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Randomized Comparison of Everolimus- and Paclitaxel-Eluting Stents

2-Year Follow-Up From the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV Trial

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Objectives We sought to determine whether the differences in outcomes present between everolimus-eluting stents (EES) and paclitaxel-eluting stents (PES) in the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial at 1 year were sustained with longer-term follow-up.

Background In the SPIRIT IV trial, patients undergoing percutaneous coronary intervention who were randomized to EES compared with PES experienced lower 1-year rates of target lesion failure (cardiac death, target vessel myocardial infarction [MI], or ischemia-driven target lesion revascularization [TLR]), with significant reductions in the individual rates of MI, TLR, and stent thrombosis.

Methods We prospectively randomized 3,687 patients with up to 3 noncomplex previously untreated native coronary artery lesions to EES versus PES at 66 U.S. sites. Follow-up through 2 years is complete in 3,578 patents (97.0%).

Results Treatment with EES compared with PES reduced the 2-year rates of TLF (6.9% vs. 9.9%, p = 0.003), all MI (2.5% vs. 3.9%, p = 0.02), Q-wave MI (0.1% vs. 0.8%, p = 0.002), stent thrombosis (0.4% vs. 1.2%, p = 0.008), and ischemia-driven TLR (4.5% vs. 6.9%, p = 0.004), with nonsignificantly different rates of all-cause and cardiac mortality. Between 1 year and 2 years, there were no significant differences in adverse event rates between the 2 stent types.

Conclusions In the large-scale, prospective, multicenter, randomized SPIRIT IV trial, the benefits of EES compared with those of PES present at 1 year were sustained at 2 years. (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System; NCT01016041) (J Am Coll Cardiol 2011;58:19–25) © 2011 by the American College of Cardiology Foundation

Compared with bare-metal stents, drug-eluting stents (DES) delivering either paclitaxel or sirolimus to the site of arterial injury during percutaneous coronary intervention (PCI) safely reduce clinical restenosis, resulting in improved event-free survival (1,2). Next-generation DES have been developed for greater safety and efficacy but have mostly been evaluated in modest-sized noninferior-

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Abbreviations and Acronyms

DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
TLF = target lesion failure
TLR = target lesion revascularization

ity trials designed for regulatory approval. Given the low frequency of adverse events with contemporary DES, large-scale trials are required to determine whether significant differences exist between devices, which are clinically relevant given their annual use in more than 2 million patients worldwide.

In the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial, 3,687 patients undergoing PCI were randomized to everolimus-eluting stents (EES) versus paclitaxel-eluting stents (PES), representing the largest reported comparison of 2 DES to date (3). The 1-year primary endpoint of target lesion failure (TLF) (cardiac death, target vessel myocardial infarction [MI], or ischemia-driven target lesion revascularization [TLR]) was reduced from 6.7% with PES to 4.0% with EES (p = 0.0009), with significant reductions in the individual rates of MI, TLR, and stent thrombosis. Whether these benefits are robust over time has not been reported. In this regard, serial angiographic follow-up in a modest number of patients from the SPIRIT II trial suggested that there may be greater incremental late loss with EES than PES between 6 months and 2 years, which could theoretically narrow the clinical differences between these 2 devices (4). We therefore describe the 2-year clinical outcomes from the large-scale SPIRIT IV trial.

Methods

Patients and protocol. As previously described (3,5), SPIRIT IV was a prospective, multicenter, randomized, single-blind, active-controlled clinical trial in which 3,687 patients ≥18 years undergoing PCI were randomized 2:1 to EES (XIENCE V, Abbott Vascular, Santa Clara, California) or PES (TAXUS Express-2, Boston Scientific, Natick, Massachusetts). Patients undergoing PCI of up to 3 previously untreated native coronary artery lesions with length ≤28 mm and vessel diameter ≥2.5 to ≤3.75 mm were enrolled. Major exclusion criteria (5) included recent MI, left ventricular ejection fraction <30%, and complex lesions including left main, ostial left anterior descending, or left circumflex stenoses; totally occluded vessels; large bifurcations; excessive calcification; tortuosity; angulation; or thrombus.

Aspirin ≥300 mg was administered before catheterization, with ≥80 mg daily continued indefinitely. A loading dose of clopidogrel ≥300 mg was given, followed by 75 mg daily for ≥6 months (1 year strongly recommended). Thienopyridine use after 1 year was left to physician discretion. Clinical follow-up is ongoing through 5 years. TLF components have been defined elsewhere (5). Secondary endpoints included major adverse cardiac events (cardiac death, MI, or ischemia-

Table 1 Baseline Clinical and Angiographic Characteristics According to Stent Randomization

	EES (n = 2,458 Patients and 3,142 Lesions)	PES (n = 1,229 Patients and 1,585 Lesions)	p Value
Demographic features			
Age, yrs	63.3 ± 10.5	63.3 ± 10.2	0.80
Male	1,665/2,458 (67.7)	833/1,229 (67.8)	1.00
Hypertension	1,899/2,454 (77.4)	935/1,228 (76.1)	0.41
Hypercholesterolemia	1,834/2,411 (76.1)	917/1,214 (75.5)	0.74
Diabetes mellitus	786/2,455 (32.0)	399/1,228 (32.5)	0.80
Insulin requiring	209/2,455 (8.5)	119/1,228 (9.7)	0.24
Current smoker	527/2,411 (21.9)	269/1,200 (22.4)	0.70
Prior myocardial infarction	504/2,388 (21.1)	239/1,202 (19.9)	0.41
Unstable angina	669/2,416 (27.7)	347/1,202 (28.9)	0.46
No. of target lesions/patient	1.3 ± 0.5	1.3 ± 0.5	0.53
Target lesion characteristics			
Reference vessel diameter, mm	2.75 ± 0.48	2.75 ± 0.46	0.59
Minimal luminal diameter, mm	0.75 ± 0.38	0.76 ± 0.39	0.36
Diameter stenosis, %	72.3 ± 12.6	72.0 ± 12.8	0.44
Lesion length, mm	14.8 ± 6.7	14.5 ± 6.6	0.24
Procedural variables			
No. of stents/patient	1.49 ± 0.77	1.46 ± 0.78	0.35
No. of stents/lesion	1.17 ± 0.44	1.14 ± 0.41	0.01
Maximum stent diameter/lesion, mm	3.01 ± 0.39	3.01 ± 0.38	0.70
Total stent length/lesion, mm	22.4 ± 8.9	20.9 ± 8.9	<0.001

Data are presented as mean ± SD or n (%).
EES = everolimus-eluting stent(s); PES = paclitaxel-eluting stent(s).

Table 2 Aspirin and Thienopyridine Usage

	EES (n = 2,458)	PES (n = 1,229)	p Value
Aspirin use			
At discharge	2,434/2,458 (99.0)	1,220/1,229 (99.3)	0.58
At 1 yr	2,294/2,370 (96.8)	1,143/1,179 (96.9)	0.84
At 2 yrs	2,227/2,324 (95.8)	1,111/1,154 (96.3)	0.58
Thienopyridine use			
At discharge	2,437/2,458 (99.1)	1,221/1,229 (99.3)	0.56
At 1 yr	2,228/2,372 (93.9)	1,111/1,179 (94.2)	0.76
At 2 yrs	1,671/2,326 (71.8)	820/1,154 (71.1)	0.63
Both aspirin and thienopyridine use			
At discharge	2,422/2,458 (98.5)	1,218/1,229 (99.1)	0.16
At 1 yr	2,177/2,368 (91.9)	1,087/1,179 (92.2)	0.84
At 2 yrs	1,618/2,322 (69.7)	795/1,154 (68.9)	0.64
Neither aspirin nor thienopyridine use			
At discharge	7/2,456 (0.3)	4/1,227 (0.3)	0.76
At 1 yr	30/2,375 (1.3)	12/1,179 (1.0)	0.62
At 2 yrs	49/2,329 (2.1)	18/1,154 (1.6)	0.30

Data are presented as n (%).
Abbreviations as in Table 1.

driven TLR), target vessel failure (cardiac death, MI, or ischemia-driven target vessel revascularization), and definite or probable stent thrombosis according to the Academic Research Consortium criteria. All of these endpoints and their components were pre-specified for analysis at 2 years.

Statistical methods. Categorical variables were compared by the Fisher exact test. Continuous variables are presented as mean ± SD and were compared by *t* test. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test. A 2-sided alpha of 0.05 was used for all superiority testing. Formal interaction testing was performed to determine whether pre-specified subgroups influenced the relative risk of EES versus PES for the primary TLF endpoint at 2 years.

Results

Patients, procedures, and antiplatelet medication adherence. A total of 2,458 patients were assigned to EES, and 1,229 patients were assigned to PES. The EES and PES groups were well matched (Table 1), with the exception of the number of stents and total stent length/lesion, which were increased in EES-treated patients because of fewer EES stent lengths available. The majority of patients were

Table 3 Adverse Events at 1- and 2-Year Follow-up According to Stent Randomization

	1-Yr Outcomes				2-Yr Outcomes			
	EES (n = 2,458)	PES (n = 1,229)	HR (95% CI)	p Value	EES (n = 2,458)	PES (n = 1,229)	HR (95% CI)	p Value
Target lesion failure	4.0% (98)	6.7% (81)	0.62 (0.46–0.82)	0.0009	6.9% (166)	9.9% (119)	0.70 (0.55–0.89)	0.003
Major adverse cardiac events	4.1% (99)	6.8% (82)	0.61 (0.46–0.82)	0.0008	7.1% (171)	10.1% (121)	0.71 (0.56–0.89)	0.003
Target vessel failure	5.4% (131)	7.8% (95)	0.72 (0.55–0.93)	0.01	9.3% (224)	11.7% (140)	0.81 (0.65–0.99)	0.04
All-cause death	1.0% (24)	1.2% (15)	0.83 (0.44–1.57)	0.56	2.0% (49)	2.7% (32)	0.79 (0.51–1.23)	0.30
Cardiac	0.4% (10)	0.4% (5)	0.99 (0.34–2.91)	0.99	0.9% (21)	1.3% (15)	0.73 (0.38–1.40)	0.34
Noncardiac	0.6% (14)	0.8% (10)	0.75 (0.33–1.66)	0.47	1.2% (28)	1.4% (17)	0.85 (0.47–1.54)	0.59
All MI	1.9% (46)	3.0% (37)	0.62 (0.40–0.95)	0.03	2.5% (60)	3.9% (47)	0.64 (0.44–0.94)	0.02
Q-wave	0.1% (3)	0.4% (5)	0.30 (0.07–1.25)	0.08	0.1% (3)	0.8% (9)	0.17 (0.04–0.61)	0.002
Non–Q-wave	1.8% (43)	2.7% (33)	0.65 (0.41–1.02)	0.06	2.4% (57)	3.3% (40)	0.72 (0.48–1.08)	0.11
Target vessel MI	1.8% (45)	2.9% (35)	0.64 (0.41–1.00)	0.05	2.3% (55)	3.5% (42)	0.66 (0.44–0.99)	0.04
Cardiac death or target vessel MI	2.2% (54)	3.1% (38)	0.71 (0.47–1.07)	0.10	3.1% (75)	4.2% (51)	0.75 (0.53–1.07)	0.11
Ischemia-driven TLR	2.4% (57)	4.6% (55)	0.54 (0.38–0.78)	0.0007	4.5% (107)	6.9% (82)	0.66 (0.50–0.88)	0.004
Ischemia-driven TVR	3.7% (89)	5.9% (71)	0.67 (0.49–0.91)	0.009	6.8% (163)	8.9% (106)	0.78 (0.61–0.99)	0.04
Stent thrombosis	0.29% (7)	1.06% (13)	0.27 (0.11–0.67)	0.003	0.42% (10)	1.23% (15)	0.36 (0.17–0.79)	0.008
Definite	0.25% (6)	0.82% (10)	0.30 (0.11–0.82)	0.01	0.33% (8)	0.99% (12)	0.37 (0.16–0.88)	0.02
Probable	0.04% (1)	0.24% (3)	0.17 (0.02–1.60)	0.08	0.08% (2)	0.24% (3)	0.33 (0.06–1.99)	0.20

Data are presented as Kaplan-Meier estimates (no. of events), unless otherwise indicated.
CI = confidence intervals; HR = hazard ratio; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

maintained on dual antiplatelet therapy throughout the 2-year follow-up period (Table 2).

Clinical outcomes. Follow-up at 2 years was available in 3,578 patents (97.0%), including 2,388 assigned to EES and 1,190 assigned to PES. EES compared with PES significantly reduced the 2-year rate of TLF (6.9% vs. 9.9%; hazard ratio: 0.70, 95% confidence interval: 0.55 to 0.89; p = 0.003) (Table 3, Fig. 1). This absolute 3.0% reduction in TLF (number needed to treat [NNT]: 33) was comparable to the 2.7% absolute benefit with EES present at 1 year (NNT: 37). The 2-year reduction in TLF was driven by significant reductions in target vessel MI and ischemia-driven TLR, with nonsignificantly different rates of cardiac mortality. EES versus PES also reduced the 2-year rates of all-cause MI and Q-wave MI. The 2-year rate of Academic Research Consortium definite or probable stent thrombosis was reduced by 64% with EES compared with PES (0.4% vs. 1.2%; hazard ratio: 0.36, 95% confidence interval: 0.17 to 0.79; p = 0.008). There were no significant differences between EES and PES in clinical outcomes between 1 year and 2 years (Table 4). The 2-year reduction in TLF with EES compared with PES was consistent across 11 prespecified subgroups, with a borderline interaction present in patients with versus without diabetes (Fig. 2).

Discussion

In the large-scale, prospective, randomized SPIRIT IV trial, treatment of noncomplex lesions with EES rather than PES resulted in significant reductions in MI, stent thrombosis, and ischemia-driven TLR at 1 year, without significant differences in all-cause or cardiac mortality. As a result, the 1-year primary endpoint of TLF was reduced by 38% (absolute risk reduction 2.7%, NNT: 37). Between 1 year and 2 years, adverse events accrued equally

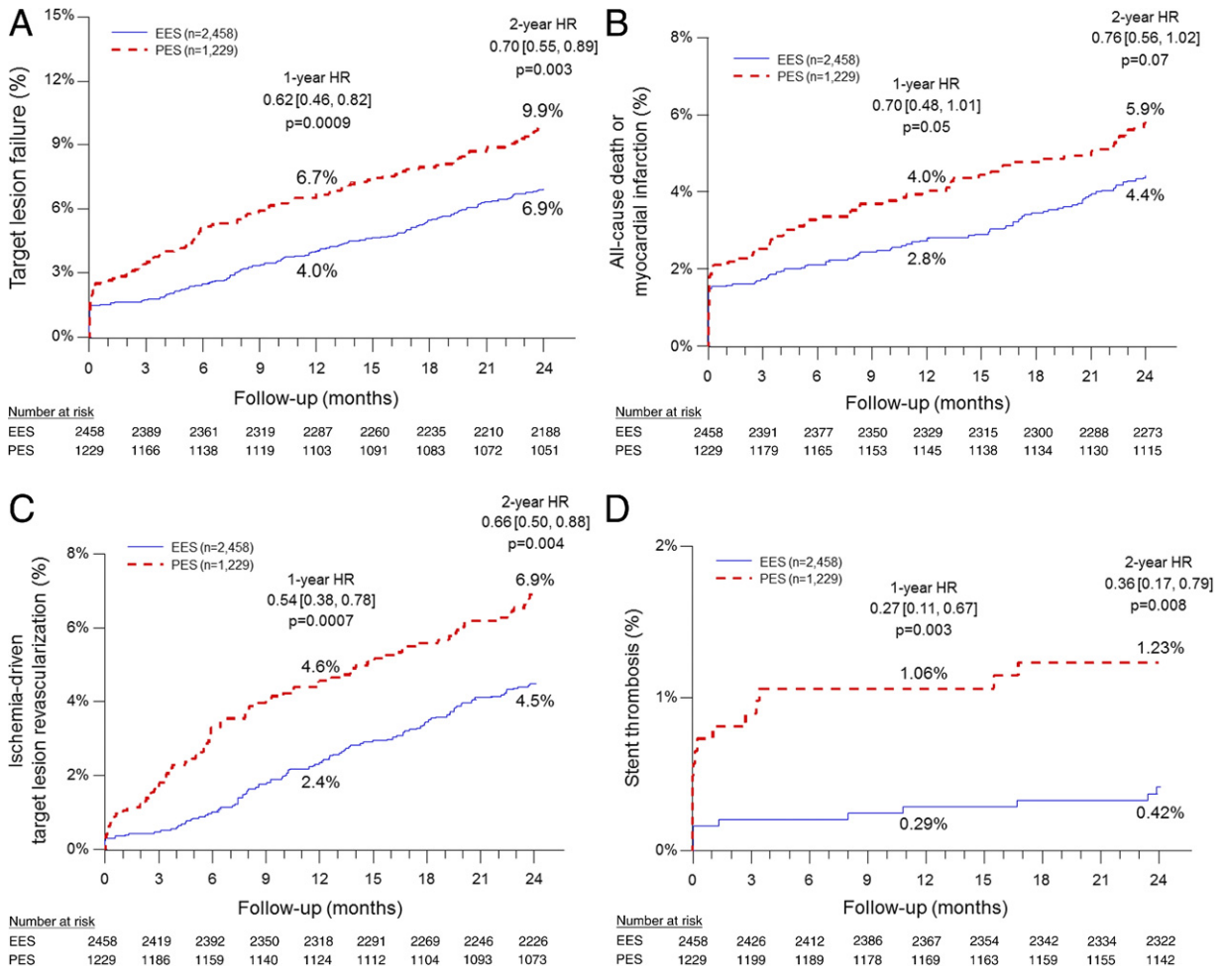

Figure 1 Time-to-Event Curves Through 2-Year Follow-up

Time-to-event curves for target lesion failure **(A)**, death or myocardial infarction **(B)**, ischemia-driven target lesion revascularization **(C)**, and definite or probable stent thrombosis **(D)**. EES = everolimus-eluting stent(s); HR = hazard ratio; PES = paclitaxel-eluting stent(s).

Table 4 Adverse Events Between 1 Year and 2 Years (Landmark Analysis)

	EES (n = 2,458)	PES (n = 1,229)	HR (95% CI)	p Value
Target lesion failure	2.9% (68)	3.9% (46)	0.80 (0.55–1.15)	0.23
Major adverse cardiac events	3.1% (72)	4.1% (48)	0.81 (0.56–1.15)	0.24
Target vessel failure	4.1% (97)	4.9% (57)	0.90 (0.65–1.24)	0.51
All-cause death	1.0% (24)	1.4% (17)	0.76 (0.41–1.40)	0.38
Cardiac	0.5% (11)	0.9% (10)	0.60 (0.26–1.38)	0.22
Noncardiac	0.6% (13)	0.6% (7)	0.99 (0.40–2.46)	0.99
All MI	0.6% (14)	0.9% (11)	0.68 (0.31–1.48)	0.32
Q-wave	0.0% (0)	0.3% (4)	—	0.005
Non–Q-wave	0.6% (14)	0.6% (7)	1.07 (0.43–2.62)	0.89
Target vessel MI	0.4% (10)	0.7% (8)	0.68 (0.27–1.70)	0.41
Cardiac death or target vessel MI	0.9% (21)	1.4% (16)	0.71 (0.38–1.35)	0.30
Ischemia-driven TLR	2.1% (49)	2.7% (32)	0.84 (0.54–1.29)	0.42
Ischemia-driven TVR	3.2% (76)	3.7% (43)	0.94 (0.65–1.35)	0.72
Stent thrombosis	0.13% (3)	0.17% (2)	0.99 (0.18–5.41)	0.99
Definite	0.09% (2)	0.17% (2)	0.74 (0.12–4.45)	0.74
Probable	0.04% (1)	0.00% (0)	—	0.48

Data are presented as Kaplan-Meier estimates (no. of events), unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

with both stent platforms such that at the end of the second year of follow-up, EES compared with PES resulted in a 30% relative and 3.0% absolute reduction in TLF (NNT: 33). A similar pattern was noted for the endpoints of MI, stent thrombosis, and ischemia-driven TLR, with the benefits of EES compared with PES realized at 1 year and maintained at the end of year 2. The 64% 2-year reduction in stent thrombosis with EES compared with PES is likely responsible for the reduction in Q-wave MI noted with EES.

The observation that the reduction in TLR with EES was durable between 1 year and 2 years with no late loss of clinical efficacy in this large-scale clinical trial is reassuring given a prior report from the SPIRIT II angiographic substudy of greater incremental late loss between 6 months and 2 years with EES compared with PES (4). Late clinical catch-up in TLR was not observed between the 2 stents in the SPIRIT II or III randomized trials (4,6), although routine angiographic follow-up in these studies may have biased the late results against the greater late loss PES. In contrast to these earlier trials, routine angiographic follow-up was not performed in SPIRIT IV, thus establishing that the reduction in clinical restenosis with EES compared with PES is stable over time, at least through 2-year follow-up.

Although no loss of the safety or efficacy advantages of EES versus PES was apparent between 1 year and 2 years of follow-up, neither was any further incremental gain present. These results differ from the COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial) (7), in which the advantages of EES versus PES continued to increase over time. Whether these differences between the trials are due to enrollment of diverse patient populations (mostly stable ischemic heart disease without complex lesions in SPIRIT IV vs. a more complex "all-comers" cohort in COMPARE), differences in prolonged dual antiplatelet therapy administration (frequent at 2 years in SPIRIT IV vs. infrequent at 2 years in COMPARE), or chance cannot be answered with certainty.

The 2-year benefits of EES compared with those of PES were consistent across 11 pre-specified subgroups, except possibly patients with diabetes versus those without diabetes, in whom a borderline interaction effect ($p = 0.08$) was present (as also suggested in SPIRIT III) (8). In patients without diabetes, EES versus PES resulted in a significant 39% reduction in TLF at 2 years versus a nonsignificant 7% reduction in patients with diabetes. A recent pooled patient-level analysis from the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials found this interaction to be statistically significant (9). Additional studies are warranted to understand the mechanisms and influence of the glycemic state on the differential vascular responses to rapamycin analogue-eluting stents and PES (10,11).

The present study results do not apply to excluded patients, such as those with acute thrombotic syndromes and complex lesions. Whether the frequent use of dual antiplatelet therapy at 2 years in the present trial was beneficial in either stent arm is unknown and is the subject of ongoing randomized trials. Subgroup analysis is inherently underpowered (12) and should be considered exploratory and hypothesis generating. Finally, 5-year follow-up is required to fully characterize the late differences between the 2 stent platforms. Nonetheless, the current results were consistent with the 3-year pooled results from the SPIRIT II and III trials (13).

Conclusions

In the large-scale, prospective, multicenter, randomized SPIRIT IV trial, the benefits of EES compared with those of

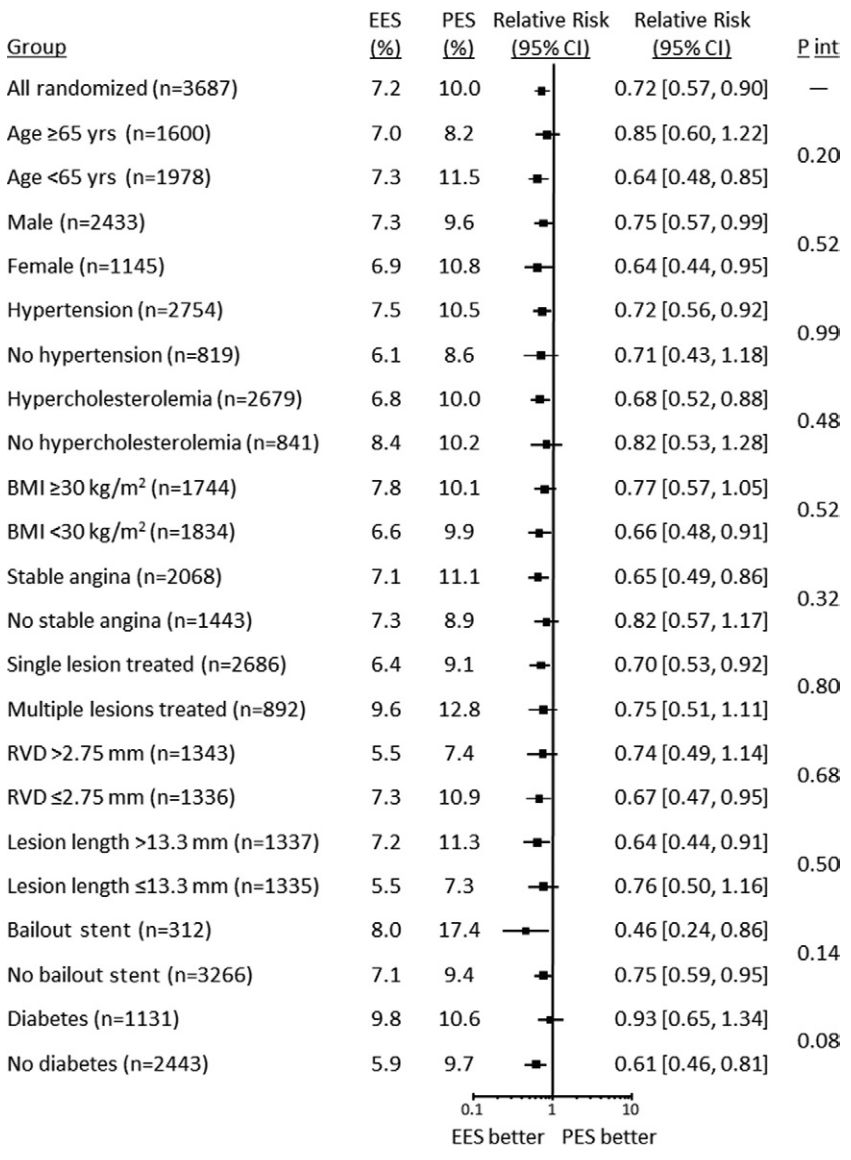

Figure 2 **2-Year Rates of Target Lesion Failure in 11 Pre-Specified Subgroups According to Stent Randomization**

Median values were used for reference vessel diameter (RVD) and lesion length cutoffs. Single lesion treated data were used for RVD and lesion length subgroup analyses. BMI = body mass index; CI = confidence interval; P int = p value for interaction; RVD = reference vessel diameter; other abbreviations as in Figure 1.

PES present at 1 year in reducing TLF, MI, stent thrombosis, and ischemia-driven TLR were sustained at 2 years.

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