One-Year Clinical and Angiographic Outcomes from the RESET Trial

Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial

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On behalf of the RESET Investigators

Disclosures

Takeshi Kimura, MD

Scientific advisory boards for and honoraria from Abbott Vascular, Cordis Cardiology, and Terumo Company.

Study Sponsor of the RESET Study

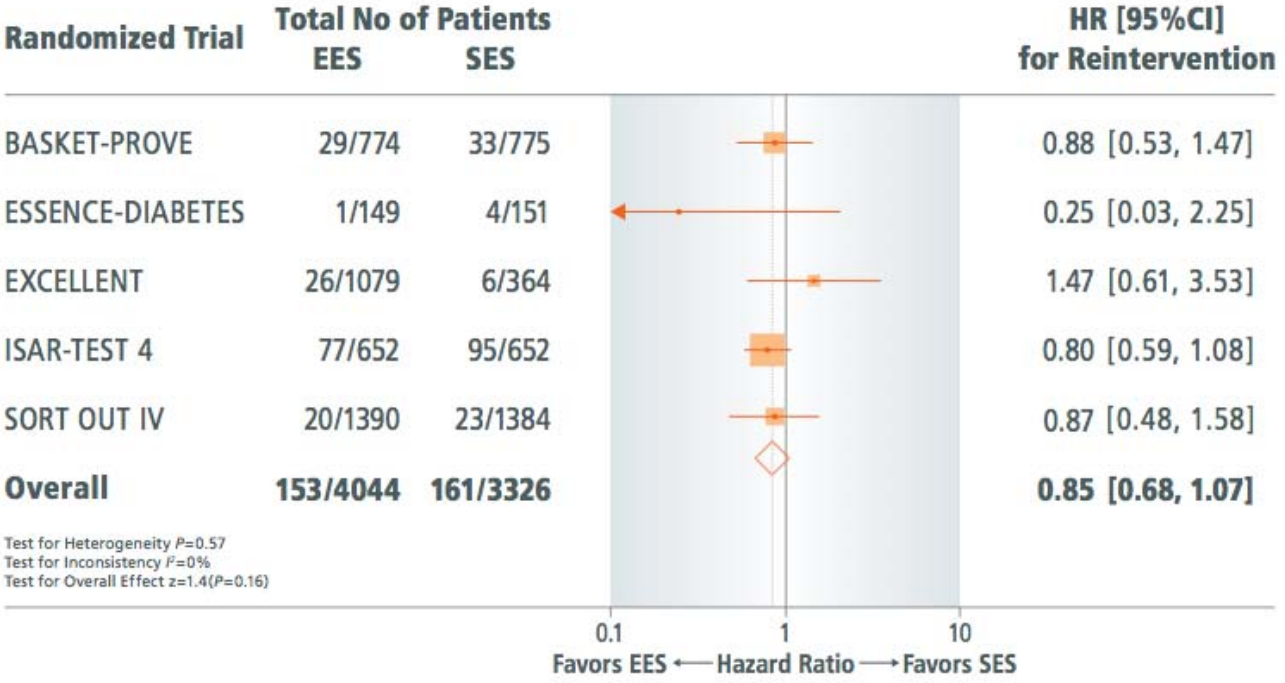
Abbott Vascular

Backgrounds

Several recent randomized trials suggested similar one-year clinical outcomes between everolimus-eluting stent (EES) and sirolimus-eluting stent (SES).

However, none of these trials was adequately powered to evaluate the efficacy outcomes after stent implantation such as TLR or TVR.

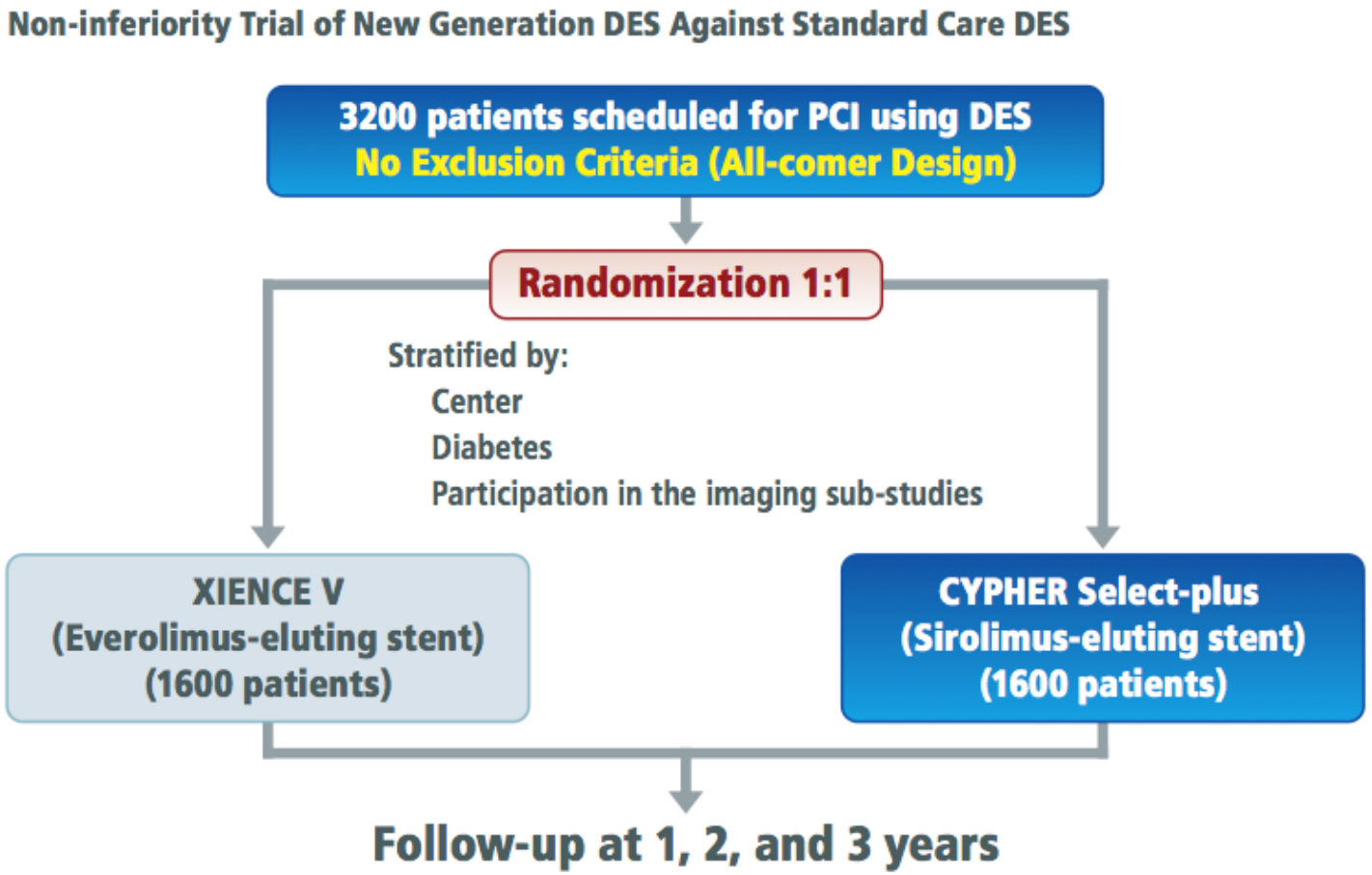
Forest Plot with Hazard Ratio for Target Vessel Revascularization



Kastrati A, et al. *Circ Cardiovasc Interv.* 2011;4: e-pub ahead of print.

RESET Trial

(Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial)



Imaging Sub-studies at 8-12 months:

Angiography (500 patients), IVUS/OCT (120 patients), Endothelial function (100 patients)

(Scheduled follow-up angiography by local site protocol was allowed beyond 240 days.)

RESET: Study Organization

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Primary Endpoints and Sample Size Calculation

- **Primary Clinical Endpoint for Efficacy:**

  Any Target-lesion Revascularization at 12 months

- **Estimated event rate at 12 months:**

  Sirolimus-eluting stent group: 6.9% (j-Cypher registry)

  Non-inferiority margin of 3.4% and one-sided type I error of 0.025

  3000 patients would yield > 95% power to detect non-inferiority.

  90% power to detect superiority with 2.7-percentage-point difference between the stent types at a level of one-sided type 1 error of 0.025

Primary Endpoints and Sample Size Calculation

- **Primary Clinical Endpoint for Safety:**

  Death or Myocardial Infarction at 3 years

- **Estimated event rate at 3 years:**

  Sirolimus-eluting stent group: 12.2% (j-Cypher registry)

  Non-inferiority margin of 4.3% and one-sided type I error of 0.025

  3000 patients would yield 91% power to detect non-inferiority.

- A total of 3200 patients were to be enrolled considering possible drop-out during follow-up.

Angiographic Primary Endpoint and Sample Size Calculation

- **Primary Angiographic Endpoint:**

  In-segment Late Loss at 8-12 Months

- **Estimated in-segment late loss at 8-12 months:**

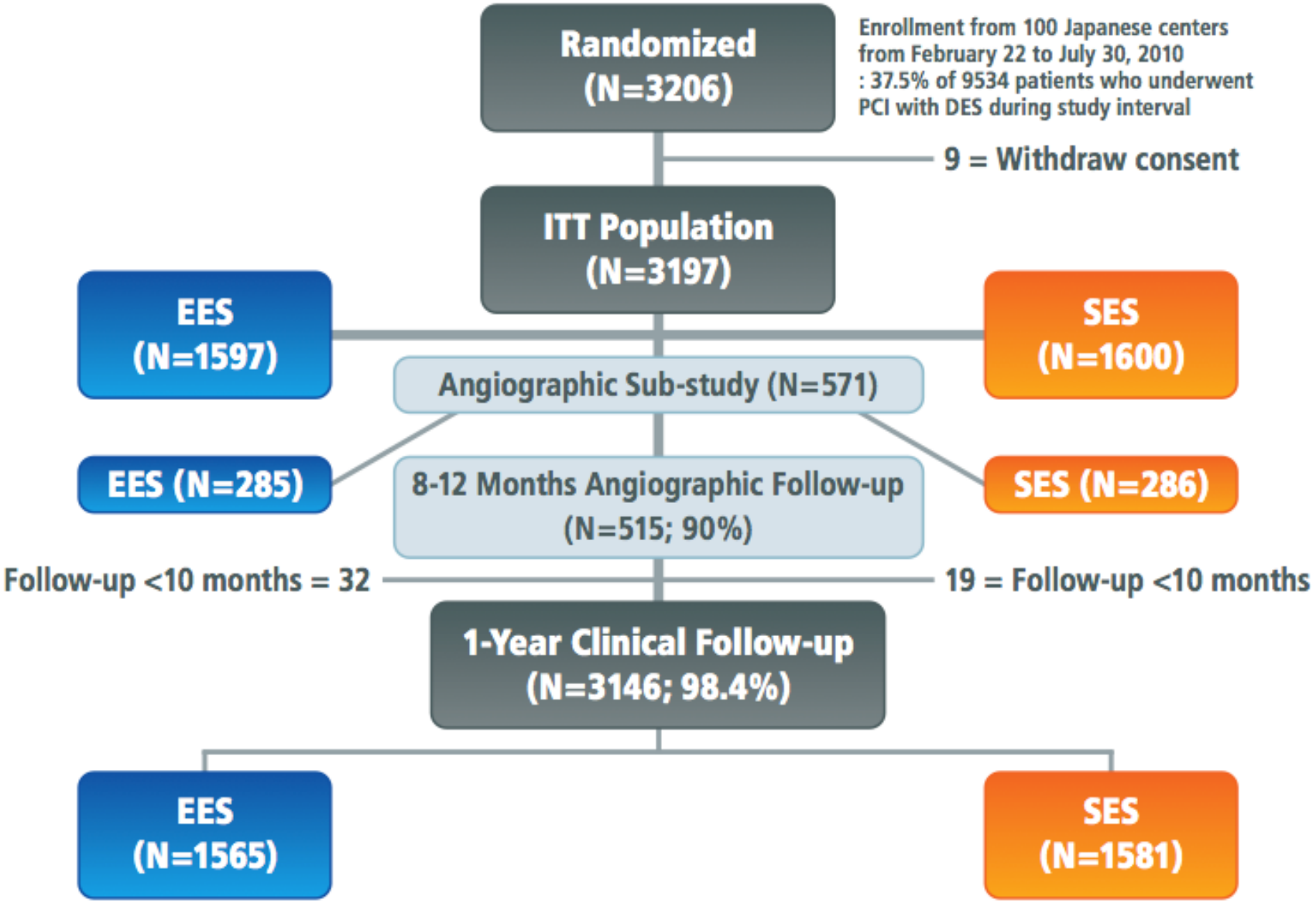
  Sirolimus-eluting stent group: 0.20 ± 0.50 mm (Cypher PMS Japan)

  Non-inferiority margin of 0.195 mm (SPIRIT III trial) and one-sided type I error of 0.025

  400 patients would yield 97% power to detect non-inferiority.

- A total of 500 patients were to be enrolled considering possible drop-out from the follow-up angiography. Due to the need for further patient enrollment in the endothelial function sub-study, a total of 571 patients were ultimately enrolled in the angiographic sub-study.

RESET Patient Flow



Baseline Patient Characteristics

	EVEROLIMUS-ELUTING STENT	SIROLIMUS-ELUTING STENT	p value
No. of patients	1597	1600	
Age (years)	68.9±9.7	69.3±9.6	0.33
Male gender	78%	76%	0.33
Body mass Index (kg/m²)	24.2±3.6	24.3±3.5	0.5
Diabetes	45%	45%	0.61
Insulin-treated	11%	10%	0.48
Hypertension	79%	81%	0.41
Current smoker	21%	20%	0.77
Statin use	77%	77%	0.99
Prior PCI	47%	51%	0.06
Prior CABG	3.9%	6.2%	0.003

Baseline Patient Characteristics

	EVEROLIMUS-ELUTING STENT	SIROLIMUS-ELUTING STENT	p value
No. of patients	1597	1600	
Clinical diagnosis			0.08
Acute myocardial infarction	6.5%	5.2%	
Unstable angina	11%	13%	
Stable coronary artery disease	82%	82%	
Prior myocardial infarction	29%	31%	0.35
Prior stroke	11%	10%	0.29
Heart failure	13%	13%	0.9
Hemodialysis	5.8%	5.0%	0.3
Peripheral vascular disease	9.0%	8.6%	0.7
Multivessel disease	47%	47%	0.77
SYNTAX score	11.3±7.4 (N=1132)	11.1±7.1 (N=1131)	0.6

Baseline Lesion Characteristics

	EVEROLIMUS-ELUTING STENT	SIROLIMUS-ELUTING STENT	p value
No. of lesions	1967	1960	
Target vessel location			0.16
LMCA	2.4%	1.8%	
LAD	43%	43%	
LCx	22%	23%	
RCA	32%	31%	
Graft	0.4%	1.0%	
STEMI culprit lesions	3.8%	2.8%	0.08
Bifurcation lesions	18%	19%	0.5
Chronic total occlusion	6.2%	6.0%	0.86
In-stent restenosis	11%	11%	0.57
Reference vessel size <= 2.75 mm	64%	65%	0.47
Lesion length > 18 mm	34%	33%	0.83

Procedural Characteristics

	EVEROLIMUS-ELUTING STENT	SIROLIMUS-ELUTING STENT	p value
No. of lesions treated per patient	1.23±0.51	1.23±0.48	0.7
No. of stent			
Per patient	1.51±0.78	1.48±0.74	0.25
Per lesion	1.23±0.61	1.21±0.56	0.32
Total stent lengh (mm)			
Per patient	31.0±19.1	31.4±18.9	0.62
Per lesion	25.9±15.3	26.3±15.3	0.42
Stent diameter (mm)	2.97±0.38	2.96±0.37	0.16
Direct stenting	26%	23%	0.01
Maximum inflation pressure (atm)	14.5±5.2	17.2±4.7	< 0.0001
Bifurcation 2-stent	4.8%	6.2%	0.39
IVUS use	81%	82%	0.44
Multivessel treatment	12%	10%	0.13
Staged Procedures	23%	25%	0.24

Baseline QCA Data

Variables – no. (%)	EES (1441 lesions)	SES (1475 lesions)	p value
Before procedure			
Lesion length – mm	16.7±10.8	16.9±10.7	0.53
Reference vessel diameter – mm	2.59±0.63	2.57±0.62	0.37
Minimal luminal diameter – mm	0.83±0.48	0.81±0.45	0.34
Diameter stenosis – %	68.5±16.2	68.8±15.8	0.71
Immediately after procedure			
Minimal luminal diameter – mm			
In stent	2.46±0.49	2.45±0.47	0.57
In segment	2.06±0.55	2.03±0.54	0.23
Diameter stenosis – %			
In segment	22.4±11.7	23.5±12.4	0.01
Acute gain – mm			
In stent	1.63±0.54	1.63±0.52	0.77
In segment	1.22±0.58	1.22±0.56	0.83

Procedural Results

	EVEROLIMUS-ELUTING STENT	SIROLIMUS-ELUTING STENT	p value
No. of lesions	1967	1960	
Acute device success	1895/1898 (99.8%)	1866/1875 (99.5%)	0.07
Successful stenting	1907/1908 (99.95%)	1895/1900 (99.7%)	0.09
Lesion Success	99.6%	99.0%	0.02
No. of patients	1597	1600	
At least one stented lesion	99.6%	99.1%	0.07
Treatment with study stent only	98.9%	98.0%	0.03
Patient success	97.8%	96.6%	0.04
Procedure duration (minutes)	68.0±40.3	69.4±45.2	0.36

Stent implantation was not attempted in 16 patients (EES: 5 patients, and SES: 11 patients) due to guidewire failure, undilatable lesions, or complications, etc.

Non-study stents were attempted without attempt of the study stent in 11 patients (EES: 4 patients, and SES: 7 patients). (Protocol violation)

Non-inferiority Assessment for the Primary Efficacy Endpoint

Target-Lesion Revascularization

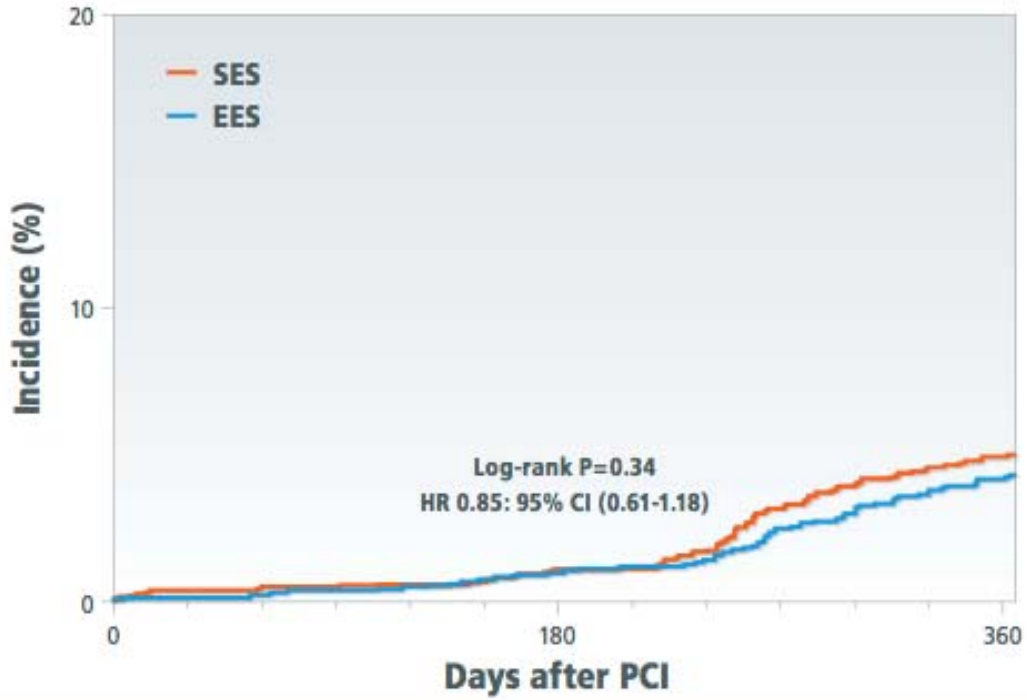
EES 4.3% vs. SES 5.0%

$P_{non\text{-}inferiority} < 0.0001$

Difference: – 0.7%

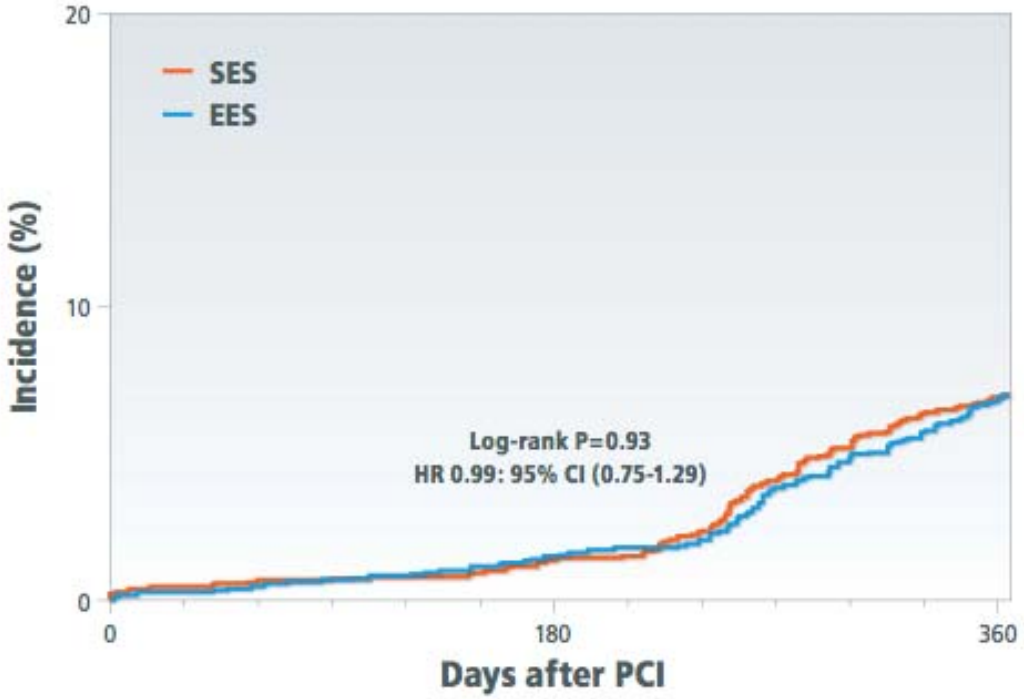
Upper one-sided 95% CI: 0.8%

Target-Lesion Revascularization



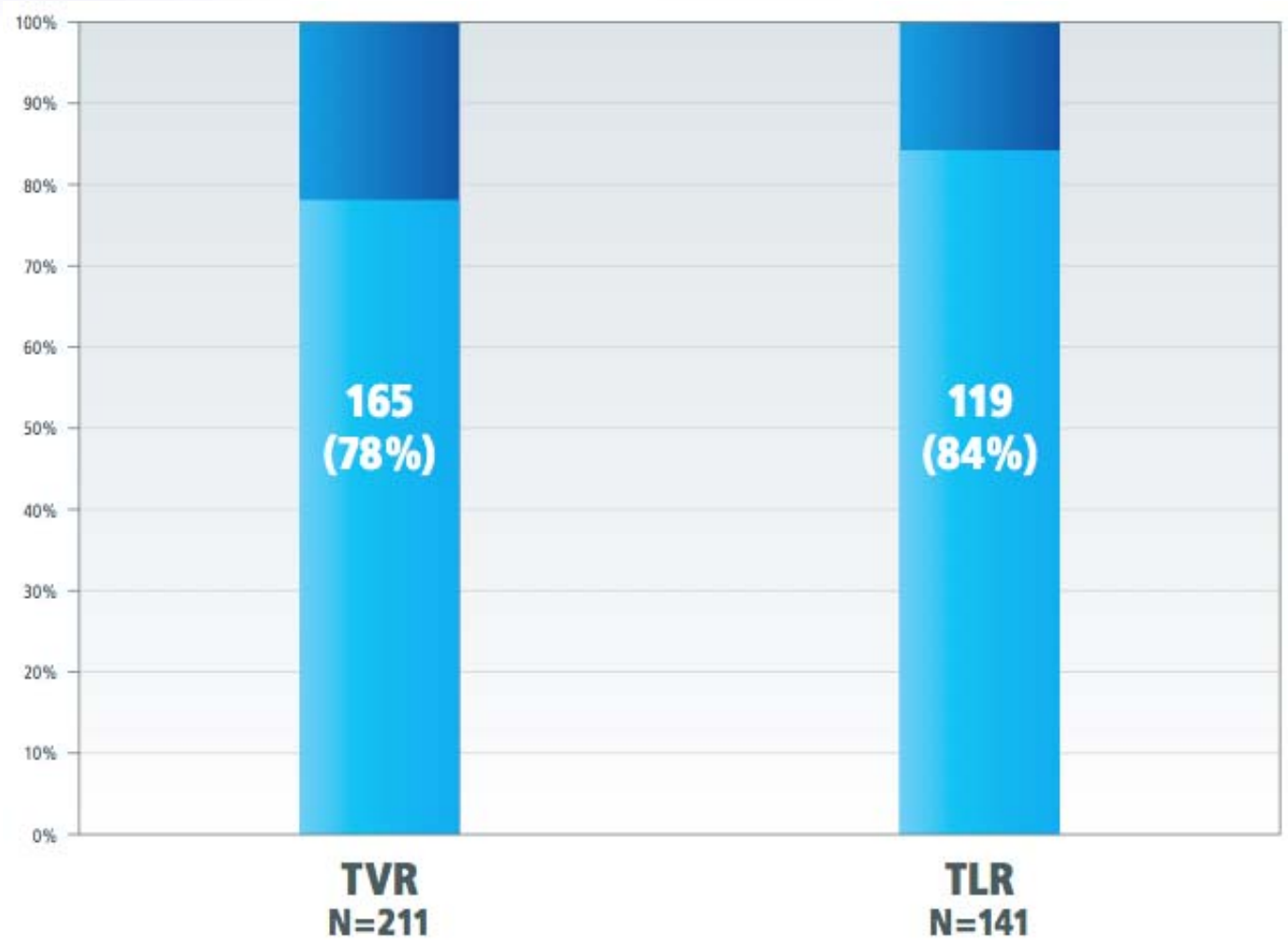
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		2	16	22	65
N of patients at risk	1597	1583	1552	1534	1193
Incidence		0.1%	1.0%	1.4%	4.3%
SES group					
N of events		5	17	27	76
N of patients at risk	1600	1585	1547	1526	1193
Incidence		0.3%	1.1%	1.7%	5.0%

Target-Vessel Revascularization



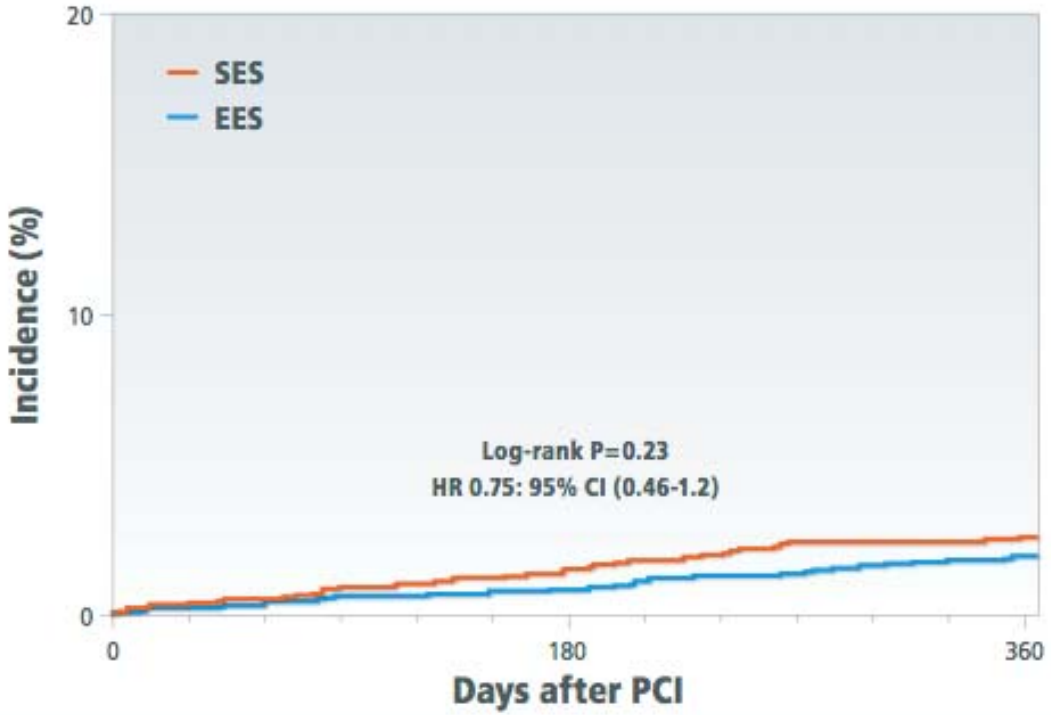
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		3	23	31	105
N of patients at risk	1597	1583	1546	1527	1161
Incidence		0.2%	1.5%	2.0%	**6.9%**
SES group					
N of events		6	21	36	106
N of patients at risk	1600	1585	1544	1517	1171
Incidence		0.4%	1.3%	2.3%	**6.9%**

Proportion of TLR/TVR Events Adjudicated by the Angiographic Core Laboratory



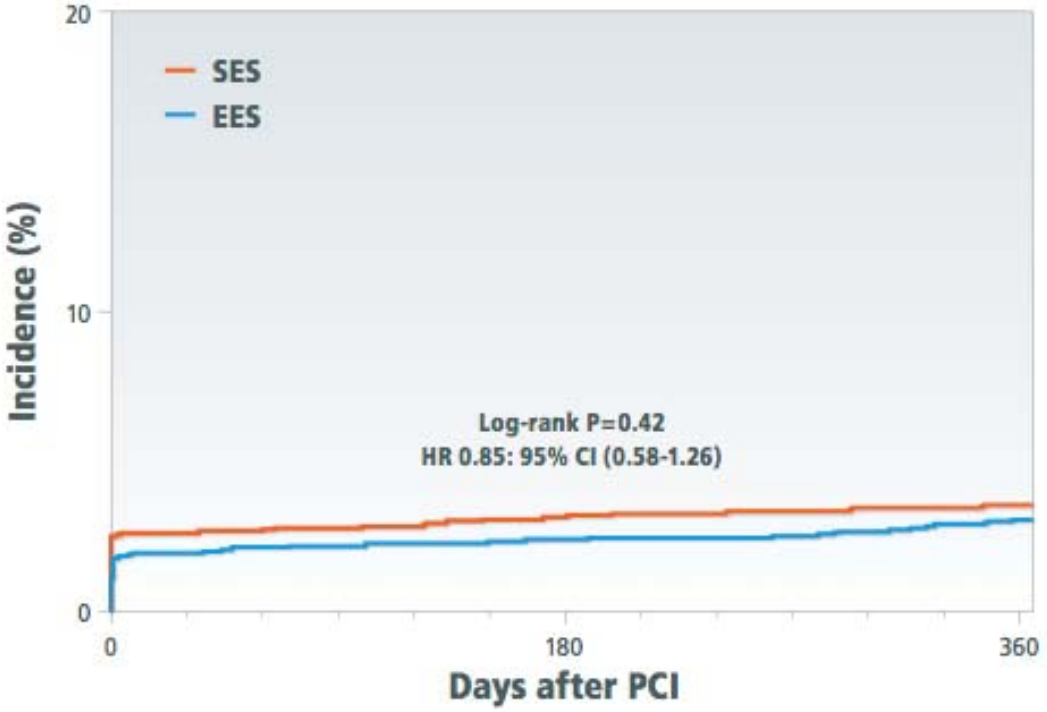
All the angiograms of patients with TVR were to be analyzed by the angiographic core laboratory in an attempt to discriminate TLR from non-TLR TVR and to identify clinically-driven TLR.

All-cause Death



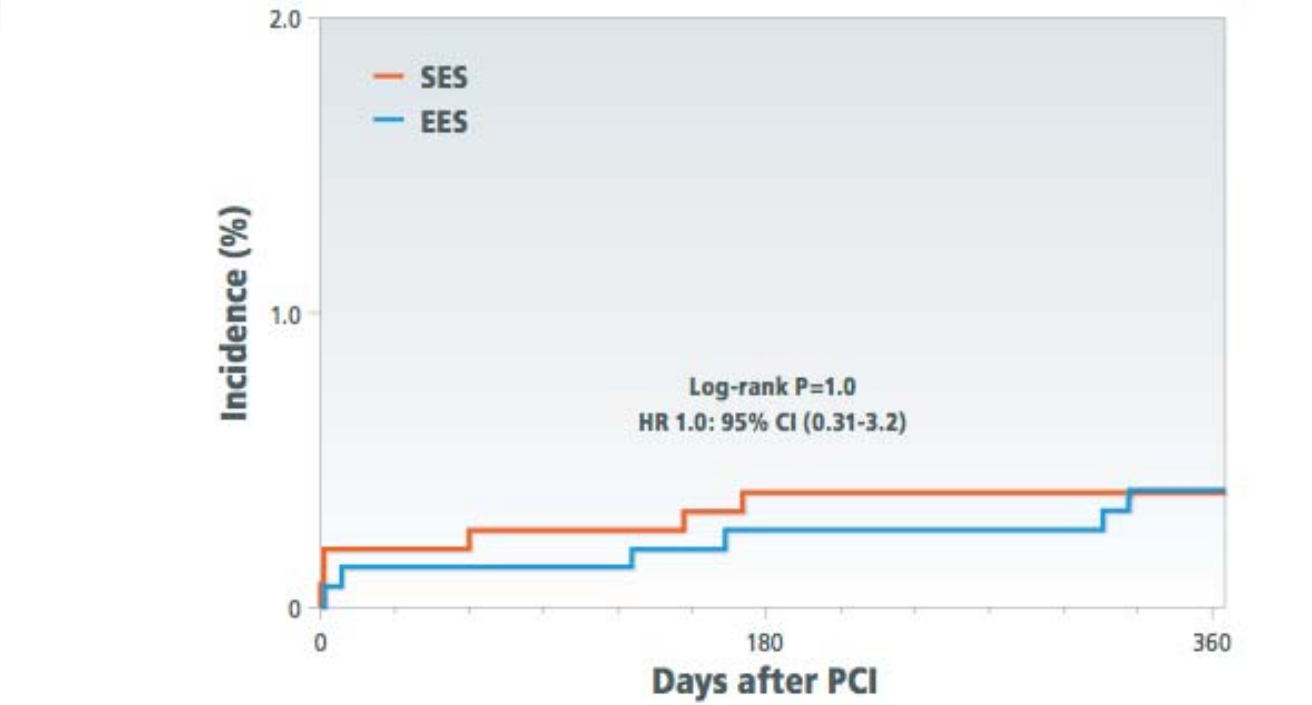
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		3	13	20	30
N of patients at risk	1597	1585	1572	1563	1272
Incidence		0.2%	0.8%	1.3%	1.9%
SES group					
N of events		6	24	31	40
N of patients at risk	1600	1590	1569	1558	1271
Incidence		0.4%	1.5%	1.9%	2.5%

Myocardial Infarction



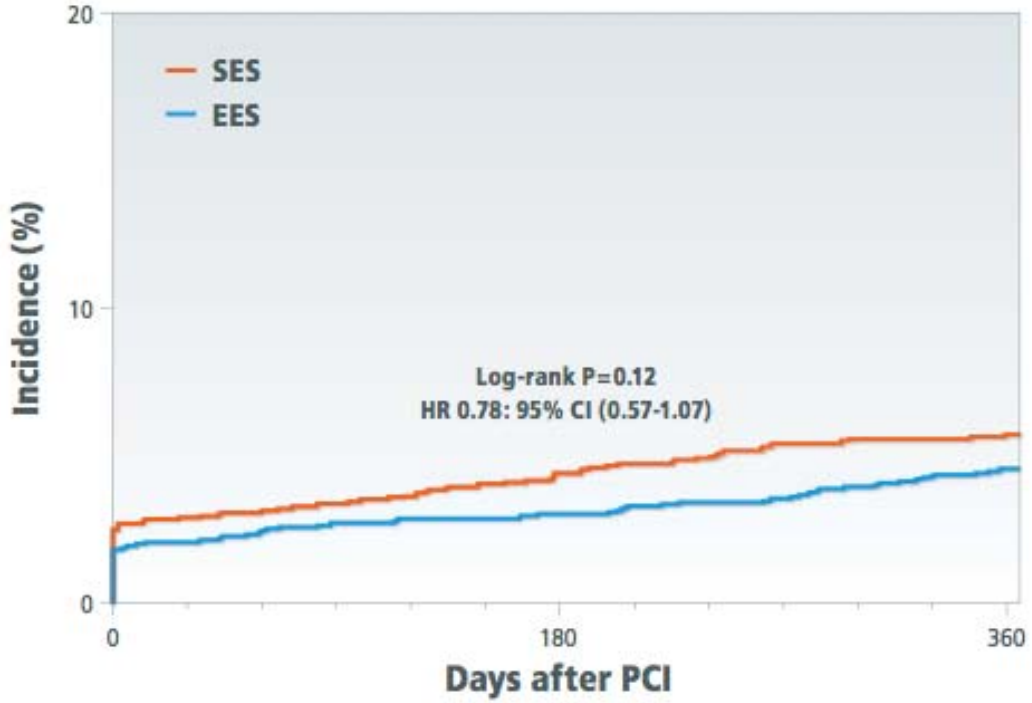
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		30	38	38	47
N of patients at risk	1597	1555	1534	1523	1216
Incidence		1.9%	2.4%	2.4%	3.0%
SES group					
N of events		41	50	51	55
N of patients at risk	1600	1551	1517	1504	1210
Incidence		2.6%	3.1%	3.2%	3.5%

Definite/Probable Stent Thrombosis



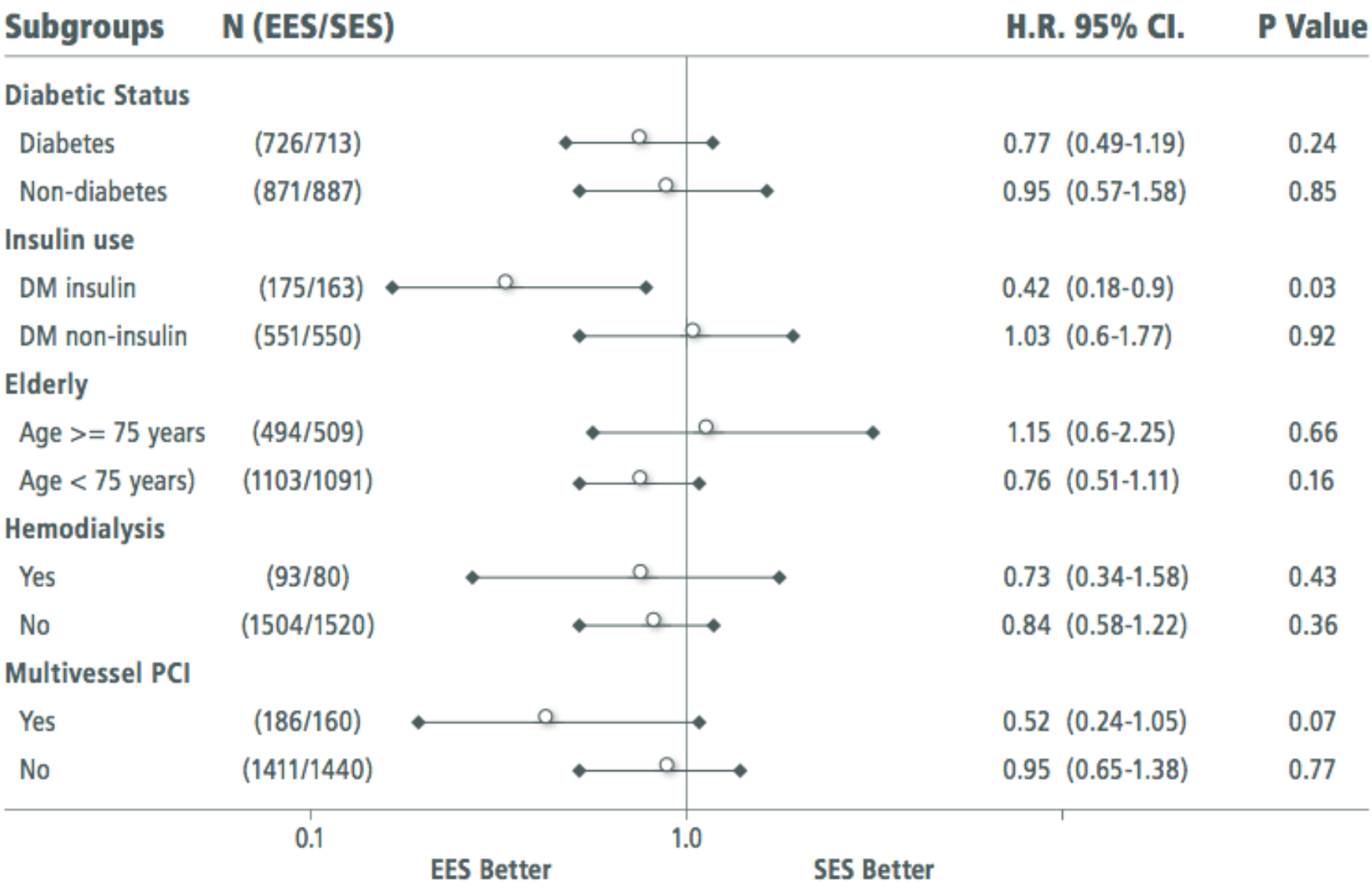
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		2	4	4	6
N of patients at risk	1597	1583	1565	1553	1242
Incidence		0.13%	0.25%	0.25%	**0.39%**
SES group					
N of events		3	6	6	6
N of patients at risk	1600	1586	1559	1547	1239
Incidence		0.19%	0.38%	0.38%	**0.38%**

Death/Myocardial Infarction

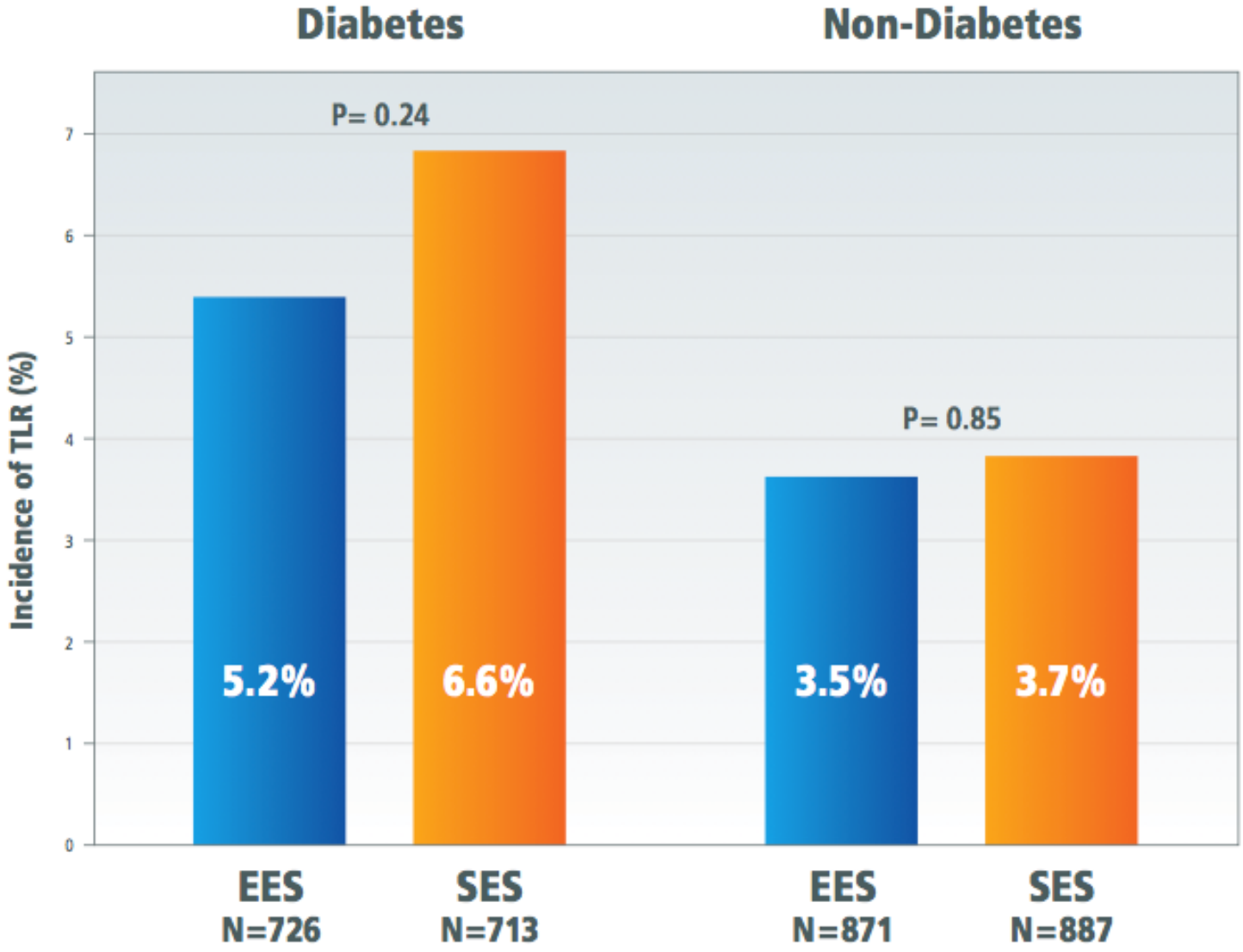


Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		32	47	53	70
N of patients at risk	1597	1555	1534	1523	1216
Incidence		2.0%	3.0%	3.3%	4.5%
SES group					
N of events		45	69	77	89
N of patients at risk	1600	1551	1517	1504	1210
Incidence		2.8%	4.5%	4.8%	5.6%

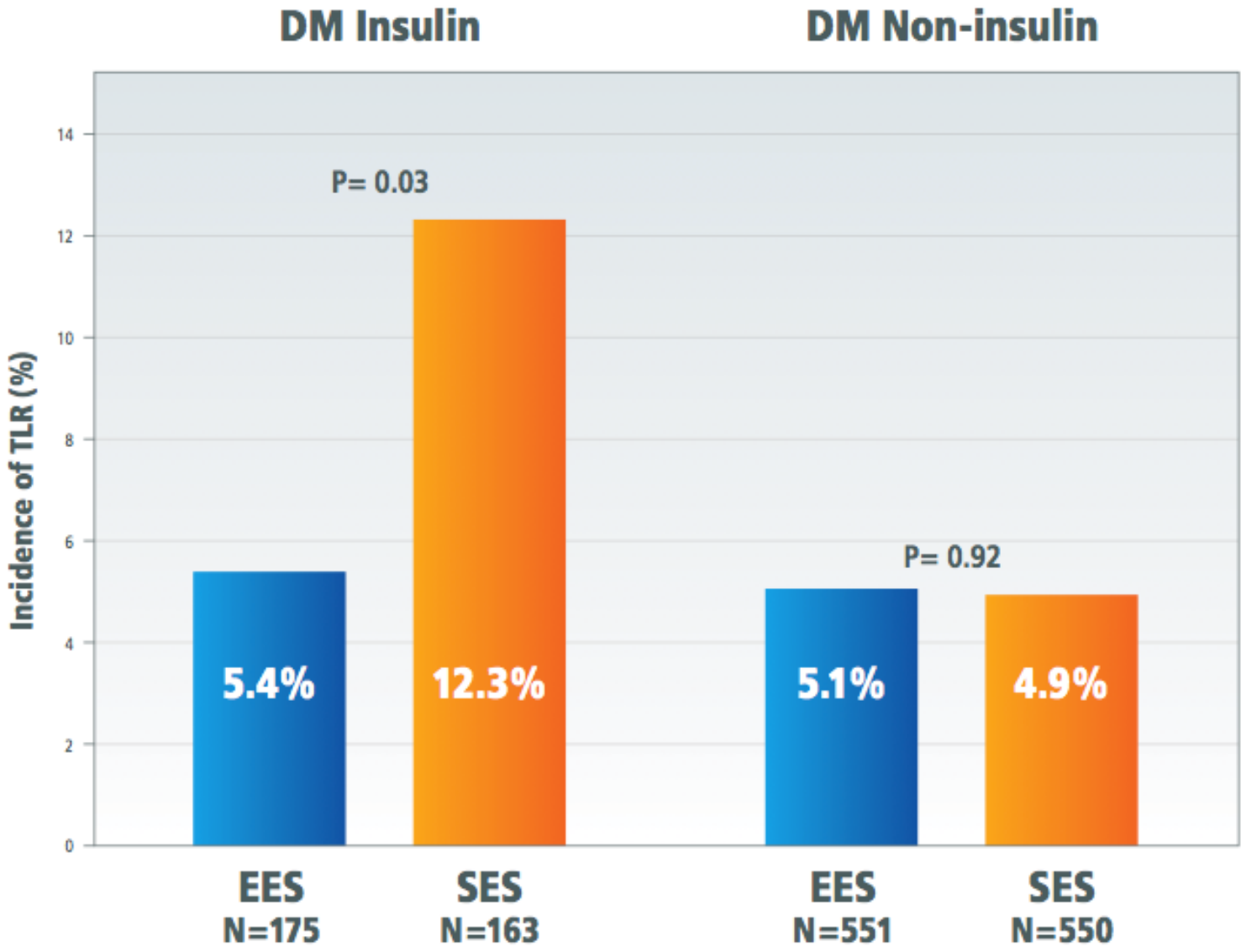
Pre-specified Subgroup Analysis for TLR
EES versus SES



Impact of Diabetes on TLR



Impact of Insulin-treated Diabetes on TLR



RESET

Non-inferiority Assessment for the Primary Angiographic Endpoint

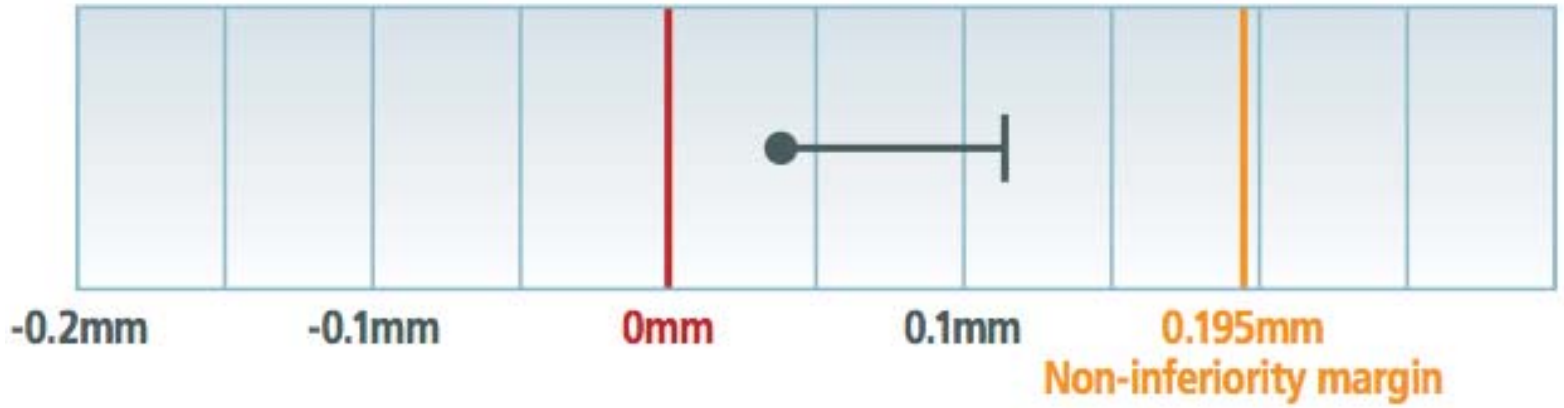
In-segment Late Loss

EES 0.07 mm vs. SES 0.03 mm

$P_{non\text{-}inferiority} < 0.0001$

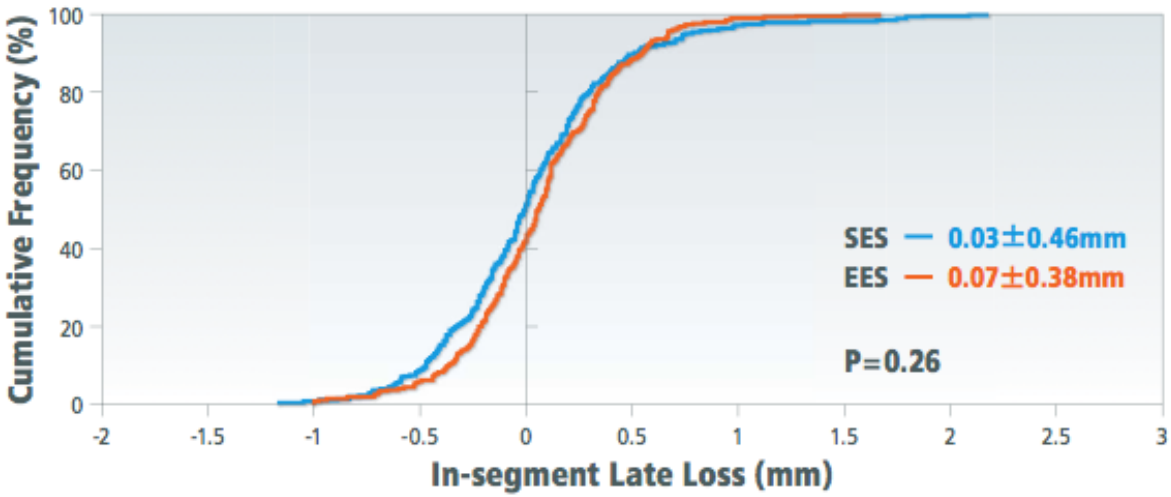
Difference: 0.04mm

Upper one-sided 95% CI: 0.11mm

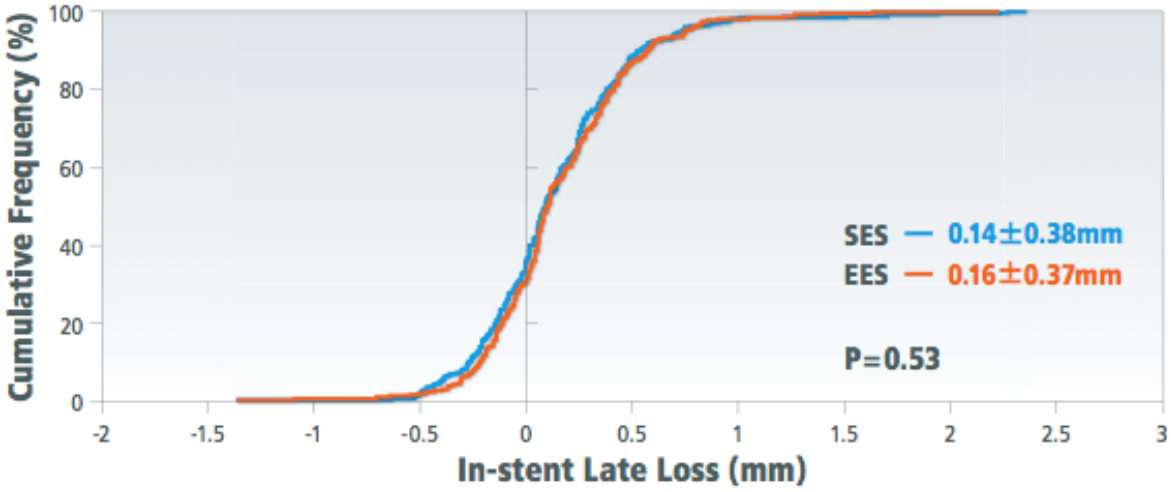


Cumulative Distribution Function Curves of Late Loss

In-segment Late Loss



In-stent Late Loss



Limitations and Implications

- *Cypher™ (SES) had already left the coronary DES arena.*

  Therefore, the current trial result could not provide guidance regarding selection of coronary DES in clinical practice.

  However, sirolimus-eluting stent (SES) was the most widely used and most extensively studied first generation DES.

  Clinical outcome after SES implantation should be regarded as the benchmark for the current and future generation drug-eluting stents.

Limitations and Implications

- *Despite the all-comers trial design, the study population actually enrolled seemed to represent relatively low-risk patients, resulting in event rates lower than anticipated. Furthermore, the trial strategy of evaluating only the index procedure also lead to the observed low TLR rates. TLR outcome favoring EES in the insulin-treated diabetic subgroup (one of the highest risk subset) is intriguing and hypothesis generating, although we should be very careful in interpreting the observation in the subgroup analysis.*

In the DES versus DES trials, it might be difficult to demonstrate clinically meaningful differences in TLR rates among low risk patients. Future stent trials should focus more on complex patients, in whom coronary artery bypass grafting could be a reasonable alternative.

Conclusions

- *In this large scale randomized controlled trial comparing EES with SES, EES was demonstrated to be non-inferior to SES with respect to target-lesion revascularization rate at 1 year and angiographic in-segment late loss at 8-12 months.*

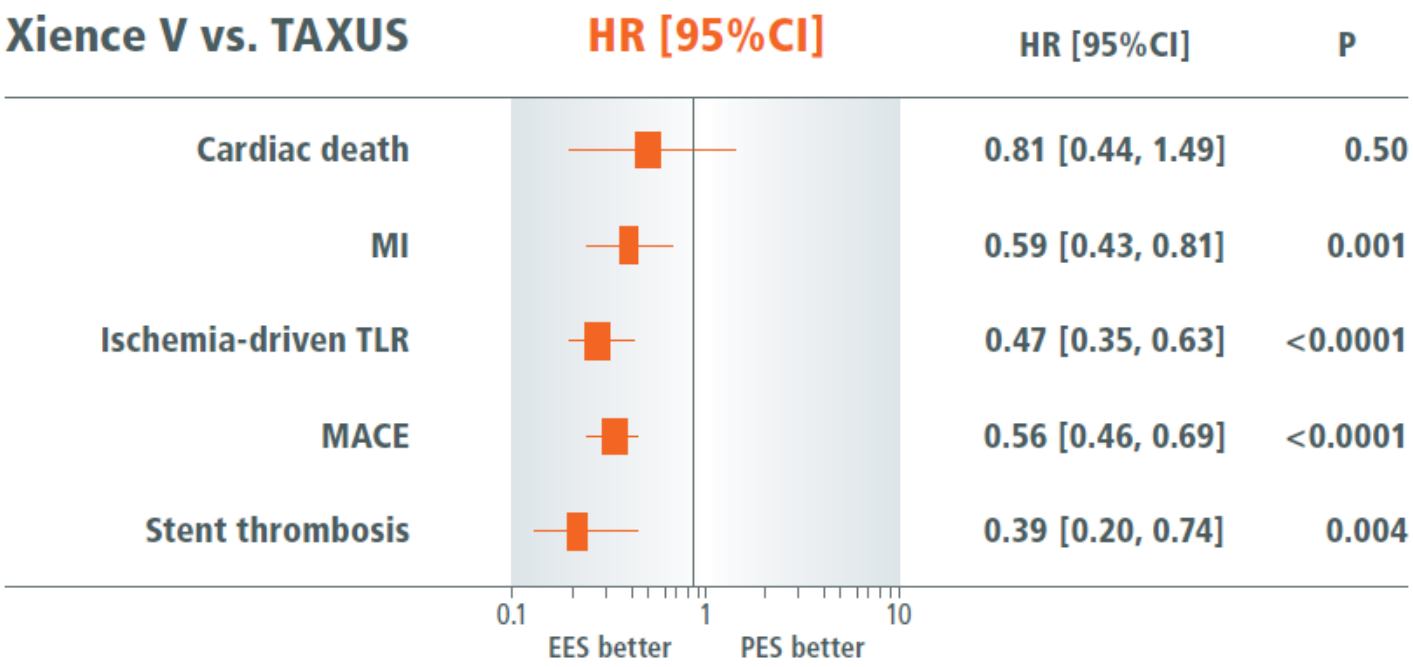
- *One-year clinical outcome after both EES- and SES-use was excellent with low rate of target-lesion revascularization and very low rate of stent thrombosis.*

- *Longer-term follow-up is important to address whether EES could positively affect the late adverse events beyond 1 year reported after SES implantation such as late restenosis and very late stent thrombosis.*

Backgrounds

In the recent large randomized controlled trials comparing everolimus-eluting stent (EES) with paclitaxel-eluting stent (PES), EES demonstrated consistent clinical benefit over PES in terms of reduced rates of myocardial infarction, stent thrombosis, and target-lesion revascularization up to 2 years of follow-up.

Covariate adjusted 1-year outcomes in SPIRIT II, SPIRIT III, SPIRIT IV, COMPARE (N=6,789)



Definition and Adjudication of Endpoints

- **Target-lesion Revascularization**

Either PCI or CABG due to restenosis or thrombosis of the target-lesion that included the proximal and distal edge segments as well as the ostium of the side branches.

A target-lesion was defined as the entire segment involving the implanted stent and the 5-mm proximal and distal edges adjacent to the stent. A segment to be treated with multiple overlapping stents was regarded as a single target segment.

Only those lesions treated at the time of the index PCI procedure were regarded as target-lesions, while those lesions treated at the time of scheduled staged PCI procedures were not regarded as target-lesions.

All the angiograms of patients with TVR were to be analyzed by the angiographic core laboratory in an attempt to discriminate TLR from non-TLR TVR and to identify clinically-driven TLR.

Secondary Endpoints

- **Secondary Endpoints for Device Performance:**

  Acute devise success *(successful deployment of all the study stents attempted)*

  Procedure duration *(interval between insertion and removal of the guiding catheter)*

- **Secondary Endpoints for Efficacy:**

  Clinically-driven target-lesion revascularization (TLR)

  Target-vessel revascularization (TVR)

  Any coronary revascularization

- **Secondary Endpoints for Safety:**

  Death, Cardiac death, Myocardial infarction, Stent thrombosis,

  Hospitalization for heart failure, Stroke, and Bleeding

- **Composite Endpoints:**

  A device-oriented composite: cardiac death, target vessel MI, or TLR

  A patient-oriented composite: death, MI, or any coronary revascularization

Definition and Adjudication of Endpoints

- **Clinically-driven TLR**

A TLR was considered clinically indicated, if angiography during follow-up showed a diameter stenosis greater than or equal to 50 percent (core laboratory QCA assessment), and if one of the following occurred:

(1) a positive history of recurrent angina pectoris, presumably related to the target vessel;

(2) objective signs of ischemia at rest or during stress test;

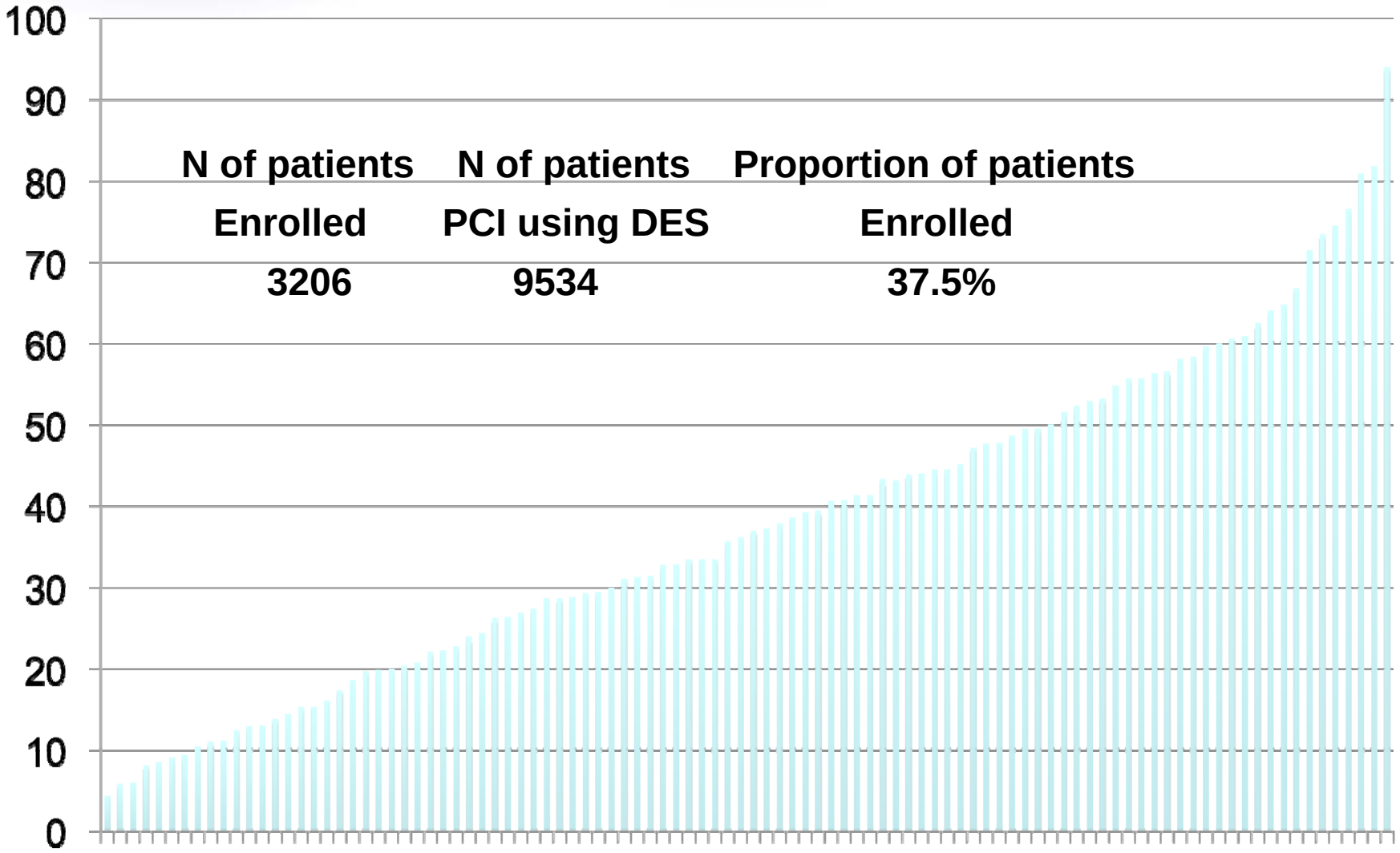
(3) abnormal results of any invasive functional diagnostic test (e.g. fractional flow reserve);

(4) a TLR with a diameter stenosis greater than 70% even in the absence of the above-mentioned ischemic signs or symptoms.

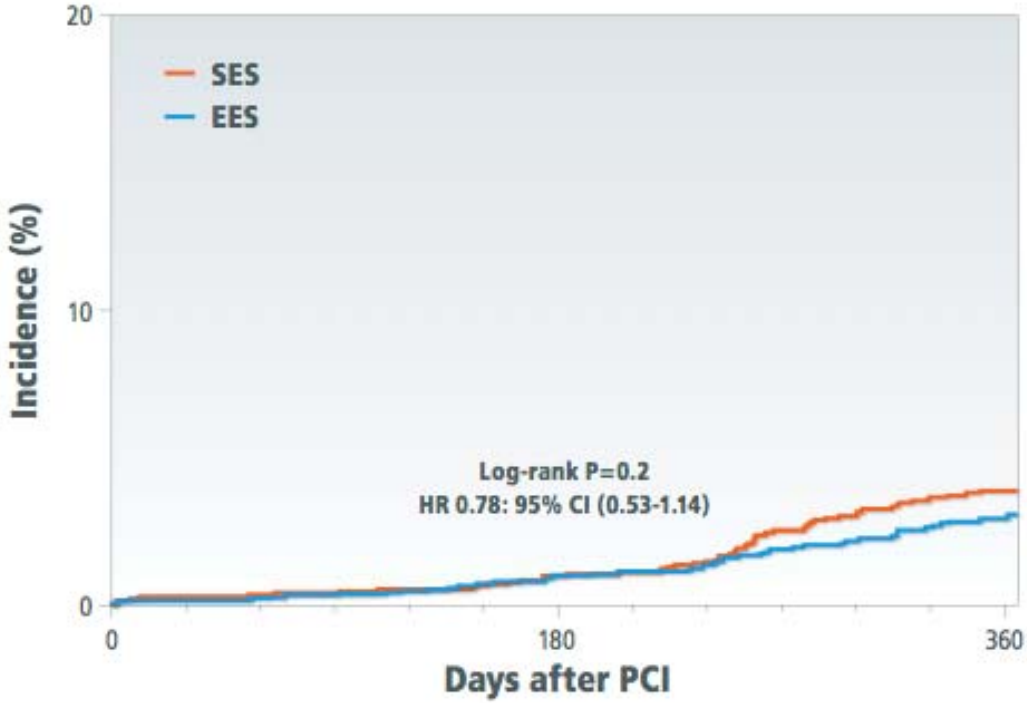
Definition of Secondary Endpoints

- ***Cardiac Death***
  Death w/o obvious non-cardiac causes or death during the index hospitalization
- ***Myocardial Infarction and Stent Thrombosis***
  According to the Academic Research Consortium definitions
  Periprocedural MI; CKMB>= 3 times ULN
  or CK >= 3 times ULN in the absence of CKMB measurement
- ***Hospitalization for Heart Failure***
  Hospitalization due to worsening heart failure requiring IV drug therapy
- ***Stroke***
  Ischemic or hemorrhagic stroke requiring hospitalization with Sx. lasting > 24 hour
- ***Bleeding***
  TIMI and GUSTO classifications
- ***Any Coronary Revascularization***
  Excluding scheduled staged PCI procedures declared at the index hospitalization

Proportion of Patients Enrolled in the RESET According to Participating Centers

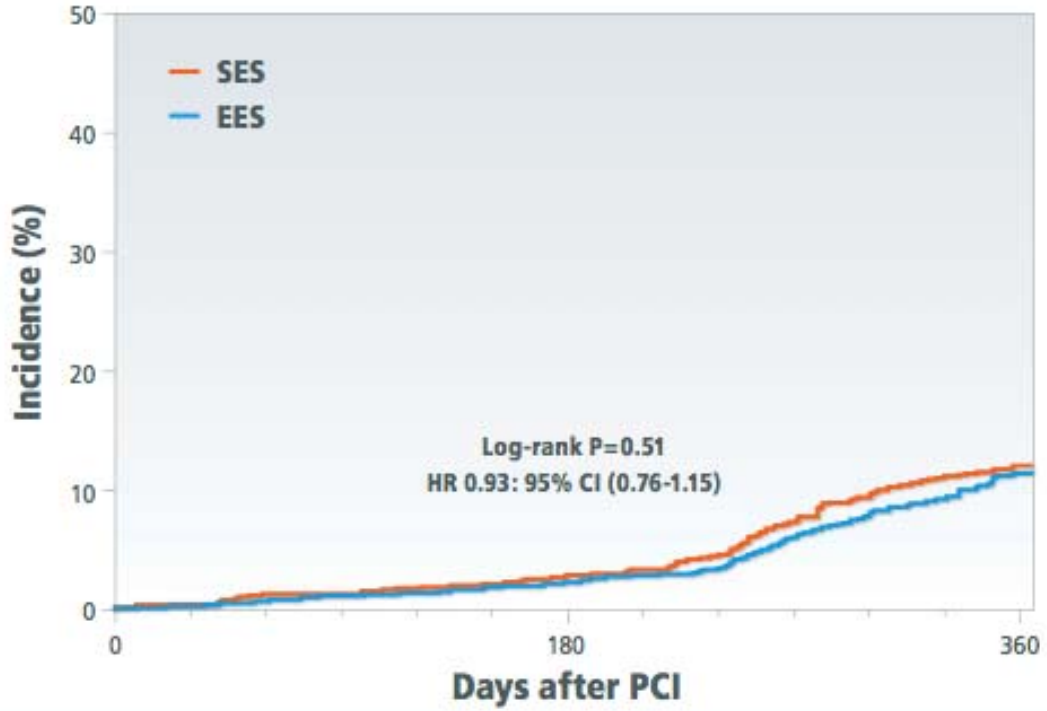


Clinically-driven Target-Lesion Revascularization



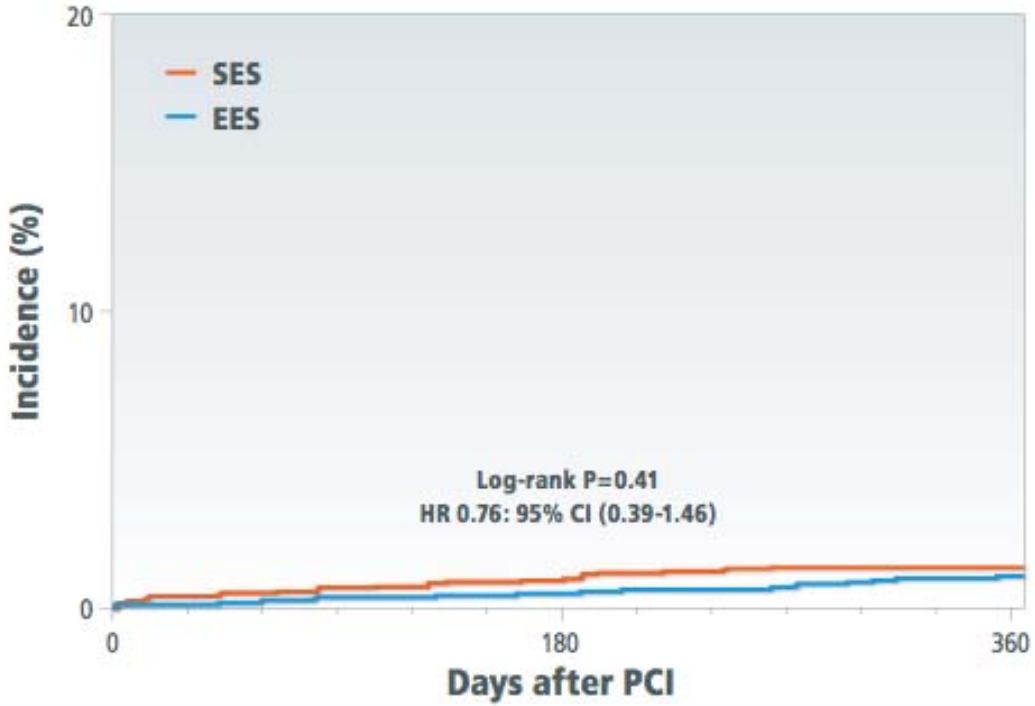
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		2	15	21	46
N of patients at risk	1597	1583	1552	1534	1193
Incidence		0.1%	1.0%	1.3%	**3.0%**
SES group					
N of events		4	16	23	59
N of patients at risk	1600	1586	1547	1526	1193
Incidence		0.3%	1.0%	1.5%	**3.9%**

Any Coronary Revascularization



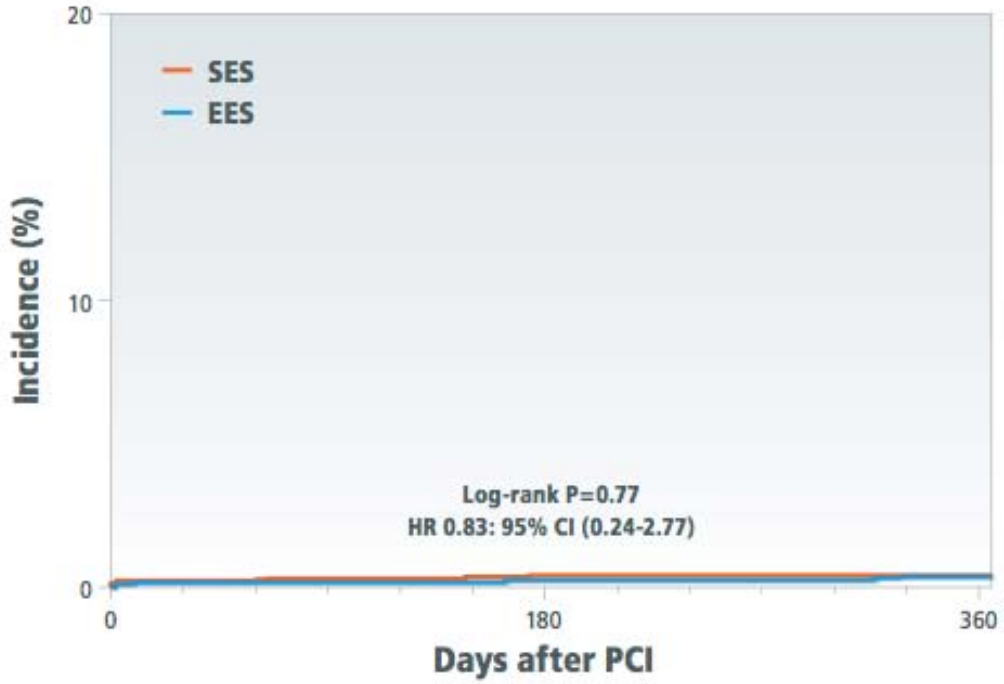
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		4	35	54	178
N of patients at risk	1597	1581	1533	1503	1097
Incidence		0.3%	2.2%	3.4%	**11.7%**
SES group					
N of events		7	43	71	189
N of patients at risk	1600	1584	1522	1483	1113
Incidence		0.4%	2.7%	4.5%	**12.3%**

Cardiac Death



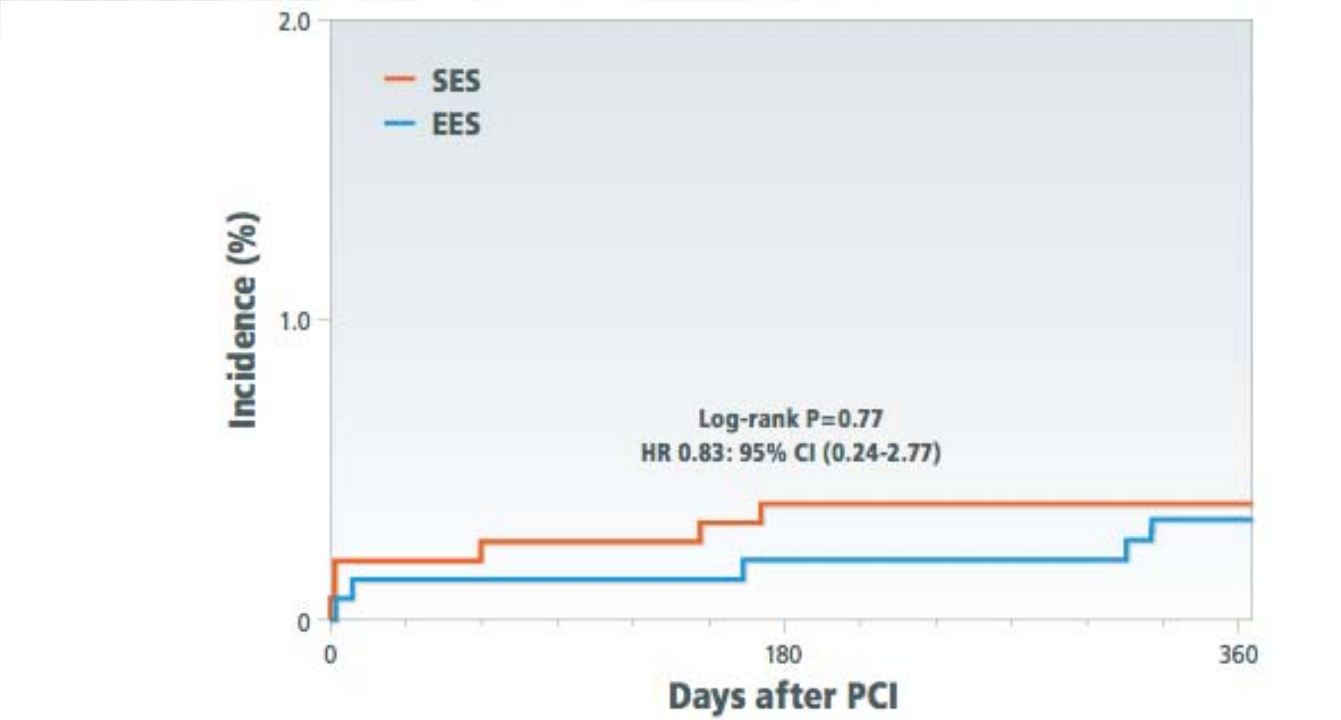
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		1	7	9	16
N of patients at risk	1597	1585	1572	1563	1272
Incidence		0.1%	0.4%	0.6%	1.0%
SES group					
N of events		5	6	19	21
N of patients at risk	1600	1590	1569	1558	1271
Incidence		0.3%	0.9%	1.2%	1.3%

Definite Stent Thrombosis



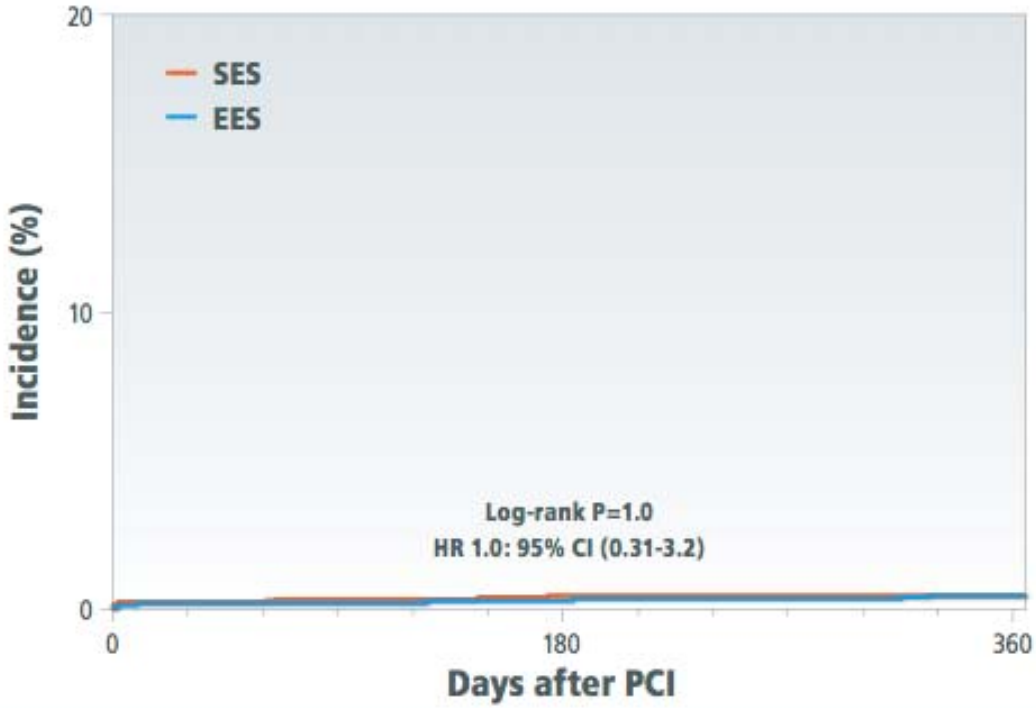
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		2	3	3	5
N of patients at risk	1597	1583	1565	1553	1242
Incidence		0.13%	0.19%	0.19%	**0.32%**
SES group					
N of events		3	6	53	6
N of patients at risk	1600	1588	1559	1547	1246
Incidence		0.19%	0.38%	0.38%	**0.38%**

Definite Stent Thrombosis



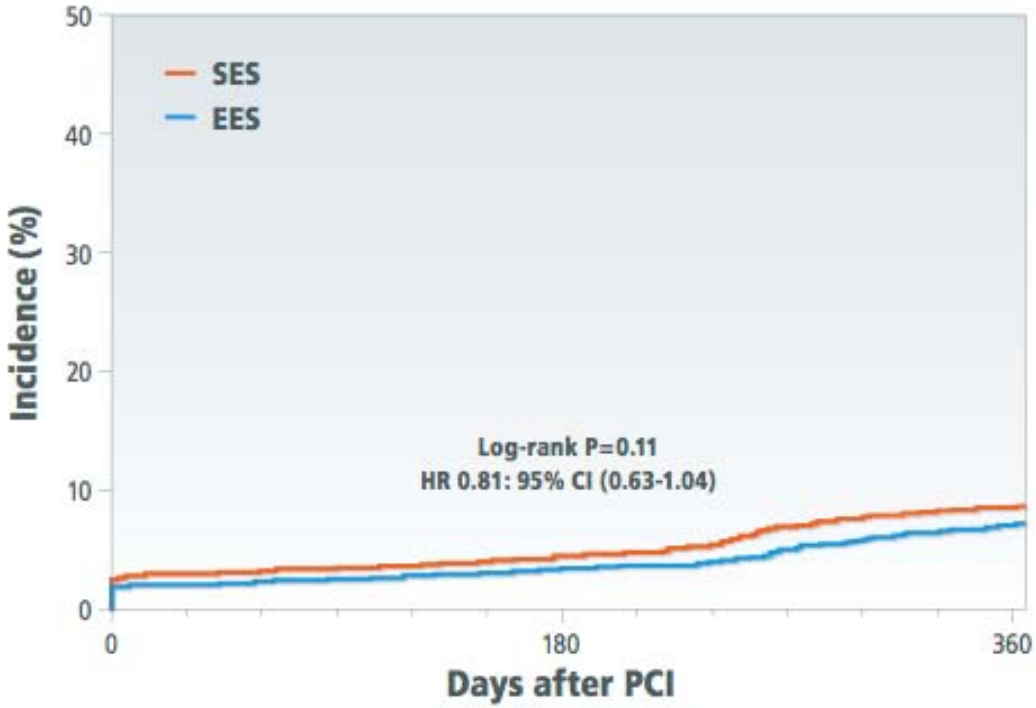
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		2	3	3	5
N of patients at risk	1597	1583	1565	1553	1242
Incidence		0.13%	0.19%	0.19%	0.32%
SES group					
N of events		3	6	53	6
N of patients at risk	1600	1588	1559	1547	1246
Incidence		0.19%	0.38%	0.38%	0.38%

Definite/Probable Stent Thrombosis



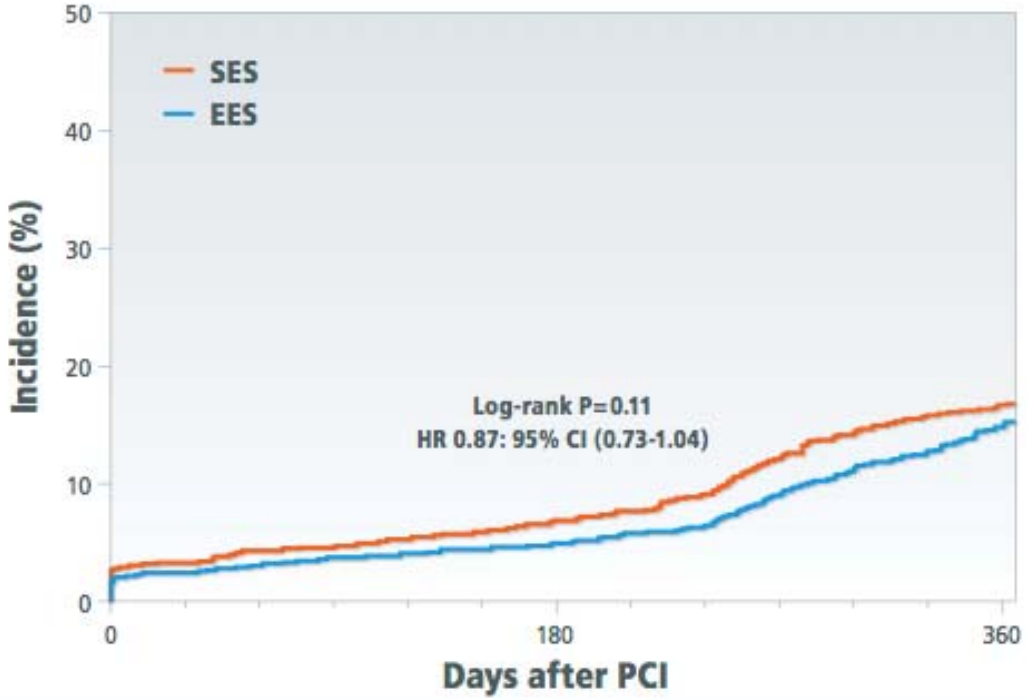
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		2	4	4	6
N of patients at risk	1597	1583	1565	1553	1242
Incidence		0.13%	0.25%	0.25%	**0.39%**
SES group					
N of events		3	6	6	6
N of patients at risk	1600	1586	1559	1547	1239
Incidence		0.19%	0.38%	0.38%	**0.38%**

A device-oriented composite
Cardiac death, Target vessel MI, or TLR



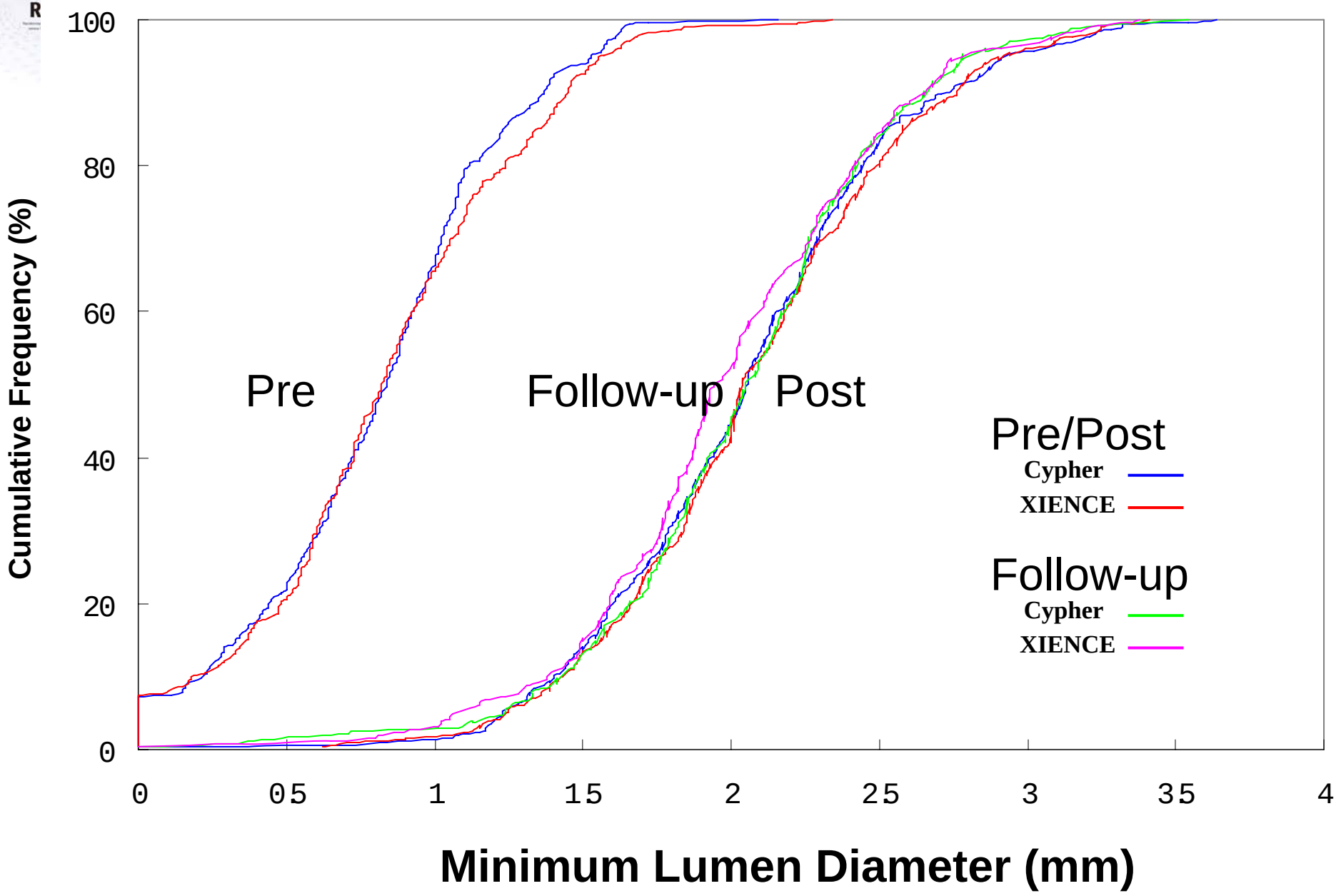
Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		32	53	61	110
N of patients at risk	1597	1555	1525	1507	1173
Incidence		2.0%	3.3%	3.8%	7.1%
SES group					
N of events		47	70	84	134
N of patients at risk	1600	1547	1507	1486	1162
Incidence		2.9%	4.4%	5.3%	8.5%

A patient-oriented composite
Death, MI, or Any Coronary Revascularization



Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		35	74	99	231
N of patients at risk	1597	1553	1508	1479	1079
Incidence		2.2%	4.7%	6.2%	14.9%
SES group					
N of events		50	105	140	262
N of patients at risk	1600	1546	1483	1443	1084
Incidence		3.1%	6.6%	8.8%	16.7%

Minimum Lumen Diameter

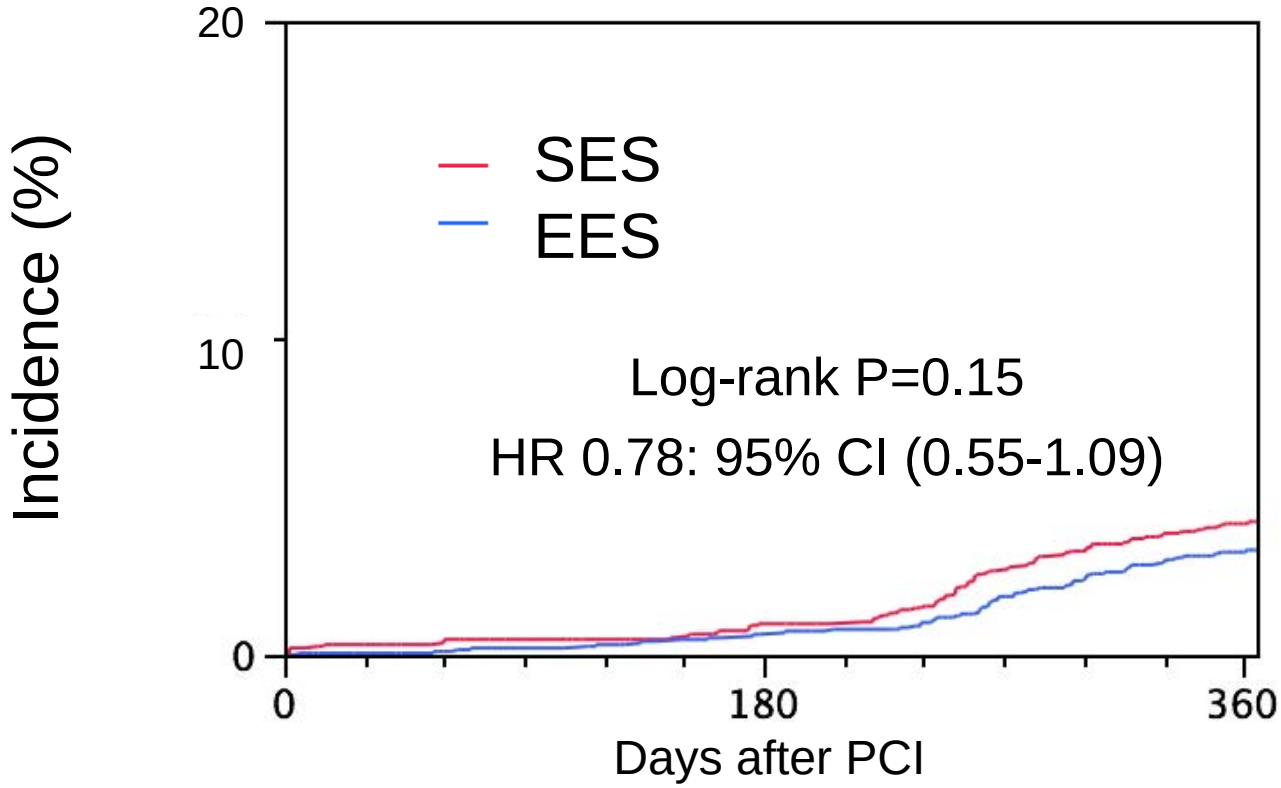


Follow-up QCA Data in Angiographic Sub-study

Variables – no. (%)	EES (261 lesions)	SES (276 lesions)	p value
Follow-up at 9 months			
Minimal luminal diameter – mm			
In stent	2.34±0.52	2.34±0.49	0.87
In segment	1.99±0.52	2.04±0.52	0.24
Diameter stenosis – %			
In stent	14.3±11.3	15.0±12.7	0.52
In segment	24.4±13.6	23.8±14.6	0.64
Late luminal loss – mm			
In stent	0.16±0.37	0.14±0.38	0.53
In segment	0.07±0.38	0.03±0.46	0.26
Binary restenosis – %			
In segment	13 (5.0)	11 (4.0)	0.58
Restenosis pattern – %			0.46
Focal	9 (69)	8 (67)	
Diffuse	4 (31)	3 (25)	
Total occlusion	0	1 (8.3)	

Target-Lesion Revascularization

Lesion-based Analysis Among Lesions Treated Exclusively With the Assigned Stents



Interval	0 day	30 days	180 days	240 days	365 days
EES group					
N of events		1	13	19	61
N of patients at risk	1889	1874	1846	1824	1421
Incidence		0.1%	0.7%	1.0%	**3.3%**
SES group					
N of events		6	18	28	74
N of patients at risk	1858	1841	1799	1777	1382
Incidence		0.3%	1.0%	1.5%	**4.2%**