Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46. DOI: 10.1056/NEJMoa1004130.

Supplementary Appendix

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Contents

I. Supplementary Methods

Quantitative Coronary Angiographic (QCA)

All available QCA data for independent variables such as percent diameter stenosis and binary restenosis were calculated using unmatched data, whilst matched paired QCA data was used in the analysis of serial angiographic endpoints. All angiographic measurements of the target lesion were obtained in the "in-stent" zone, within 5 mm proximal and distal to each stent edge, and over the entire segment ("in-segment" zone). The following QCA parameters were calculated: minimal lumen diameter, reference vessel diameter, percent diameter stenosis (difference between the reference vessel diameter and minimal lumen diameter/reference vessel diameter x 100) and late lumen loss (difference between the post-procedure and follow-up minimal lumen diameter). Binary restenosis was defined as stenosis of 50 percent or greater in the target lesion or segment at angiographic follow-up.

Definitions

All deaths were considered cardiac unless an undisputed non-cardiac cause was present. Myocardial infarction was defined according to an extended historical protocol definition and according to ARC definitions.[1-2] A Q-wave myocardial infarction required, in the absence of cardiac enzyme data, a history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in two or more contiguous ECG leads as assessed by the core lab or clinical events committee. In the presence of elevated cardiac enzymes, new pathological Q waves in two or more contiguous ECG leads as assessed by the core lab or clinical events committee were sufficient to diagnose a Q-wave myocardial infarction. In the absence of an ECG, a Q-wave myocardial infarction could be adjudicated on the basis of the clinical scenario and appropriate cardiac enzyme data. A target

lesion revascularization was considered clinically indicated if angiography during follow-up showed a diameter stenosis greater than 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 (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g. fractional flow reserve); (4) a target lesion revascularization with a diameter stenosis greater than 70% even in the absence of the above-mentioned ischemic signs or symptoms. Device success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50 percent using only the assigned study device. Lesion success was defined as the attainment of a final residual diameter stenosis of less than 50 percent using any percutaneous method. Procedure success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50 percent, together with the absence of any in-hospital major adverse cardiac events.

Statistical Methods

Hypothesis of Non-Inferiority for Primary Clinical Endpoint

Based on the event rates from previously reported all comer studies,[3-4] we predicted composite endpoint rates at 12 months for both treatment groups to be 8%. Based on a non-inferiority margin of 0.035 (3.5%) as the acceptable difference between the Resolute zotarolimus-eluting stent and the Xience-V everolimus-eluting stent groups (claiming the former to be non-inferior) and a one-sided type I error of 0.05, a total of 2300 patients (1150 patients in each group) will yield at least 90% power to detect non-inferiority. Non-inferiority will be achieved if the upper limit of the one sided 95% confidence interval of the difference is less than the margin.

Non-Inferiority for Secondary Angiographic Endpoint Analysis

This trial was also powered for non-inferiority testing of the angiographic endpoint in-stent percent diameter stenosis. It was anticipated that 1.5 lesions per patient would be treated. Therefore, a mixed model analysis of variance was used, allowing for the correlation of multiple lesions within patients, using patients as a random effect. The mean in-stent percent diameter stenosis was expected to be equal (16%) in both treatment groups, with a common standard deviation of 16%. With a non-inferiority margin of 5% and a one-sided type I error of 0.05, it is estimated that 460 patients (with on average 1.5 lesion per patient) will yield a power of at least 90% to detect non-inferiority, assuming an attrition rate of 20%.

II. Supplementary Results

a. Stent Thrombosis (Supplementary Table 2)

Thirteen patients (1.2%) allocated to zotarolimus-eluting stents had a definite stent thrombosis, of whom 12 were on dual antiplatelet therapy at the time of the event, whilst one patient had discontinued therapy. Stent thrombosis was associated with seven (54%) ARC defined myocardial infarctions, and 12 (92%) target lesion revascularizations. The majority (10/13, 77%) of stent thrombosis events occurred in the left anterior descending artery. Conversely, three (0.3%) patients allocated to everolimus-eluting stents had a definite stent thrombosis, all of whom were on dual antiplatelet therapy at the time of the event. Stent thrombosis was associated with a non-fatal ARC defined myocardial infarction in all patients (100%), and a subsequent target lesion revascularization in two patients (67%).

b. Per Protocol Analysis

The main results of the study are reported on an intention-to-treat basis. Importantly, analysis using only those patients who had all their lesions treated with a study stent (i.e. per protocol) does not result in any changes to the overall conclusions of the study, as the pre-specified criterion for non-inferiority for both the clinical and angiographic endpoint is still achieved. For the record, per protocol, the rate of the primary clinical end point, target lesion failure (a composite of cardiac death, myocardial infarction [not clearly attributable to a non-target vessel], and clinically-indicated target lesion revascularization), occurred in 84 (7.7%) patients treated with the zotarolimus-eluting stent and 84 (7.6%) patients treated with the everolimus-eluting stent (absolute risk difference 0.1%, upper limit of the one-sided 95% CI at 1.9%, one-sided $P_{non\text{-}inferiority}$=0.001). Similarly, the in-stent percent diameter stenosis at 13-months follow-up on a per protocol basis was 21.65±14.42% for the zotarolimus-eluting stent

and 19.75±14.68% for everolimus-eluting stent (difference in least square means 2.05%, upper limit of the one-sided 95% CI 4.75, one-sided $P_{non\text{-}inferiority}$=0.04).

c. Adverse Events

No serious adverse events were noted with any unusual frequency, or preponderance to a particular stent.

Supplementary Figure 1: Patient Flow

Supplementary Figure 2: Odd ratio plot for the primary end point in pre-specified sub-groups**.**

Supplementary Figure 3: Cumulative frequency curves for (A) in-segment and (B) in-stent late loss.

Supplementary Table 1. Additional Clinical Outcomes at 12 Months on an Intention-to-treat Basis

	ZES (N=1119)	EES (N=1126)	Difference (95% CI)	P value for Difference
Target Lesion Failure#	8.2% (92)	8.3% (94)	-0.1% [-2.4%, 2.2%]	0.94
Death (all)	1.6% (18)	2.8% (31)	-1.1% [-2.4%, 0.1%]	0.08
Cardiac	1.3% (15)	1.7% (19)	-0.3% [-1.4%, 0.7%]	0.61
MI (all)*	4.6% (51)	4.4% (49)	0.2% [-1.5%, 1.9%]	0.84
Q-wave	0.9% (10)	0.5% (6)	0.4% [-0.3%, 1.1%]	0.33
Non-Q-wave	3.8% (42)	3.8% (43)	-0.1% [-1.6%, 1.5%]	1.00
Target Vessel MI*	4.2% (47)	4.1% (46)	0.1% [-1.5%, 1.8%]	0.92
Q-wave	0.7% (8)	0.4% (5)	0.3% [-0.4%, 0.9%]	0.42
Non-Q-wave	3.6% (40)	3.6% (41)	-0.1% [-1.6%, 1.5%]	1.00
MI†	13.5% (151)	13.6% (153)	-0.1% [-2.9%, 2.7%]	0.95
Q-wave	0.9% (10)	0.5% (6)	0.4% [-0.3%, 1.1%]	0.33
Non-Q-wave	12.8% (143)	13.1% (147)	-0.3% [-3.1%, 2.5%]	0.85
Any repeat revascularization‡	10.5% (117)	9.1% (102)	1.4% [-1.1%, 3.9%]	0.29
CABG	1.3% (14)	1.1% (12)	0.2% [-0.7%, 1.1%]	0.70
PCI	9.5% (106)	8.3% (93)	1.2% [-1.1%, 3.6%]	0.34
Any TVR	7.2% (81)	6.1% (69)	1.1% [-1.0%, 3.2%]	0.31
CABG	0.9% (10)	0.9% (10)	0.0% [-0.8%, 0.8%]	1.00
PCI	6.3% (71)	5.5% (62)	0.8% [-1.1%, 2.8%]	0.42
Clinically indicated TVR	4.9% (55)	4.8% (54)	0.1% [-1.7%, 1.9%]	0.92
CABG	0.6% (7)	0.8% (9)	-0.2% [-0.9%, 0.5%]	0.80
PCI	4.3% (48)	4.3% (48)	0.0% [-1.6%, 1.7%]	1.00
Any TLR	5.3% (59)	3.8% (43)	1.5% [-0.3%, 3.2%]	0.11
CABG	0.7% (8)	0.7% (8)	0.0% [-0.7%, 0.7%]	1.00
PCI	4.6% (51)	3.2% (36)	1.4% [-0.2%, 3.0%]	0.10

Clinically indicated TLR	3.9% (44)	3.4% (38)	0.6% [-1.0%, 2.1%]	0.50
CABG	0.5% (6)	0.7% (8)	-0.2% [-0.8%, 0.5%]	0.79
PCI	3.4% (38)	2.8% (31)	0.6% [-0.8%, 2.1%]	0.39
Cardiac Death or TV MI*	5.4% (60)	5.4% (61)	-0.1% [-1.9%, 1.8%]	1.00
Death or TV MI*	5.6% (63)	6.4% (72)	-0.8% [-2.7%, 1.2%]	0.48
MACE[§]	8.7% (97)	9.7% (109)	-1.0% [-3.4%, 1.4%]	0.42
Target Vessel Failure[‖]	9.0% (101)	9.6% (108)	-0.6% [-3.0%, 1.8%]	0.66
Patient Composite End Point[¶]	14.6% (163)	14.6% (164)	0.0% [-2.9%, 2.9%]	1.00
Definite stent thrombosis				
Acute (0-1 day)	0.4% (4)	0.1% (1)	0.3% [-0.1%, 0.7%]	0.22
Sub-acute (2-30 days)	0.4% (5)**††	0.0% (0)	0.4% [0.1%, 0.8%]	0.03
Late (31-360 days)	0.4% (5)**	0.2% (2)	0.3% [-0.2%, 0.7%]	0.29
All (0-360 days)	1.2% (13)	0.3% (3)	0.9% [0.2%, 1.6%]	0.01
Probable stent thrombosis				
Acute (0-1 day)	0.1% (1)††	0.1% (1)	0.0% [-0.2%, 0.2%]	1.00
Sub-acute (2-30 days)	0.3% (3)	0.4% (4)	-0.1% [-0.5%, 0.4%]	1.00
Late (31-360 days)	0.2% (2)	0.0% (0)	0.2% [-0.1%, 0.4%]	0.25
All (0-360 days)	0.5% (6)	0.4% (5)	0.1% [-0.5%, 0.7%]	0.77
Possible stent thrombosis				
Acute (0-1 day)	0.0% (0)	0.0% (0)	0.0% [-]	No p value
Sub-acute (2-30 days)	0.0% (0)	0.0% (0)	0.0% [-]	No p value
Late (31-360 days)	0.8% (9)	0.8% (9)	0.0% [-0.7%, 0.7%]	1.00
All (0-360 days)	0.8% (9)	0.8% (9)	0.0% [-0.7%, 0.7%]	1.00
Definite or probable stent thrombosis				
Acute (0-1 day)	0.4% (5)††	0.2% (2)	0.3% [-0.2%, 0.7%]	0.29
Sub-acute (2-30 days)	0.7% (8)**††	0.4% (4)	0.4% [-0.2%, 1.0%]	0.26
Late (31-360 days)	0.6% (7)**	0.2% (2)	0.4% [-0.1%, 1.0%]	0.11
All (0-360 days)	1.6% (18)	0.7% (8)	0.9% [0.0%, 1.8%]	0.05

Definite, probable or possible stent thrombosis				
Acute (0-1 day)	0.4% (5)††	0.2% (2)	0.3% [-0.2%, 0.7%]	0.29
Sub-acute (2-30 days)	0.7% (8)**††	0.4% (4)	0.4% [-0.2%, 1.0%]	0.26
Late (31-360 days)	1.3% (15)**	1.0% (11)	0.4% [-0.5%, 1.2%]	0.49
All (0-360 days)	2.3% (26)	1.5% (17)	0.8% [-0.3%, 1.9%]	0.17

Data expressed as percent (number of events).

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TLR, target lesion revascularization; TVR, target vessel revascularization; TV=Target vessel

[#] Target Lesion Failure: cardiac death, myocardial infarction* (not clearly attributable to a non-target vessel) and clinically indicated target lesion revascularization

* Extended historical definition[2]

[†] Defined according to the ARC[1]

[‡] Includes all staged target vessel procedures[2]

[§] MACE: major adverse cardiac events, a composite of death, myocardial infarction (Q-wave and non-Q wave), emergent coronary artery bypass surgery, or repeat target lesion revascularization (clinically indicated) by percutaneous or surgical revascularization.

[‖] Target Vessel Failure: cardiac death, myocardial infarction* (not clearly attributable to a non-target vessel) and clinically indicated target vessel revascularization

[¶] Patient Composite End Point: all-cause mortality, myocardial infarction (Q- and non-Q wave) or any revascularization.

** One patient had a definite stent thrombosis at day 4 and day 31

††One patient had a probable stent thrombosis on day 0 and a definite stent thrombosis on day 5.

Supplementary Table 2: Detailed Information on Definite and Probable Stent Thrombosis Events out to 12-month Follow-up.

Days to Stent Thrombosis	Stent	Stented Vessel	Compliant to DAPT at Time of Stent Thrombosis	Events at Time of Stent Thrombosis§	Worst Hierarchical Outcome at 12-months (days to outcome) §
Definite Stent Thrombosis					
0	ZES	LAD	Yes	Non-Q-wave MI TLR	Non-Q-wave MI (0)
0	ZES	LAD	Yes	Q-wave MI TLR	Q-wave MI (0)
0	ZES	LAD	Yes	No event at time of stent thrombosis	TLR (111)
0	ZES	LAD	Yes	TLR	TLR (0)
1	EES	LAD	Yes	Q-wave MI TLR	Q-wave MI (1)
2	ZES	LAD	Yes	TLR	Q-wave MI (1)
4*****	ZES	LAD	Yes	TLR	Non-Q-wave MI (0)
5#	ZES	LAD	Yes	Non-Q-wave MI TLR Non-TVR	Q-wave MI (10)
5¶	ZES	LAD	Yes	Q-wave MI TLR	Q-wave MI (5)
10#	ZES	LAD	Yes	Q-wave MI TLR Non-TVR	Q-wave MI (10)
21	ZES	LCx	Yes	Q-wave MI TLR	Q-wave MI (21)
31*****	ZES	LAD	Yes	Non-Q-wave MI TLR	Non-Q-wave MI (0)
31	ZES	LCx	Yes	Q-wave MI TLR Non TVR	Cardiac Death (58)
71	ZES	LAD	No	Non-Q-wave MI TLR	Non-Q-wave MI (71)
73	ZES	LAD	Yes	TLR	TLR (73)
81†	EES	RCA	Yes	Non-Q-wave MI TLR	Non-Q-wave MI (79)

124	ZES	RCA	Yes	TLR TVR	Non-Q-wave MI (111)
279†	EES	RCA	Yes	Non-Q-wave TLR	Non-Q-wave MI (79)
341	EES	SVG	Yes	Non-Q-wave MI	Non-Q-wave MI (341)

Probable Stent Thrombosis

0¶	ZES	LAD	Yes	Q-wave MI	Q-wave MI (5)
1	EES	LAD	Yes	Non-Q-wave MI	Non-Q-wave MI (1)
2	EES	LMS	Yes	Q-wave MI Cardiac death	Cardiac Death (2)
4	ZES	LAD/ RCA	Unknown	Cardiac death	Cardiac Death (4)
5	ZES	LCx	Unknown	Non-Q-wave MI	Non-Q-wave MI (5)
21	EES	RCA	Unknown	Q-wave MI Cardiac death	Cardiac death (21)
25	EES	RCA	Unknown	Cardiac death	Cardiac death (25)
25	ZES	LAD	Unknown	Cardiac death	Cardiac death (25)
29	EES	RCA	Unknown	Cardiac death	Cardiac Death (29)
108	ZES	SVG	Unknown	Cardiac death	Cardiac death (108)
214	ZES	Cx	Yes	Q-wave MI	Q-wave MI (214)

*,#,†,¶ indicates the same patient having the event

ZES, zotarolimus-eluting stent
EES, everolimus-eluting stent
LAD, left anterior descending coronary artery
RCA, right coronary artery
LCx, circumflex artery
SVG, saphenous vein graft
MI, myocardial infarction
TLR, target lesion revascularization
TVR, target vessel revascularization

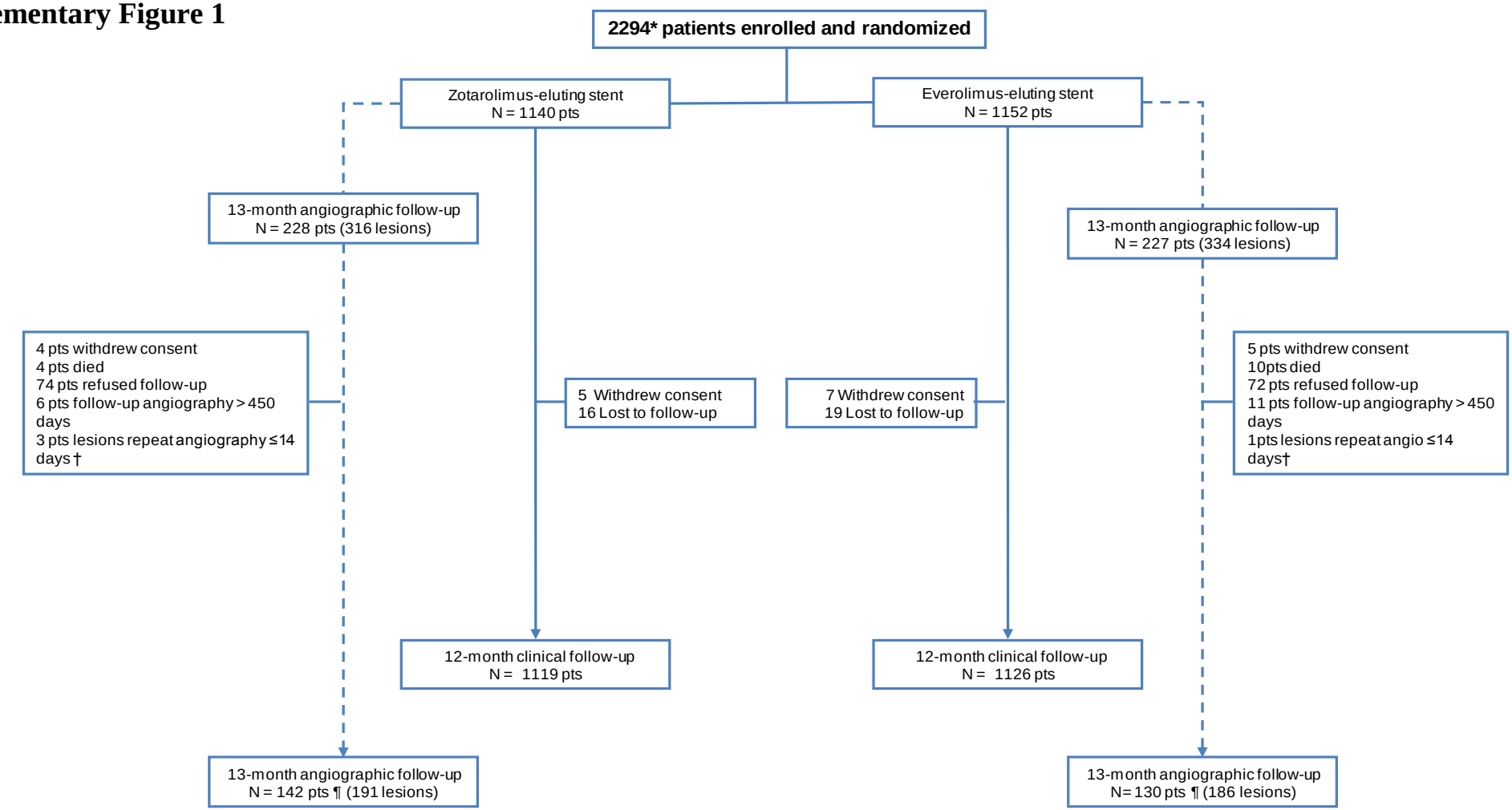
§Events adjudicated according to the Academic Research Consortium.[1]

Supplementary Table 3. Angiographic Follow-up on an Intention-to-treat Basis

	ZES	EES	Difference [95% CI]	P value
Unmatched Angiographic Analysis				
13-months				
Diameter stenosis (%)	**(N_L =191)**	**(N_L=186)**		
In-stent	21.65±14.42	19.76±14.64	1.89 [-1.05, 4.83]	0.21
In-segment	26.51±14.01	25.50±15.02	1.01 [-1.93, 3.95]	0.50
Binary restenosis (%)	**(N_L =191)**	**(N_L=186)**		
In-stent	4.2% (8)	3.8% (7)	0.4% [-3.5%, 4.4%]	1.00
In-segment	5.2% (10)	6.5% (12)	-1.2% [-6.0%, 3.5%]	0.67
Matched Paired Angiographic Analysis				
Post Procedure	**(N_L =183)**	**(N_L=177)**		
Minimum lumen diameter (mm)				
In-stent	2.46±0.53	2.42±0.50	0.05 [-0.06, 0.15]	0.39
In-segment	2.18±0.56	2.06±0.49	0.12 [0.01, 0.23]	0.03
13-months				
Minimum lumen diameter (mm)	**(N_L =183)**	**(N_L=177)**		
In-stent	2.20±0.62	2.23±0.59	-0.03 [-0.16, 0.10]	0.64
In-segment	2.03±0.61	2.01±0.56	0.03 [-0.09, 0.15]	0.65
Late loss (mm)				
In-stent	0.27±0.43	0.19±0.40	0.08 [-0.01, 0.16]	0.08
In-segment	0.15±0.43	0.06±0.40	0.09 [0.01, 0.18]	0.04

Data are presented as mean±standard deviation and percent (number of events).

Supplementary Figure 1



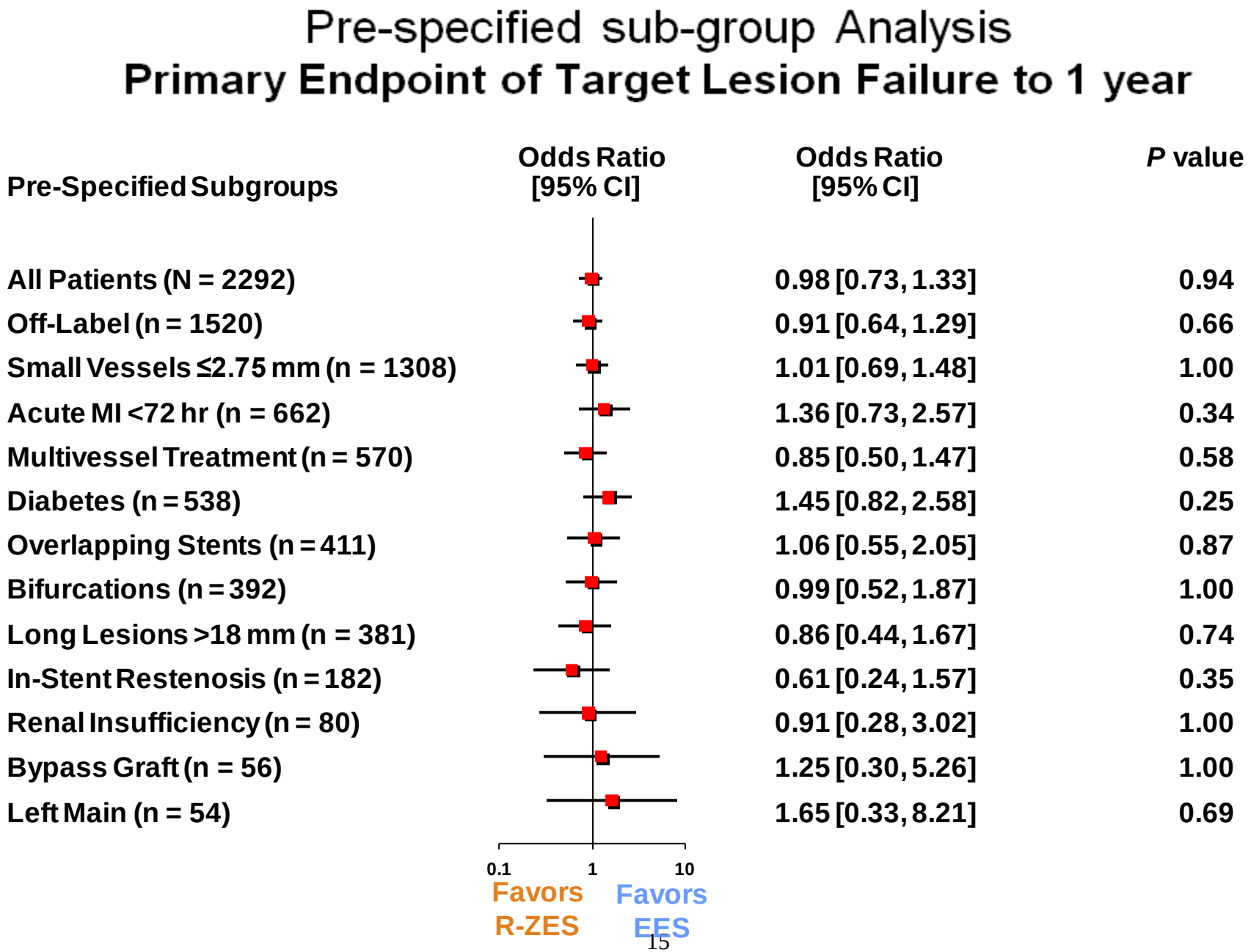
*2 patients randomized to zotarolimus-eluting stents were not included in analysis because no PCI was performed for medical reasons, and consent was subsequently withdrawn.

¶ Number of patients do not add up, as some patients had multiple lesions, that were not all excluded.

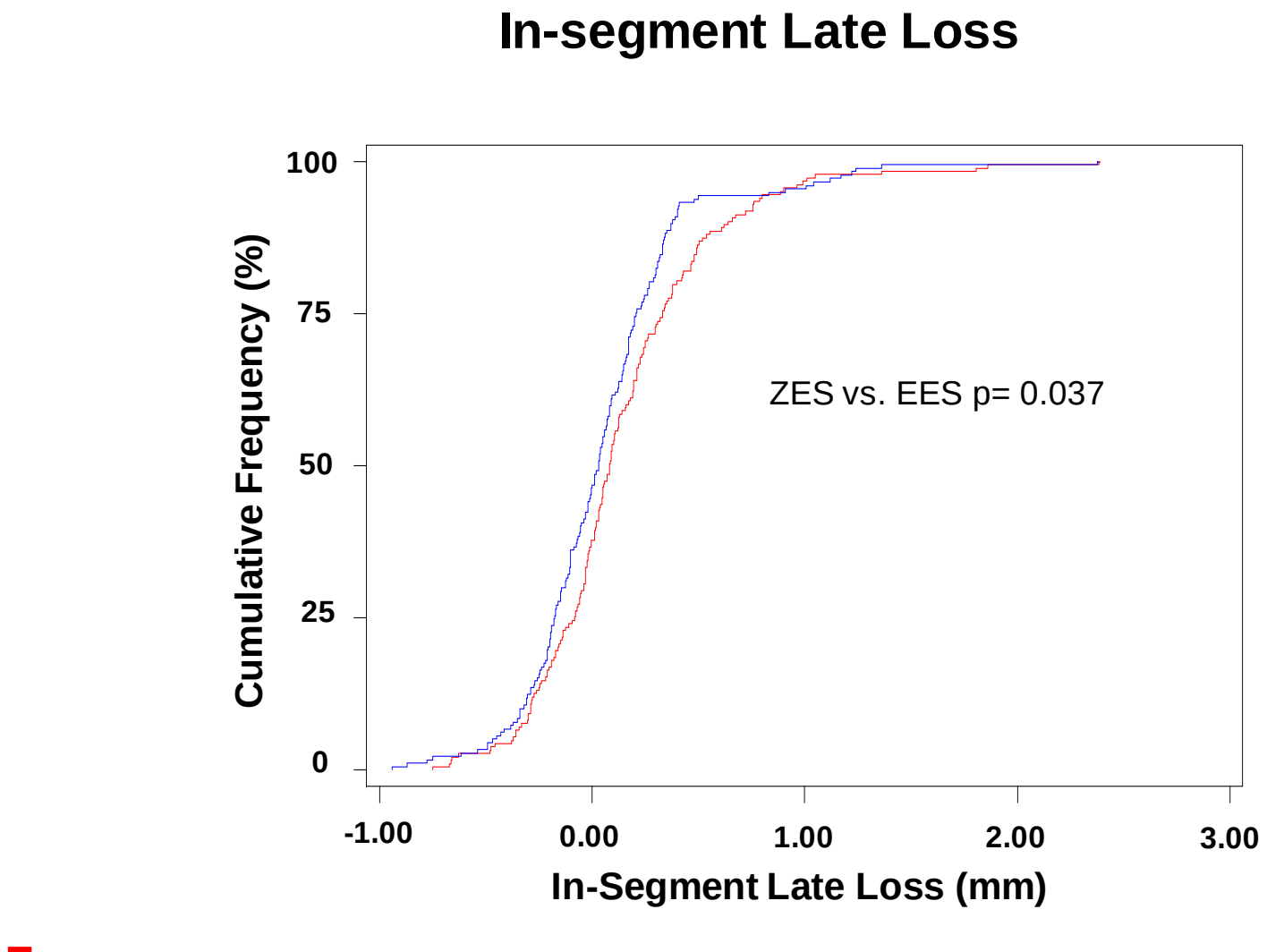
† Clinical events in these patients are still included in the final clinical results.

Pts, patients

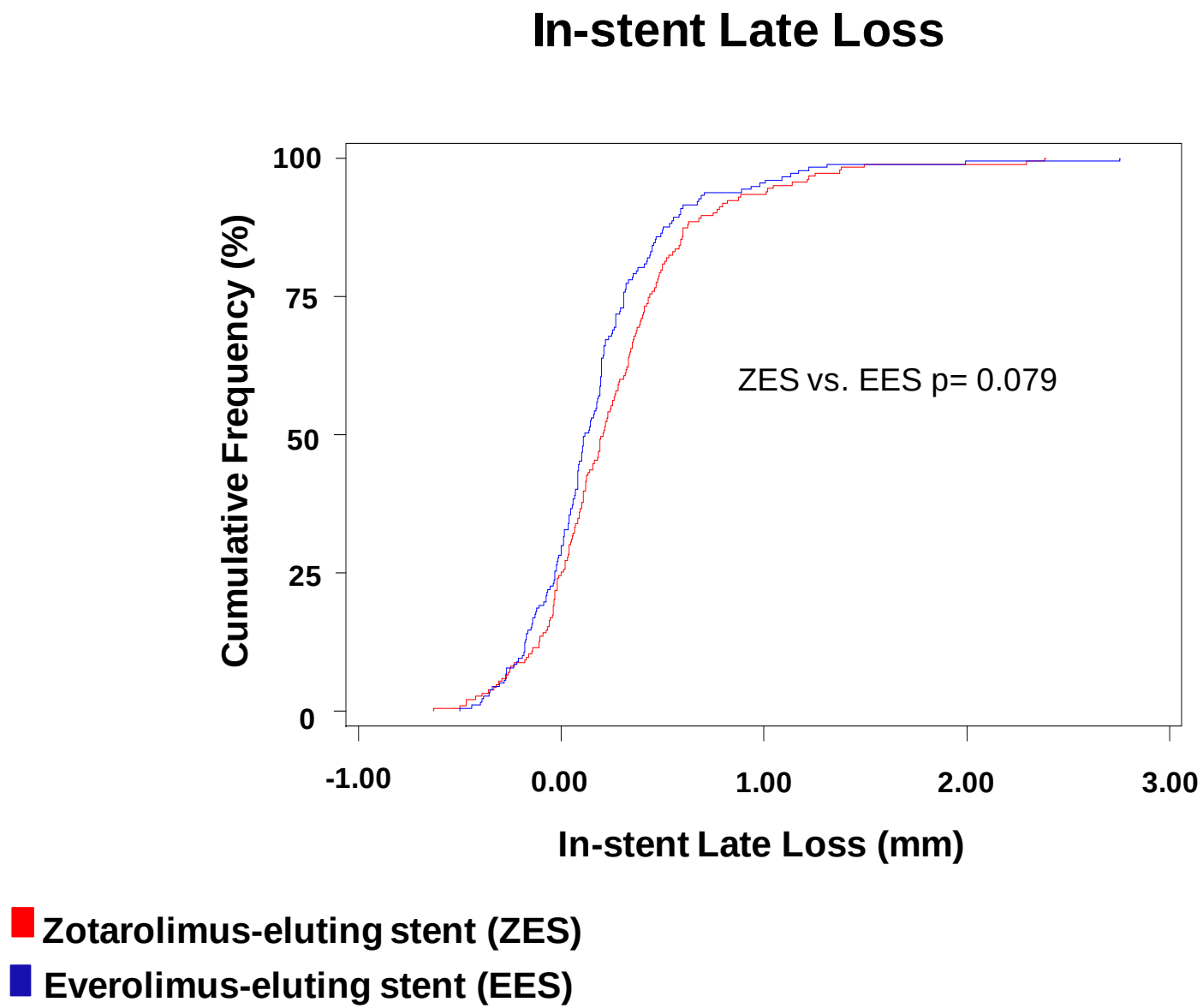
Supplementary Figure 2



Supplementary Figure 3A



Supplementary Figure 3B



Trial Appendix I

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