stent Length per Patient During 3-Year Follow-Up

	Quartile 1 (8–18 mm)	Quartile 2 (18–24 mm)	Quartile 3 (24–36 mm)	Quartile 4 (≥36 mm)	
	n = 782 (14.0%)	n = 1,706 (32.0%)	n = 1,329 (25.0%)	n = 1,586 (29.0%)	p Value
MACE					
0–3 yrs	60 (9.17%)	158 (11.05%)	167 (14.36%)	260 (19.58%)	<0.0001
0–1 yr	41 (5.27%)	89 (5.27%)	128 (9.72%)	201 (12.79%)	<0.0001
1–3 yrs	19 (4.11%)	69 (6.10%)	39 (5.14%)	59 (7.79%)	0.0449
Key safety endpoint					
0–3 yrs	41 (6.20%)	95 (6.69%)	114 (9.81%)	173 (12.66%)	<0.0001
0–1 yr	30 (3.86%)	51 (3.01%)	87 (6.59%)	141 (8.94%)	<0.0001
1–3 yrs	11 (2.43%)	44 (3.79%)	27 (3.44%)	32 (4.09%)	0.4991
All-cause death or MI					
0–3 yrs	39 (5.93%)	94 (6.63%)	112 (9.71%)	172 (12.61%)	<0.0001
0–1 yr	28 (3.60%)	50 (2.95%)	84 (6.36%)	140 (8.88%)	<0.0001
1–3 yrs	11 (2.42%)	44 (3.78%)	28 (3.57%)	32 (4.10%)	0.5157
All-cause death					
0–3 yrs	24 (3.83%)	57 (4.19%)	65 (6.08%)	78 (6.40%)	0.0062
0–1 yr	15 (1.93%)	22 (1.31%)	38 (2.89%)	49 (3.12%)	0.0021
1–3 yrs	9 (1.93%)	35 (2.92%)	27 (3.28%)	29 (3.38%)	0.4988
Cardiac death					
0–3 yrs	12 (1.97%)	26 (2.79%)	37 (4.17%)	46 (4.61%)	0.0146
0–1 yr	8 (1.08%)	16 (1.37%)	26 (2.34%)	33 (2.55%)	0.0390
1–3 yrs	4 (0.89%)	10 (1.44%)	11 (1.87%)	13 (2.12%)	0.4480
MI					
0–3 yrs	15 (2.12%)	43 (2.85%)	60 (4.80%)	108 (7.43%)	<0.0001
0–1 yr	13 (1.67%)	32 (1.89%)	55 (4.17%)	99 (6.30%)	<0.0001
1–3 yrs	2 (0.46%)	11 (0.98%)	5 (0.65%)	9 (1.21%)	0.5001
Definite/probable ST					
0–3 yrs	5 (0.65%)	18 (1.18%)	15 (1.22%)	15 (1.09%)	0.7397
0–1 yr	5 (0.65%)	12 (0.71%)	14 (1.08%)	12 (0.77%)	0.6560
1–3 yrs	0 (0.00%)	6 (0.48%)	1 (0.14%)	3 (0.33%)	0.2531
TLR					
0–3 yrs	27 (4.07%)	80 (5.51%)	68 (5.95%)	113 (9.13%)	<0.0001
0–1 yr	19 (2.48%)	50 (2.97%)	53 (4.11%)	79 (5.14%)	0.0023
1–3 yrs	8 (1.63%)	30 (2.62%)	15 (1.93%)	34 (4.23%)	0.0131

Values are n (Kaplan-Meier %). The key safety endpoint was defined as a composite of all-cause death, myocardial infarction, or definite/probable ST.
Abbreviations as in Tables 1 and 3.

cessation may account for some differences in risk for thrombotic events between the groups. We extend the findings of previous studies in this large cohort of women treated with new-generation stents while highlighting the risk for non-stent-related recurrent thrombotic events. These data encourage careful considerations for selection of type and duration of post-PCI DAPT in women treated with greater stent length, especially because bleeding risk is a particular challenge in women (15,16). In addition, secondary prevention and the use of guideline-directed therapies including statins should be optimized to reduce risk for ischemic outcomes.

STUDY LIMITATIONS. First, total stent length in 5 of the 14 included trials may have been a function of restrictions on the eligibility criteria on the basis of individual lesion length or number of lesions treated. Second, management strategies varied over the study period, including nonuniform durations of DAPT in the different trials, although we adjusted for possible trial effect. Third, pooled data were restricted to women, and comparison with men was therefore not possible. However, because women are typically underrepresented in stent trials, the present study offers the advantage of a robust analysis in a large sample of women receiving new-generation DES.

TABLE 6 Cumulative Incidence of Clinical Outcomes by Quartiles of Total Stent Length per Lesion During 3-Year Follow-Up

	Quartile 1 (8–18 mm) n = 1,014 (19.0%)	Quartile 2 (18–20 mm) n = 1,601 (31.0%)	Quartile 3 (20–27 mm) n = 1,143 (22.0%)	Quartile 4 (≥27 mm) n = 1,474 (28.0%)	p Value
MACE					
0–3 yrs	99 (11.97%)	165 (11.73%)	136 (13.93%)	229 (18.19%)	<0.0001
0–1 yr	69 (6.86%)	90 (5.67%)	106 (9.38%)	182 (12.46%)	<0.0001
1–3 yrs	30 (5.49%)	75 (6.43%)	30 (5.02%)	47 (6.55%)	0.5383
Key safety endpoint					
0–3 yrs	68 (8.24%)	99 (7.09%)	84 (8.47%)	158 (12.27%)	<0.0001
0–1 yr	49 (4.86%)	52 (3.27%)	67 (5.90%)	130 (8.88%)	<0.0001
1–3 yrs	19 (3.55%)	47 (3.95%)	17 (2.73%)	28 (3.73%)	0.5975
All-cause death or MI					
0–3 yrs	65 (7.93%)	98 (7.03%)	84 (8.47%)	156 (12.22%)	<0.0001
0–1 yr	46 (4.56%)	51 (3.21%)	67 (5.90%)	127 (8.67%)	<0.0001
1–3 yrs	19 (3.53%)	47 (3.95%)	17 (2.73%)	29 (3.89%)	0.5774
All-cause death					
0–3 yrs	39 (5.09%)	58 (4.31%)	52 (5.66%)	68 (6.05%)	0.1020
0–1 yr	23 (2.29%)	21 (1.33%)	34 (3.00%)	41 (2.81%)	0.0112
1–3 yrs	16 (2.86%)	37 (3.02%)	18 (2.74%)	27 (3.33%)	0.9107
Cardiac death					
0–3 yrs	21 (2.70%)	25 (3.13%)	35 (3.96%)	36 (4.40%)	0.2992
0–1 yr	15 (1.58%)	14 (1.43%)	27 (2.59%)	24 (2.04%)	0.2161
1–3 yrs	6 (1.14%)	11 (1.72%)	8 (1.40%)	12 (2.40%)	0.5654
MI					
0–3 yrs	30 (3.39%)	49 (3.35%)	41 (3.84%)	99 (7.13%)	<0.0001
0–1 yr	26 (2.58%)	36 (2.26%)	38 (3.35%)	93 (6.36%)	<0.0001
1–3 yrs	4 (0.83%)	13 (1.11%)	3 (0.51%)	6 (0.82%)	0.5967
Definite/probable ST					
0–3 yrs	10 (1.12%)	18 (1.22%)	4 (0.36%)	20 (1.52%)	0.0693
0–1 yr	9 (0.90%)	12 (0.75%)	4 (0.36%)	17 (1.18%)	0.1431
1–3 yrs	1 (0.23%)	6 (0.47%)	0 (0.00%)	3 (0.35%)	0.2706
TLR					
0–3 yrs	44 (5.24%)	86 (6.05%)	58 (6.23%)	96 (8.13%)	0.0507
0–1 yr	32 (3.23%)	52 (3.29%)	44 (3.98%)	70 (4.90%)	0.0855
1–3 yrs	12 (2.07%)	34 (2.86%)	14 (2.35%)	26 (3.41%)	0.4540

The key safety endpoint was defined as a composite of all-cause death, myocardial infarction, or definite or probable ST.
Abbreviations as in Tables 1 and 3.

CONCLUSIONS

Among women undergoing PCI with new-generation DES, increasing stent length per patient and per lesion are independent predictors of 3-year MACE but not ST, with the greatest risk being established within the first year. Attention to judicious stent implantation and stent optimization, intensity, and duration of post-PCI DAPT is necessary to decrease long-term recurrent adverse events. Concurrently, prescription of and compliance to other guideline-directed therapies are key issues to improve outcomes and should be accurately ascertained and reported.

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PERSPECTIVES

WHAT IS KNOWN? Stent length was associated with an adverse impact on outcomes in the era of bare-metal stents and first-generation DES. Although women have less extensive coronary artery disease than men, the randomized trial evidence base in women is limited because of lower recruitment to clinical trials.

WHAT IS NEW? In this pooled analysis of women undergoing PCI from 26 randomized controlled trials, we included >5,000 women receiving new-generation DES. In both total stent length per-patient and per-lesion analyses, a stepwise increase was observed with increasing stent length in the adjusted risk for 3-year MACE (a composite of all-cause death, MI, or TLR) (per-patient analysis, p for trend <0.0001; per-lesion analysis, p for trend = 0.002) but not definite or probable ST.

WHAT IS NEXT? With further improvements in stent technology and greater uptake of fractional flow reserve, instantaneous wave-free ratio testing, and imaging-guided PCI, future studies should report on these technical factors as well as on the rates of post-dilation and optimal stent deployment, to assess plausible correlations with adverse outcomes. Along with judicious stent implantation, post-PCI prescription and compliance to guideline-directed therapies are key issues for reduction of recurrent events and should be accurately ascertained and presented.

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APPENDIX For supplemental tables, please see the online version of this paper.