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Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type

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Aim To investigate the putative modifying effect of dual antiplatelet therapy (DAPT) use on the incidence of stent thrombosis at 3 years in patients randomized to Endeavor zotarolimus-eluting stent (E-ZES) or Cypher sirolimus-eluting stent (C-SES).

Methods and results Of 8709 patients in PROTECT, 4357 were randomized to E-ZES and 4352 to C-SES. Aspirin was to be given indefinitely, and clopidogrel/ticlopidine for ≥3 months or up to 12 months after implantation. Main outcome measures were definite or probable stent thrombosis at 3 years. Multivariable Cox regression analysis was applied, with stent type, DAPT, and their interaction as the main outcome determinants. Dual antiplatelet therapy adherence remained the same in the E-ZES and C-SES groups (79.6% at 1 year, 32.8% at 2 years, and 21.6% at 3 years). We observed a statistically significant ($P = 0.0052$) heterogeneity in treatment effect of stent type in relation to DAPT. In the absence of DAPT, stent thrombosis was lower with E-ZES vs. C-SES (adjusted hazard ratio 0.38, 95% confidence interval 0.19, 0.75; $P = 0.0056$). In the presence of DAPT, no difference was found (1.18; 0.79, 1.77; $P = 0.43$).

Conclusion A strong interaction was observed between drug-eluting stent type and DAPT use, most likely prompted by the vascular healing response induced by the implanted DES system. These results suggest that the incidence of stent thrombosis in DES trials should not be evaluated independently of DAPT use, and the optimal duration of DAPT will likely depend upon stent type (Clinicaltrials.gov number NCT00476957).

Keywords Drug-eluting stent • Dual antiplatelet therapy • Stent thrombosis • Endothelialization • Healing • Sirolimus • Zotarolimus

Introduction

The importance of dual antiplatelet therapy (DAPT) to prevent in-stent thrombotic events in patients implanted with a drug-eluting stent (DES) has been widely reported.[1–3] Interruption of DAPT is also a major independent predictor of stent thrombosis,[4] underscoring the importance of this therapy in the prevention of early and late thrombotic events after deployment of a DES.

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The Patient Related OuTcomes with Endeavor vs. Cypher stenting Trial (PROTECT)[5] was designed as a superiority trial comparing the incidence of stent thrombosis in a broad population of patients and involving two widely used DES with different potency profiles and nearly opposite healing characteristics: the Endeavor zotarolimus-eluting stent (E-ZES; Medtronic CardioVascular) and the Cypher sirolimus-eluting stent (C-SES; Cordis, Johnson & Johnson).[6,7] Both devices prevent the occurrence of restenosis yet have different antiproliferative potencies due to drug, polymer, and drug-release characteristics.[8] Therefore, the key design element of PROTECT was the selection of two DES systems with contrasting site-specific vascular healing responses, with E-ZES more closely mirroring the healing response following bare-metal stent implantation.[6,7]

In PROTECT, the primary outcome of definite or probable stent thrombosis at 3 years did not differ between E-ZES and C-SES [1.42% (predicted 1.5%) vs. 1.79% (predicted 2.5%); log-rank $P = 0.22$], respectively.[9] During the period from 1 to 3 years when the use of DAPT was low, however, a significant 0.75% difference emerged in the incidence of stent thrombosis (E-ZES 0.32% vs. C-SES 1.07%; log-rank $P < 0.0001$). We hypothesized that DAPT use influenced the rate of stent thrombosis to a different extent, depending upon the type of implanted DES.

Methods

PROTECT is a two-arm, multinational superiority trial, with a prospective randomized open-label blinded-endpoints design.[5] The trial involved 196 centres in 36 countries across five continents. Patients were randomized 1 : 1 to E-ZES or C-SES and mandated to undergo an electrocardiogram at 3-year follow-up. Source documentation of all events was 100% monitored. Other data monitoring was performed in 30% of randomly selected patients at all centres.

Patients provided informed consent to participate. The protocol was approved by the institutional ethical committee and/or centralized national ethical board according to the rules specific to the country.

Stent thrombosis (definite or probable) was defined according to the Academic Research Consortium definitions.[10] In accordance with the main results paper,[9] the composite of definite or probable stent thrombosis at 3 years was the primary endpoint and definite stent thrombosis the secondary endpoint. Dual antiplatelet therapy was defined as the combination of aspirin plus clopidogrel or ticlopidine (both pro-drugs metabolized in the liver) and no DAPT ('off-DAPT') was defined as either single antiplatelet (aspirin or clopidogrel/ticlopidine) or no antiplatelet therapy.

Statistical methods

We systematically analysed if (and to what extent) DAPT use modified the effect of stent type on the primary and secondary endpoints.

Follow-up visits were scheduled up to 36 months, and information on actual DAPT use was collected. We calculated cumulative patient-years of follow-up in relation to DAPT exposure. The 'on'/'off' DAPT status at each visit determined the status for the period between this and the next visit. Thus, an individual could potentially contribute to patient-years 'on' as well as 'off' DAPT, and any treatment change was taken into account. We report the number of patients who reached a study endpoint relative to the cumulative patient-years of follow-up in relation to DAPT exposure (i.e. DAPT-specific incidence rates). We do not report multiple events per patient and follow-up time was not counted after a study endpoint was reached.

Univariate Cox proportional hazard regression models were fitted, with stent thrombosis as the outcome and stent treatment and DAPT use as the determinants. We defined DAPT use as a time-dependent covariate, in agreement with the definition described above. Multivariable Cox models were subsequently fitted, and the following variables were considered as potential covariates: age, medical history (diabetes mellitus, cigarette smoking, prior myocardial infarction, or stroke), serum creatinine, stent length and diameter, overlapping stents, lesion characteristics, assigned treatment (E-ZES vs. C-SES), and a time-dependent covariate for DAPT. To avoid over-fitting the model, the number of covariates (i.e. the associated degrees of freedom) was limited to 1 for each 10 incident endpoints. Covariates with the lowest *P*-values in univariate analysis were selected. We then applied the backward-deletion model reduction strategy so that in the final model all covariates had a *P*-value <0.15. The final multivariable model was enriched with the interaction term 'stent-treatment * DAPT' (as the time-dependent covariate).

P-values of <0.05 were considered statistically significant and no formal adjustment was made for multiple testing. Analyses were performed using SAS, version 9.2.

Results

Between 21 May 2007 and 22 December 2008, 8791 patients were identified, of which 8709 provided consent and were eligible for inclusion: 4357 patients were randomized to E-ZES and 4352 to C-SES. Data for 8340 (95.8%) patients were available at 3-year follow-up.

The groups were similar in terms of their clinical characteristics. Lesion characteristics revealed more lesions treated in the main stem and in the right coronary as well as calcified lesion in the C-SES group; procedural characteristics revealed a greater number of stents per lesion and overlapping stents, and lower use of predilatation in the E-ZES group (*Table 1*).

Dual antiplatelet therapy and stent type as determinants of stent thrombosis

Incidence and incidence rate of stent thrombosis are shown in *Table 2*. Adherence to DAPT at day 30 and at all follow-up intervals up to 3 years was similar in both groups (*Table 3* and *Figures 1* and *2*). 'Off-DAPT' patients were evenly distributed among aspirin alone, thienopyridine alone, and no DAPT up to 3 years in both groups, with the exception of a slightly higher use of thienopyridine in the E-ZES group at 1 year (*Table 3*). Cumulative follow-up patient-years in the presence ('on-DAPT') or absence ('off-DAPT') of DAPT according to stent type were also similar (*Figure 1* and *2 subtables*).

A statistically significant heterogeneity was observed in treatment effect of stent type in relation to DAPT use for definite or probable stent thrombosis ($P = 0.0052$) and for definite stent thrombosis ($P = 0.012$). *Figure 3* and *Table 4* summarize the outcomes of the interaction between DAPT and stent type on the incidence of stent thrombosis. From the perspective of DAPT use, no significant DAPT effect was observed in E-ZES patients in terms of the incidence rate of stent thrombosis, whereas a significant effect was seen in C-SES patients. From the perspective of stent type, off-DAPT the incidence rate and incidence for both definitions of stent thrombosis at 3 years (1080 days) were lower with E-ZES than with C-SES (*Table 2*,

Table 1 Patient, lesion, and procedure characteristics at baseline (reproduced with permission)

Characteristic	E-ZES stent ($n = 4357$)	C-SES stent ($n = 4352$)	*P*-value (E-ZES vs. C-SES)
Age, years	62.3 ± 10.6	62.1 ± 10.7	0.50
Male sex	76.7	76.0	0.48
Body mass index, kg/m^2	27.8 ± 4.4	27.9 ± 4.5	0.24
Diabetes mellitus	26.9	28.4	0.13
Insulin dependent	6.5	7.4	0.11
Hypertension	64.6	63.4	0.26
Hyperlipidaemia	61.8	62.8	0.34
History of smoking	57.7	57.4	0.80
Current smoker	24.9	25.2	0.71
Premature coronary artery disease in first-degree relative ($n = 7540$)	34.2	34.8	0.59
Previous myocardial infarction	20.3	20.8	0.53
Previous CABG	4.6	5.1	0.21
Previous PCI	12.3	12.8	0.48
Previous stroke	3.1	3.1	0.85
Procedure indication			
All (acute) myocardial infarctions	25.8	26.0	0.85
ST-elevation	8.2	8.8	0.28
Non-ST-elevation	17.6	17.1	0.57
Unstable angina	18.3	19.3	0.21
Stable angina	49.5	48.3	0.27
Silent ischaemia	6.5	6.4	0.93
Left ventricular ejection fraction (%) ($n = 4489$)	58.8 ± 12.6	58.3 ± 12.6	0.17
Serum creatinine (μmol/L) ($n = 8152$)	87.6 ± 31.5	88.3 ± 38.4	0.37
Complex patients[a]	58.0	58.1	0.93
Lesion characteristics			
Vessel location (by patient)			
Left anterior descending	58.0	56.4	0.13
Left circumflex	28.9	28.6	0.76
Right coronary artery	32.4	34.7	0.026
Left main	0.9	1.4	0.047
Bypass graft	0.3	0.4	0.49
In-stent restenosis	2.2	2.2	1.00
Chronic total occlusion[b]	3.4	3.6	0.69
Bifurcation	21.9	20.5	0.10
Moderate/severe calcification (vs. none or mild)	30.1	32.4	0.018
Tortuosity: moderate or severe (vs. mild)	26.0	25.7	0.83
Presence of thrombus (vs. none)	9.9	10.4	0.52
Procedure characteristics			
Number of vessels treated per patient	1.20 ± 0.45	1.20 ± 0.46	0.46
Number of lesions treated per patient	1.40 ± 0.71	1.39 ± 0.71	0.85
Number of stents per patient	1.63 ± 0.99	1.59 ± 0.96	0.06
Total stent length/patient (mm)	31.28 ± 20.80	31.20 ± 20.77	0.86
Number of stents per lesion	1.16 ± 0.49	1.13 ± 0.46	0.001
≥1 stent ≤2.75 mm in diameter (%)	44.3	46.2	0.077
≥1 overlapping stent (%)	15.8	13.2	<0.001
Lesions with predilatation	67.5	69.4	0.023
Periprocedure medication			
Unfractionated heparin	92.1	92.0	0.91

Continued

Table 1 *Continued*

Characteristic	E-ZES stent (n = 4357)	C-SES stent (n = 4352)	P-value (E-ZES vs. C-SES)
Low-molecular-weight heparin	5.0	5.4	0.38
Direct thrombin inhibitor	4.2	3.8	0.44
Glycoprotein IIb/IIIa inhibitor	17.9	18.4	0.60

Data given as percentage or means ± standard deviation.
[a]Defined as placement of a stent in a patient with at least one of the following clinical or lesion characteristics: renal insufficiency [creatinine level: ≥140 μmol/L (1.6 mg/dL)], ejection fraction: <30%, acute myocardial infarction ≤72 h, >1 lesion per vessel, >2 vessels with stents, lesion length >27 mm, bifurcation lesion, lesion in bypass graft, in-stent restenosis, unprotected left main artery, lesion with thrombus, or total occlusion.[22]
CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.
[b]Thrombolysis in myocardial infarction (TIMI) 0; no unstable angina; no myocardial infarction.
C-SES, Cypher sirolimus-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent.

Table 2 Incidence and incidence rate of definite or probable and definite stent thrombosis at 1080 days

	Definite or probable stent thrombosis		Definite stent thrombosis	
	Incidence[a] n (%)	Incidence rate[b] $\times 10^{-2}$	Incidence[a] n (%)	Incidence rate[b] $\times 10^{-2}$
Overall	136/8340 (1.6)	0.5 (136/25 017)	82/8340 (1.0)	0.3 (82/25 017)
E-ZES	61/4181 (1.5)	0.5 (61/12 535)	31/4181 (0.7)	0.2 (31/12 535)
C-SES	75/4159 (1.8)	0.6 (75/12 482)	51/4159 (1.2)	0.4 (51/12 482)
E-ZES off-DAPT	11/4181 (0.3)	0.2 (11/4573)	3/4181 (0.1)	0.1 (3/4573)
C-SES off-DAPT	31/4159 (0.8)	0.7 (31/4553)	19/4159 (0.5)	0.4 (19/4553)
E-ZES on-DAPT	50/4181 (1.2)	0.6 (50/7962)	28/4181 (0.7)	0.4 (28/7962)
C-SES on-DAPT	44/4159 (1.1)	0.6 (44/7928)	32/4159 (0.8)	0.4 (32/7928)
Off-DAPT	42/8340 (0.5)	0.5 (42/9126)	22/8340 (0.3)	0.2 (22/9126)
On-DAPT	94/8340 (1.1)	0.6 (94/15 891)	60/8340 (0.7)	0.4 (60/15 891)

C-SES, Cypher sirolimus-eluting stent; DAPT, dual antiplatelet therapy; E-ZES, Endeavor zotarolimus-eluting stent.
[a]Incidence: number of events/number of patients randomized to either E-ZES, C-ZES, or all. Dual antiplatelet therapy status is not taken into account in the denominator.
[b]Incidence rate: number of events/number of follow-up years.

Figures 1A and *2A*) whereas no difference was found on-DAPT (*Table 2*, *Figures 1B* and *2B*).

Further determinants of stent thrombosis

Independent predictors of stent thrombosis (*Table 4*) show a similar pattern to the univariate predictors (Table 2, Appendix 2), with diabetes mellitus, ≥1 stent ≤2.75 mm in diameter, and current smoking being strongly significant for both definitions of stent thrombosis.

Discussion

These data from PROTECT suggest that adherence to DAPT modifies the outcome of stent thrombosis to a greater extent after C-SES deployment than after E-ZES deployment, most likely due to differential healing characteristics. These findings suggest that DAPT use should be taken into consideration when interpreting the incidence of stent thrombosis in studies evaluating different DES.

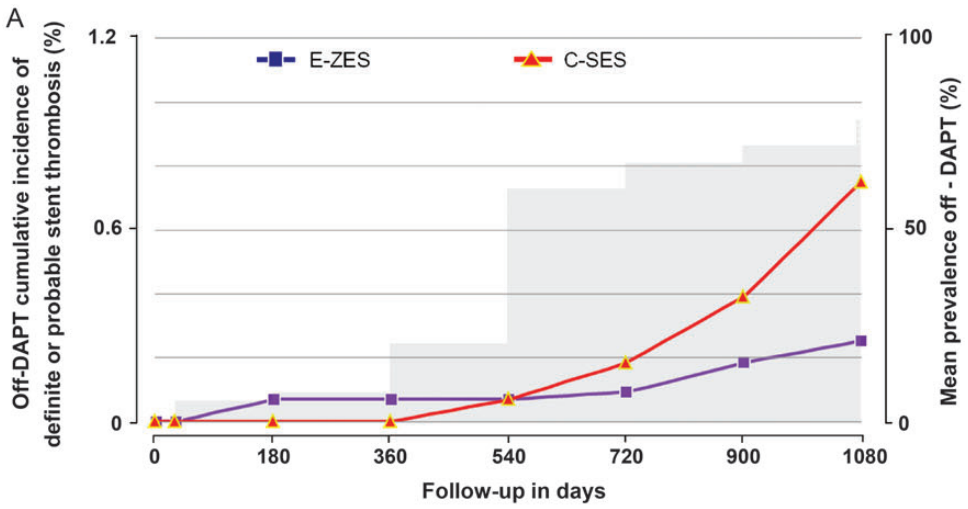
Irrespective of the definition of stent thrombosis used (i.e. definite or probable or definite alone) a highly significant interaction was observed between DES type and DAPT use. From the perspective of stent type, this interaction revealed a higher incidence and incidence rate of stent thrombosis in the C-SES arm off-DAPT. Conversely, in patients on-DAPT, both stent types showed a similar incidence and incidence rate of stent thrombosis. This analysis did not evaluate a differentiated effect of either single antiplatelet vs. no antiplatelet therapy or different types of single antiplatelet therapies. From earlier literature one can assume that the less potent the antiplatelet regimen the higher the incidence of stent thrombosis.[11] Thus, the current analysis comparing the influence of a standard DAPT regimen with a pooled mix of single or no antiplatelet therapy may have attenuated the current findings between E-ZES and C-SES.

The risk assessment expressed as cumulative incidence rate shows a greater sensitivity to detect safety signals off-DAPT. Further, the cumulative incidence curves for definite/probable and definite stent thrombosis for E-ZES vs. C-SES start to separate at 18 months (540 days) and continue to diverge up to 1080 days. Conversely, while on-DAPT, the incidence curves of stent thrombosis for both stent types remain close, running almost parallel from 720 days

Table 3 Use of antiplatelet therapy (aspirin, clopidogrel, or ticlopidine) from day 30 to 3 years at exact time points of follow-up

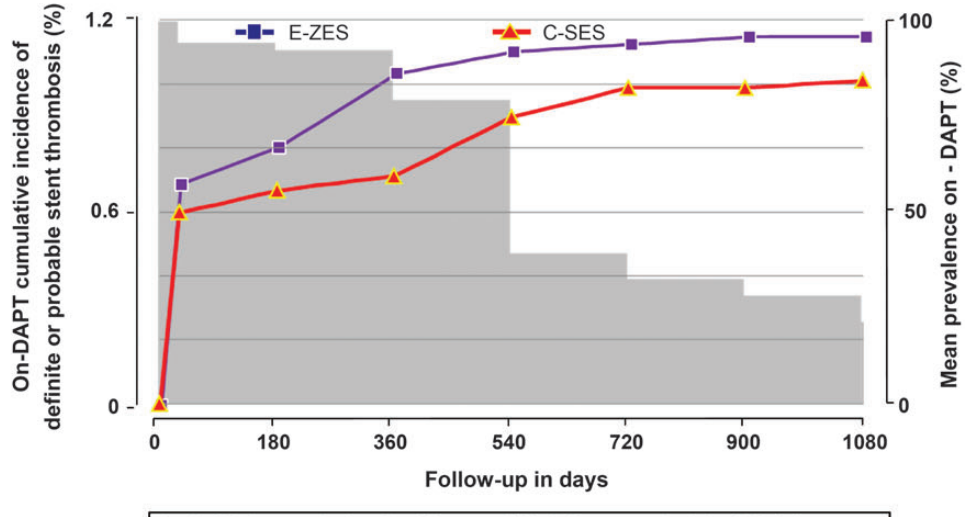
	E–ZES stent (n = 4357)	C–SES stent (n = 4352)	Difference (95% confidence interval)	P-value
At 30 days				
DAPT[a]	4110 (94.3)	4112 (94.5)	−0.2 (−1.1, 0.8)	0.78
No DAPT:	247 (5.7)	240 (5.5)	0.2 (−0.8, 1.1)	0.78
Aspirin[b]	72 (1.7)	77 (1.8)	−0.1 (−0.7, 0.4)	0.68
Thienopyridine[c]	109 (2.5)	114 (2.6)	−0.1 (−0.8, 0.5)	0.74
None[d]	66 (1.5)	49 (1.1)	0.4 (−0.1, 0.9)	0.13
At 180 days				
DAPT[a]	4040 (92.7)	4006 (92.0)	0.7 (−0.4, 1.8)	0.24
No DAPT:	317 (7.3)	346 (8.0)	−0.7 (−1.8, 0.4)	0.241
Aspirin[b]	124 (2.8)	142 (3.3)	−0.4 (−1.1, 0.3)	0.26
Thienopyridine[c]	109 (2.5)	97 (2.2)	0.3 (−0.4, 0.9)	0.44
None[d]	84 (1.9)	107 (2.5)	−0.5 (−1.1, 0.1)	0.09
At 360 days				
DAPT[a]	3468 (79.6)	3459 (79.5)	0.1 (−1.6, 1.8)	0.89
No DAPT:	889 (20.4)	893 (20.5)	−0.1 (−1.8, 1.6)	0.89
Aspirin[b]	594 (13.6)	624 (14.3)	−0.7 (−2.2, 0.8)	0.35
Thienopyridine[c]	149 (3.4)	111 (2.6)	0.9 (0.2, 1.6)	0.02
None[d]	146 (3.4)	158 (3.6)	−0.3 (−1.1, 0.5)	0.48
At 540 days				
DAPT[a]	1728 (39.7)	1695 (38.9)	0.7 (−1.3, 2.8)	0.50
No DAPT:	2629 (60.3)	2657 (61.1)	−0.7 (−2.8, 1.3)	0.497
Aspirin[b]	2238 (51.4)	2270 (52.2)	−0.8 (−2.9, 1.3)	0.47
Thienopyridine[c]	147 (3.4)	144 (3.3)	0.1 (−0.7, 0.8)	0.91
None[d]	244 (5.6)	243 (5.6)	0.0 (−0.9, 1.0)	1.00
At 720 days				
DAPT[a]	1430 (32.8)	1424 (32.7)	0.1 (−1.9, 2.1)	0.93
No DAPT:	2927 (67.2)	2928 (67.3)	−0.1 (−2.1, 1.9)	0.93
Aspirin[b]	2450 (56.2)	2455 (56.4)	−0.2 (−2.3, 1.9)	0.88
Thienopyridine[c]	162 (3.7)	155 (3.6)	0.2 (−0.6, 0.9)	0.73
None[d]	315 (7.2)	318 (7.3)	−0.1 (−1.2, 1.0)	0.90
At 900 days				
DAPT[a]	1220 (28.0)	1241 (28.5)	−0.5 (−2.4, 1.4)	0.60
No DAPT:	3137 (72.0)	3111 (71.5)	0.5 (−1.4, 2.4)	0.60
Aspirin[b]	2555 (58.6)	2544 (58.5)	0.2 (−1.9, 2.3)	0.86
Thienopyridine[c]	174 (4.0)	172 (4.0)	0.0 (−0.8, 0.9)	0.96
None[d]	408 (9.4)	395 (9.1)	0.3 (−0.9, 1.5)	0.66
At 1080 days				
DAPT[a]	919 (21.1)	959 (22.0)	−0.9 (−2.7, 0.8)	0.29
No DAPT:	3438 (78.9)	3393 (78.0)	0.9 (−0.8, 2.7)	0.29
Aspirin[b]	2142 (49.2)	2097 (48.2)	1.0 (−1.1, 3.1)	0.37
Thienopyridine[c]	146 (3.4)	148 (3.4)	−0.0 (−0.8, 0.7)	0.91
None[d]	1150 (26.4)	1148 (26.4)	0.0 (−1.8, 1.9)	1.00

[a]DAPT: aspirin plus thienopyridine (clopidogrel or ticlopidine).
[b]Aspirin only (thienopyridine stopped).
[c]Thienopyridine only (aspirin stopped).
[d]Both thienopyridine and aspirin stopped.
C-SES, Cypher sirolimus-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent.



Off-DAPT cumulative incidence of definite or probable ST (*n*)						
0 0	3	3	3	4	8	11
0 0	0	0	3	8	17	31
Off-DAPT cumulative follow-up patient-years per DES type (*n*)						
0	86	211	600	1832	3182	4573
0	83	215	596	1833	3177	4553

E-ZES vs. C-SES in patients off-DAPT: HR 0.38 (95% CI 0.19–0.75) *P* = 0.0056



On-DAPT cumulative incidence of definite or probable ST (*n*)						
0 30	35	45	48	49	50	50
0 26	29	31	39	43	43	44
On-DAPT cumulative follow-up patient-years per DES type (*n*)						
361	2068	4079	5805	6661	7368	7962
361	2067	4059	5779	6620	7329	7928

E-ZES vs. C-SES in patients on-DAPT: HR 1.18 (95% CI 0.79–1.77) *P* = 0.43

Figure 1 Cumulative incidence of definite or probable stent thrombosis and mean prevalence (*A*) off-dual antiplatelet therapy and (*B*) on-dual antiplatelet therapy in Endeavor zotarolimus-eluting stent and Cypher sirolimus-eluting stent groups. C-SES, Cypher sirolimus-eluting stent; DAPT, dual antiplatelet therapy; E-ZES, Endeavor zotarolimus-eluting stent.

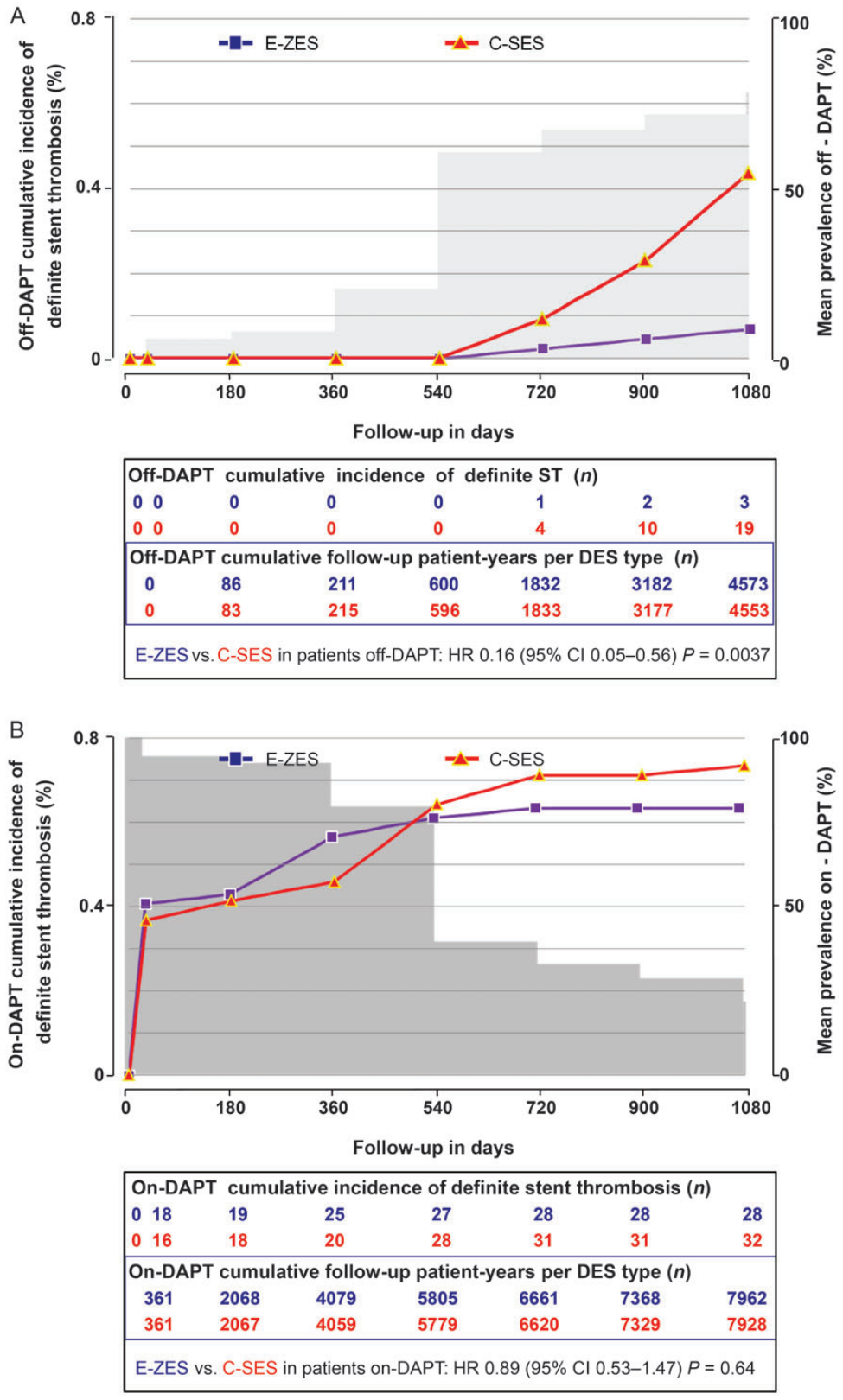


Figure 2 Cumulative incidence of definite stent thrombosis and mean prevalence (*A*) off-dual antiplatelet therapy and (*B*) on-dual antiplatelet therapy in Endeavor zotarolimus-eluting stent and Cypher sirolimus-eluting stent groups. C-SES, Cypher sirolimus-eluting stent; DAPT, dual antiplatelet therapy; E-ZES, Endeavor zotarolimus-eluting stent.

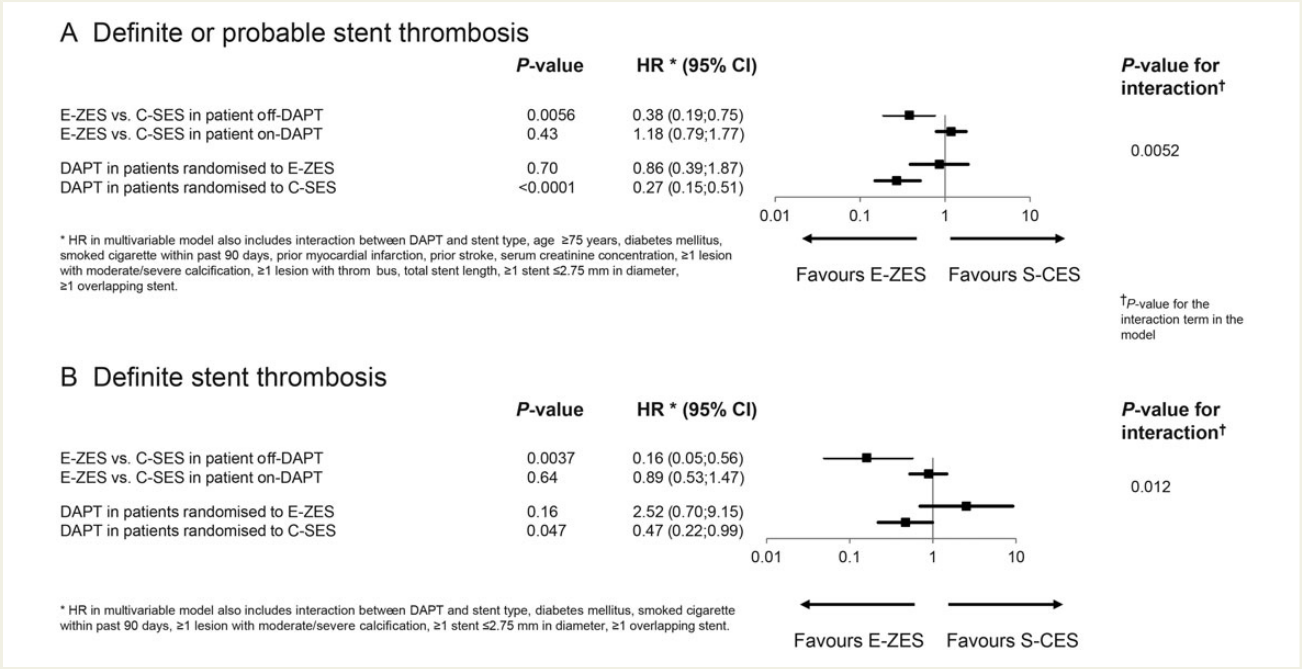


Figure 3 Risk of (*A*) definite or probable or (*B*) definite stent thrombosis up to 1080 days according to drug-eluting stent-type and dual antiplatelet therapy-use. C-SES, Cypher sirolimus-eluting stent; DAPT, dual antiplatelet therapy; E-ZES, Endeavor zotarolimus-eluting stent.

Table 4 Multivariable predictors of stent thrombosis

Predictor	Definite or probable stent thrombosis ($n = 136$)		Definite stent thrombosis ($n = 82$)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
E-ZES vs. C-SES in patients off-DAPT	0.38 (0.19, 0.75)	0.0056	0.16 (0.05, 0.56)	0.0037
E-ZES vs. C-SES in patients on-DAPT	1.18 (0.79, 1.77)	0.43	0.89 (0.53, 1.47)	0.64
DAPT in patients randomized to E-ZES	0.86 (0.39, 1.87)	0.70	2.52 (0.70, 9.15)	0.16
DAPT in patients randomized to C-SES	0.27 (0.15, 0.51)	<0.0001	0.47 (0.22, 0.99)	0.047
Diabetes mellitus	1.88 (1.33, 2.67)	0.0004	1.78 (1.14, 2.78)	0.012
≥1 stent ≤2.75 mm in diameter	1.93 (1.33, 2.80)	0.0006	1.96 (1.23, 3.12)	0.0044
Smoked cigarette within past 90 days	1.79 (1.23, 2.61)	0.0024	1.77 (1.11, 2.80)	0.016
Prior myocardial infarction	1.54 (1.07, 2.23)	0.021	—	>0.15[a]
≥1 lesion with thrombus	1.72 (1.07, 2.76)	0.025	—	>0.15[a]
≥1 lesion with calcification (moderate/severe)	1.41 (1.00, 2.00)	0.052	1.50 (0.96, 2.33)	0.08
Prior stroke	1.91 (0.96, 3.77)	0.06	—	>0.15[a]
Serum creatinine concentration (μmol/L)	1.00 (1.00, 1.01)	0.06	—	>0.15[a]
Age ≥75 years	1.53 (0.97, 2.41)	0.07	—	>0.15[a]
Total stent length per patient (mm)	1.01 (1.00, 1.01)	0.10	—	>0.15[a]
≥1 overlapping stent	1.42 (0.90, 2.23)	0.13	1.74 (1.05, 2.89)	0.032

CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio.
[a]Variable did not meet the criteria (*P*-value <0.15) to stay in the multivariable model.

onwards, revealing little sensitivity to detect stent-thrombosis-related safety signals and thus having similar long-term stent-thrombosis-related safety profiles. Thus, the incidence of stent thrombosis over time was distributed differentially according to DAPT-adherence pattern: off-DAPT the difference started to emerge after 18 months; on-DAPT both devices had a very similar

incidence of (early and) very late stent thrombosis, but E-ZES had a numerically higher incidence of late stent thrombosis (> 30 days to 1 year). Pathophysiologically, a less DAPT-dependent mechanism seems to play a role in E-ZES late events and a more DAPT-dependent mechanism in C-SES very late events (>1 year), suggesting different mechanisms of stent occlusion (i.e. occlusive restenosis in the E-ZES group vs. thrombotic occlusion secondary to delayed healing and/or plaque rupture in the context of neo-atherosclerosis[12] in the C-SES group).

Because almost all the patients were on-DAPT during the first year, we looked at the period after 360 days (very late), when adherence started to drop <80% and thus the cumulative follow-up patient-years off-DAPT started to increase substantially as did the rate of events. We found that 3350 cumulative patient-years off-DAPT per group would have provided the protocol-mandated statistical power of 90%[5] to reveal a coherent safety signal between the two stent systems according to the primary endpoint, representing slightly over 1.5 years.

From the perspective of DAPT use, patients randomized to E-ZES showed no significant DAPT effect on the incidence of stent thrombosis up to 3 years, whereas a significant effect could be demonstrated in the C-SES group. Therefore, the 'DAPT effect' is more apparent after deployment of the potent C-SES DES, inducing a longer-term altered healing response, and reflecting both a persistent in-stent pro-thrombotic environment and a likely need for prolonged antithrombotic administration. Not unexpectedly other strong univariate and multivariable predictors of stent thrombosis, which could guide tailoring DAPT duration on an individual basis, were also related—at least in part—to stent or vessel-healing properties. Patients with multiple characteristics that alter vessel recovery and favour persistency of a site-specific in-stent pro-thrombotic milieu are likely to need a more prolonged duration of DAPT. Of interest, in this context, the strongest criterion to pursue long-term thromboprotective DAPT was diabetes mellitus.

The strong interaction between the treatment modalities 'DES type' and 'DAPT use', an aspect linked to clinical trial methodology neglected thus far, may also be relevant when re-evaluating the literature on DES. The key points are the following:

First, the period off-DAPT shows a greater sensitivity to detect safety signals after DES deployment. Therefore, long-term follow-up (with sufficient events and patient-years) is essential to ensure sufficient off-DAPT time to detect a difference between DES types. This is particularly true in randomized trials in which DAPT duration is not mandated in the protocol, as demonstrated in the primary analysis from PROTECT.[9] When DAPT duration is mandated but DAPT use at follow-up is missing and a balanced use of DAPT among groups can be assumed, long-term follow-up remains essential to detect safety signals, as demonstrated in the 3-year follow-up of SORT OUT III—a trial similar by design to PROTECT, and using an administrative-guided clinical endpoint.[13] Not surprisingly, the first long-term safety signals became apparent in the very first trials in which duration of DAPT was defined and when physicians were not aware of the risk of late or very late thrombotic events.[14–16]

Second, high adherence to DAPT prevents a reliable evaluation of the safety profiles of stent systems as assessed by the incidence of stent thrombosis. Therefore, randomized trials with short follow-up (up to 1 year) and high adherence to DAPT over the study-period have limited validity to determine long-term safety profiles of study stents using stent thrombosis as a criterion.[17–25] One should not neglect, however, the impact of stent thrombosis secondary to occlusive restenosis[23–25]—a less 'DAPT-dependent' phenomenon—as a confounding factor during the first year.

Third, apparent differences in the safety profiles of DES may be due to imbalances in use of DAPT across study arms. Therefore, clinical evaluations (e.g. in sequential registries or meta-analyses) of DES systems with different adherence to DAPT or that do not factor in DAPT effect will be limited in terms of their ability to evaluate DES safety profiles using the stent-thrombosis criterion.[26,27]

Fourth, the healing characteristics associated with stent systems influence the thromboprotective efficacy of DAPT, as shown in this analysis. Therefore, pooling data from different DES types[28–33] or DAPT regimens,[34] or determination of a generalized optimal duration of DAPT after DES deployment,[28,30,32] without taking into account the specific biological attributes of each stent system will not provide a clinically valuable message. Conversely, the evaluation of a specific stent system for different durations of DAPT is clinically meaningful, but generalization of the stent-specific finding to other DES types should be avoided.[35,36]

To put this analysis of the 3-year results of PROTECT into perspective, we searched Medline for randomized trials that analysed the interaction of DES type and DAPT use in relation to clinical events. We found PRODIGY,[37] which explored prospectively in 2013 patients randomized in a 4-by-2 design to four stent types (bare-metal, zotarolimus-eluting, paclitaxel-eluting, and everolimus-eluting) and two different durations of DAPT (6 vs. 24 months). The primary endpoint was a composite of death, myocardial infarction, or cerebrovascular accident; the secondary endpoint was stent thrombosis. The authors observed heterogeneity across stent types driven by: an improved primary endpoint as well as a lower incidence of stent thrombosis after short-term DAPT in the zotarolimus arm (corresponding to E-ZES in PROTECT); and a higher incidence of stent thrombosis after short-term DAPT in the paclitaxel-eluting arm. They concluded, similar to the current analysis, that the optimal duration of DAPT may be stent-specific. However, no satisfactory answer to the pathophysiological mechanisms underlying this observation could be given.

An interaction between stent type and DAPT is likely to be present and to persist in any stent system until vascular recovery has been achieved; therefore this interaction will be clinically more important with stent systems associated with a more delayed vascular healing and/or accelerated atherosclerotic process. Novel stent technologies have been developed to improve the healing characteristics, but we will have to wait for the results of the Dual Antiplatelet Therapy Study,[32] if analysed according to stent type, to demonstrate that conceptual technological modifications have translated into a long-term decrease of thrombotic events.

Study limitations

While C-SES is no longer available, the two stents, through their biological diversity, define a 'wide therapeutic range'. As such they give a broader validity than a single stent type. Despite randomization, the groups were not matched exactly, most likely due to the play of chance, and two of the baseline characteristics affected were

independent predictors of stent thrombosis; however, the imbalance was evenly distributed between the two groups, with moderate/severe calcification more frequent in C-SES and ≥1 overlapping stent more frequent in E-ZES. Furthermore, the analysis determined the relation between DAPT use, DES type, and stent thrombosis, adjusting for potential confounders. The results are unlikely therefore to be biased by the imbalance. The mean lost to follow-up rate is <5% (4.2%) in PROTECT and the mean incidence of the primary endpoint (definite or probable stent thrombosis) is 1.6%. Hence, one may argue that the lost to follow-up may have influenced the outcome. Baseline characteristics of the lost to follow-up group—with the exception of serum creatinine concentration—as well as the criteria identified as predictors of stent thrombosis did not differ between the E-ZES and C-SES groups (*Table 3*, Appendix) and thus it is unlikely that the lost to follow-up group influenced the endpoint of stent thrombosis in a differential manner. This analysis focuses on stent thrombosis and predictors of this event, and not on the clinical sequelae of stent thrombosis. Patients were not randomized to different durations of DAPT so a specific duration of DAPT use according to DES type cannot be derived. In the off-DAPT group, at 1 year a lower use of thienopyridine alone was observed in the C-SES group compared with the E-ZES group; however, the cumulative use of single antiplatelet therapy (aspirin alone or thienopyridine alone) was close to equal, and no difference in the incidence of stent thrombosis in the following 6-month time-window was observed. Lastly, the analysis is *post hoc*; even though the results are statistically sound due to the size of the trial and the broad inclusion criteria the conclusions have to be considered as hypothesis generating.

Conclusion

A strong interaction was observed between DES type and DAPT use, most likely prompted by the vascular healing response induced by the implanted DES system and determining a DES type-specific long-term need for DAPT adherence.

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Role of funding source

The Steering Committee designed the study, in collaboration with the sponsor. An independent academic research organization (Cardialysis, Rotterdam, the Netherlands), blinded to the patients' study stent assignments, was responsible for the organization of meetings involving the clinical events committee and data safety monitoring board, and for the data analysis. Access to the unblinded database was provided to a limited number of Medtronic staff not involved in the study for vigilance and regulatory reporting requirements. E.C. wrote the manuscript. Members of the Steering Committee vouch for the completeness and accuracy of the data gathering and analysis. The authors were not restricted from disclosing the study results. All data collection (except for sites in Canada and the USA where the sponsor's staff performed the monitoring visits), data analysis, data interpretation, and writing of the report were done by independent groups, and the sponsor had only oversight of these activities. The corresponding author had full access to all data in the study and final responsibility to submit for publication.

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Appendix 1. PROTECT Steering Committee, Data Safety Monitoring Board, Clinical Event Committee, and Investigators

PROTECT steering committee

E Camenzind (Chairman), University of Geneva, Geneva, Switzerland
L Mauri, Brigham and Women's Hospital, Boston, MA, USA
W O'Neill, University of Miami Miller School of Medicine, Miami, FL, USA
P W Serruys, Erasmus MC, Thoraxcentrum, Rotterdam, the Netherlands
PhG Steg, INSERM U-698, Université Paris 7, Paris, France
W Wijns, OLV Hospital, Aalst, Belgium

Data safety monitoring board

FWA Verheugt (Chairman), Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands
ME Bertrand, Hôpital Cardiologique, Lille, France
R Califf, Duke Health ORG, Durham, NC, USA
D DeMets, University of Wisconsin Madison, Madison, Wisconsin, USA
L Wallentin, Akademiska Sjukhuset, Uppsala, Sweden

Clinical event committee

W Bocksch, Universitaitsklinikum Tubbingen, Tubbingen, Germany
J Bosmans, UZA, Edegem, Belgium
H Garcia, Erasmus Medisch centrum, Rotterdam, the Netherlands

S Garg, Royal Blackburn Hospital, Blackburn, United Kingdom
C Hanet, Cliniques Universitaires Saint-Luc, Brussels, Belgium
J-PR Herrman, Onze Lieve VrouweGasthuis, Amsterdam, the Netherlands
H Kelbaek, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark
E Mc Fadden, Cork University Hospital, Wilton, Cork, Ireland
PW Radke, Universitätsklinikum Schleswig-Holstein, Lu?beck, Germany
W Rutsch, Akademisches Lehrkrankenhaus der, Charité Universitätsmedizin Berlin, Berlin, Germany
HH Tilsted, Aalborg Hospital, Aalborg, Denmark
J Wykrzykowska, Academisch Medisch Centrum, Amsterdam, the Netherlands

Independent statistician

E Boersma, University Medical Center Rotterdam Erasmus, Rotterdam, the Netherlands

Appendix I PROTECT investigators

Country (patients enrolled)	Site	Investigator
Argentina ($n = 6$)	Hospital Italiano Regional del Sur	C Alvarez
	Sanatorio Otamendi	A Rodriguez
Australia ($n = 414$)	Southern Health, Monash Medical Center	I Meredith
	St Vincent's Sydney	D Muller
	St Vincent's Melbourne	R Whitbourn
	Royal Adelaide	S Worthley
	Fremantle	A Whelan
	The Prince Charles Hospital	D Walters
	Royal Perth Hospital	S Shetty
	Box Hill Hospital	G New
	The Wesley Hospital	S Cox
	Gold Coast Hospital	R Batra
	Northern Hospital	W van Gaal
	John Hunter Hospital	G Bellamy
Austria ($n = 144$)	Landesklinikum St Pölten	H Mayr
	Salzburger Landeskliniken	M Heigert
	Wilhelminensp der Stadt Wien	K Huber
	AKH Linz	F Leisch
Belgium ($n = 265$)	OLVrouwziekenhuis	W Wijns
	UZ Leuven (Gasthuisberg)	W Desmet
	CHR Citadelle	J Boland
	Cliniques Universitaires UCL	E Schroeder / P Chenu
	CHU Sart-Tilman	V Legrand
Canada ($n = 52$)	Ottawa Heart Institute	M Labinaz
	London Health Sciences Center	P Teefy
	Hôpital Laval	O Bertrand
China ($n = 252$)	Beijing Fuwai Hospital	R Gao
	Zhongshan Hospital Fudan Univ	J Ge
Czech Republic ($n = 19$)	Faculty Hospital Brno Bohunice	P Kala
	Mas Hospital Usti nad Labem	P Cervinka
Dominican Republic ($n = 44$)	CEDIMAT	P Ureña
Finland ($n = 29$)	Kuopio University Hospital	J Hartikainen
France ($n = 952$)	AP C Bernard - Hôpital Bichat	G Steg
	Clinique Pasteur	J Fajadet
	CHU Rangueil - Toulouse	D Carrie
	Hôpital de la Cavale Blanche	M Gilard
	Polyclinique des Fleurs	P Barragan
	CHU Lille	J-M Lablanche
	Clinique Saint-Hilaire	R Koning
	Hôpital Charles Nicolle-CHU	H Eltchaninoff
	Clinique Saint Augustin	O Darremont
	Polyclinique de la Louvière	F Leroy

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Appendix 1 ***Continued***

Country (patients enrolled)	Site	Investigator
	CHU Michallon - Grenoble	B Bertrand
	Clinique Saint- Pierre	G Robert
	CHU Jean Minjoz - Besancon	F Schiele
	Clinique Saint-Gatien	S Chassaing
	Nouvelles Cliniques Nantaises	E Bressollette / P Brunel
	Hôpital Trousseau - CHU	L Quilliet
	Clinique Rhone-Durance	J Brunet
	Hôpital Henri Duffaut	M Pansieri
	AP Lariboisiere	G Sideris / V Stratiev
	AP Henri Mondor	E Teiger
	Hôpital Pontchaillou - Rennes	H Lebreton
	Hôpital La Timone	J-L Bonnet
	Clinique Saint Martin	B Karsenty
	CH Pau	N Delarche
	CHU Clermont Ferrand	J-R Lusson / J Cassagnes
Germany ($n = 1369$)	Klinikum Coburg	J Brachmann
	Universitätsklinikum Lübeck	V Kurowski
	M Luther UnivKlin Kröllwitz	M Buerke
	Med Hochschule Hannover	B Schieffer
	Herz- und Diabeteszentrum	W Scholtz / M Wiemer
	Klinikum der J W Goethe Univ	S Fichtlscherer / V Schächinger
	Klinikum der Univ München Großhadern	C Kupatt / P Boekstegers
	Klinikum der J Gutenberg Univ	S Genth-Zotz
	Universitätsklinikum Freiburg	C Bode
	Universitätsklinikum Heidelberg	N Frey
	Herz Zentrum Bad Krozingen	F-J Neumann
	Charité - Campus B Franklin	B Witzenbichler / K Pels
	Herzzentrum Dresden	R Strasser
	Asklepios Klinik St Georg	K-H Kuck
	Krankenh der Barmh Brüder	K-E Hauptmann
	Univ Klinikum Hamburg-Eppendorf	S Baldus / T Heitzer
	Lukas Krankenhaus	M Haude
	Klinikum Bogenhausen	E Hoffmann
	Klinikum Villingen-Schwenningen	W Jung
	Vivantes Klin im Friedrichshain	S Hoffmann
	Städtisches Klinikum Karlsruhe	C Schmitt
	Vivantes Humboldt-Klinikum	M Dissmann
	Klinikum Nürnberg	M Pauschinger
	Städtische Kliniken Darmstadt	G Werner
	University Magdeburg	R Braun-Delleus
	Marienhof Koblenz	D Burkhardt / M Manz
Greece ($n = 55$)	Onassis Cardiac Surgery Center	V Voudris
	1st IKA	D Sionis
Hong Kong ($n = 59$)	Queen Elizabeth Hospital	M-L Kang-Yin
	Pamela Youde Nethersole Eastern Hospital	T-S Tse
Hungary ($n = 107$)	Semmelweis University	B Merkely
India ($n = 506$)	Jaslok Hospital & Res Centre	A Mehta
	The Heart Care Clinic	K Parikh
	Max Heart and Vascular Institute	V Kumar / P Chandra
	Apollo Hospital, Hyderabad	P Rath
	Ruby Hall Clinic	S Hiremath

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Appendix 1 ***Continued***

Country (patients enrolled)	Site	Investigator
Ireland ($n = 33$)	St James' Hospital	P Crean
	University Hospital Galway	K Daly
Israel ($n = 64$)	Rabin Med Center, Belinson Campus	R Kornowski
	Rambam Medical Center	A Kerner
	Meir MC	M Mosseri
	Barzilay MC	G Jafari
Italy ($n = 123$)	Az Osp S Giovanni di Dio e Ruggi D'Aragona	P Giudice
	Policlinico "A Gemelli"	C Trani
	Ospedale S Maria Nuova	A Manari
	Ospedale S Giovanni - Addolorata	F Prati
	Ospedale Lancisi	A Pangrazi
	S Donato USL 8	L Bolognese
(South) Korea ($n = 254$)	Chonnam University Hospital	M-H Jeong
	Dong-A University Hospital	M-Y Kim
	Seoul Nat Univ Hospital	H-S Kim
	ASAN Medical Center	S-J Park
Latvia ($n = 126$)	P Stradins University Hospital	A Erglis
	Hospital "Gailezers"	A Kalnins
Luxembourg ($n = 1$)	INCCI	D Wagner
Malaysia ($n = 74$)	National Heart Institute (IJN)	R Zambahari
	Sarawak General Hospital	T-K Ong / K Sim
Netherlands ($n = 535$)	Amphia Ziekenh Molengracht	P den Heijer
	VU Medisch Centrum	Y Appelman
	St Antonius Ziekenhuis	M-J Suttorp
	Univ Med Centrum Groningen	B de Smet
	Catharina Ziekenhuis	J Koolen
	Univ Medisch Centrum Utrecht	P Stella
New Zealand ($n = 85$)	Wellington Hospital	S Harding
	Ascot Integrated Hospital	J Warwick / A Maslowski
	Wakefield Hospital	M Abernethy
	Waikato Hospital	G Devlin
Norway ($n = 34$)	Haukeland Universitets Sykehus	S Rotevatn
	Feiringklinniken	Y Myreng
Poland ($n = 86$)	SPSK No1, ACK AMG	D Ciecwierz
	WSS imdr WlBieganskiego	J Peruga
	4 Wojskowy Szpital Kliniczny	K Reczuch
Portugal ($n = 177$)	Hospital Santa Cruz	R Campante Teles
	Hospital Fernando Fonseca	P Farto E Abreu
	Centro Hospital de Coimbra	A Leitão-Marques
	Hospital Garcia Orta	H Pereira
Romania ($n = 54$)	Univ Hospital of Bucharest	D Vinereanu
Saudi Arabia ($n = 262$)	Prince Sultan Cardiac Center	S Alkasab
	King Fahd Medical City	H Mhish / M Al Kurdi
	King Faisal Specialist Hospital	F Al Turki
Singapore ($n = 34$)	National Heart Center	P Wong
	National University Hospital	S-G Teo
Spain ($n = 328$)	Hospital Puerta de Hierro	F-J Goicolea Ruigomez
	Hospital Vírgen de la Arrixaca	M Valdés Chávarri
	Hospital de Son Dureta	A Bethencourt Gonzalez
	Hospital de Meixoeiro	A Iñiguez Romo
	Hospital Infanta Cristina	J López Minguez

Continued

Appendix 1 ***Continued***

Country (patients enrolled)	Site	Investigator
	Hospital Clín Univ V Victoria	J-M Hernández García
	Hospital Juan Ramón Jiménez	J Diaz Fernández
	Hospital Univ V de la Macarena	R Ruiz Salmeron
	Hospital Univ La Princesa	L Martinez Elbal
	Hospital Univ Marqués Valdecilla	J Zueco
	Hospital de San Juan de Alicante	RF López-Palop
	Hospital Virgen de las Nieves	R Melgares
Sweden ($n = 201$)	Centrallasarettet Västerås	E Diderholm / A Kåregren / O Herterich
	Universitetssjukhuset i Lund	G Olivencrona
	Universitetssjukhuset Örebro	O Fröbert
Switzerland ($n = 63$)	Hôpitaux Universitaire Genève	M Roffi / V Verin
	Centre Hospitalier Universitaire Vaudois	G Girod
	Kantonsspital Aarau AG	A Vuilliomenet
Taiwan ($n = 66$)	Chang Gung Memorial Hospital LK	I-C Hsieh
	Chang Gung Mem Hospital KS	C-J Wu
UK ($n = 1658$)	Glenfield Hospital	A Gershlick
	Papworth Hospital	C Densem
	Queen Elizabeth Medical Centre	S Doshi
	Royal Victoria Hospital	G Manoharan
	King's College Hospital	P McCarthy
	James Cook University Hospital	M De Belder
	Cardiothoracic Centre	J Mills
	Manchester Royal Infirmary	F Fath-Ordoubadi
	Southampton General Hospital	I Simpson
	Leeds General Infirmary	J Greenwood
	Cheltenham General Hospital	R Chamberlain-Webber / Z Khan
	New Cross Hospital	J Cotton
	City General Hospital	M Gunning
	Morriston	D Smith
	Royal Bournemouth	S Talwar
	Royal Sussex County Hospital	S Holmberg
	Freeman	I Purcell
	University Hospital of Wales	R Anderson
	Castle Hill Hospital	F Alamgir
	Mayday Hospital	K Beatt
	Basildon Hospital CTC	P Kelly
USA ($n = 178$)	Sharp Chula Vista Med Center	M Moussavian
	Cooper University Hospital	J Aji
	Ocala Regional Medical Center	R Prashad
	Dallas VA Medical Center	A Zankar / S Banerjee
	Bethesda North Hospital	S Lewis
	AnMed Health	B McLaurin
	Emory University Hospital	J Douglas
	Methodist Hospital	S Brener
	Aurora St Lukes	A Gupta
	University Hospital - Augusta	L Walters
	Bridgeport Hospital	M Driesman
	Baptist Hospital - Pensacola FL	R Aycock
	Doctors Hospital at Renaissance	C Mego
	University of Massachusetts	D Fisher
	Maimonides Medical Center	R Frankel
	Washington Hospital Center	L Satler

Appendix 2 Table Univariate predictors of stent thrombosis

Predictor	Definite or probable stent thrombosis (n = 136)		Definite stent thrombosis (n = 82)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Total stent length per patient (mm)	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	0.0006
≥1 stent ≤2.75 mm in diameter	2.27 (1.59, 3.24)	<0.0001	2.19 (1.39, 3.46)	0.0007
Diabetes mellitus	1.99 (1.42, 2.80)	<0.0001	1.80 (1.16, 2.80)	0.009
≥1 overlapping stent	2.03 (1.38, 2.99)	0.0003	2.01 (1.22, 3.31)	0.006
≥1 lesion calcification (moderate/severe)	1.71 (1.22, 2.40)	0.002	1.66 (1.07, 2.57)	0.024
Prior myocardial infarction	1.69 (1.17, 2.43)	0.005	1.52 (0.94, 2.46)	0.09
DAPT	0.45 (0.26, 0.80)	0.006	0.79 (0.40, 1.58)	0.51
Prior stroke	2.31 (1.18, 4.55)	0.015	1.67 (0.61, 4.57)	0.32
≥1 lesion with tortuosity (moderate/severe)	1.53 (1.07, 2.18)	0.018	1.00 (0.61, 1.63)	0.98
Serum creatinine concentration (μmol/L)	1.00 (1.00, 1.01)	0.023	1.00 (1.00, 1.01)	0.35
Smoked cigarette within 90 days	1.50 (1.05, 2.14)	0.027	1.57 (0.99, 2.47)	0.054
Age ≥75 years	1.61 (1.04, 2.48)	0.032	1.35 (0.74, 2.43)	0.33
≥1 lesion with thrombus	1.62 (1.02, 2.58)	0.042	1.23 (0.64, 2.39)	0.54
E-ZES vs C-SES	0.81 (0.58, 1.14)	0.22	0.61 (0.39–0.95)	0.028

DAPT, dual antiplatelet therapy; HR, hazard ratio.

Appendix 3 Patient, lesion, and procedure characteristics at baseline for patients lost to follow-up

Variables for Univariate analysis	E-ZES stent (N = 176 Patients)	C-SES stent (N = 193 Patients)	Difference [95% CI]	*P*-value
Age (Years)	61.1 ± 12.3	59.7 ± 11.2	1.4 [−1.0, 3.8]	0.263
Male	76.7%	76.2%	0.5% [−8.1%, 9.2%]	1.000
Body mass index (kg/m^2)	27.8 ± 4.8	27.3 ± 3.9	0.5 [−0.4, 1.4]	0.232
Diabetes Mellitus	30.1%	31.1%	−1.0% [−10.4%, 8.4%]	0.910
Insulin dependent	6.3%	7.8%	−1.5% [−6.7%, 3.7%]	0.685
Hypertension	62.5%	62.2%	0.3% [−9.6%, 10.2%]	1.000
Hyperlipidemia	60.2%	57.0%	3.2% [−6.8%, 13.3%]	0.597
History of smoking	64.8%	57.5%	7.3% [−2.7%, 17.2%]	0.166
Current smoker	37.5%	34.7%	2.8% [−7.0%, 12.6%]	0.589
Premature CAD in First Degree Relative	25.0%	32.6%	−7.6% [−17.6%, 2.3%]	0.110
Previous myocardial infarction	17.6%	22.8%	−5.2% [−13.4%, 3.0%]	0.245
Previous CABG	4.0%	4.7%	−0.7% [−4.8%, 3.5%]	0.803
Previous PCI	11.4%	13.0%	−1.6% [−8.3%, 5.1%]	0.750
Previous Stroke	4.0%	4.7%	−0.7% [−4.8%, 3.5%]	0.803
Procedure indication				
All (acute) myocardial infarctions	26.1%	28.0%	−1.8% [−10.9%, 7.2%]	0.726
ST-elevation	8.0%	9.3%	−1.4% [−7.1%, 4.4%]	0.713
Non-ST-elevation	18.2%	18.7%	−0.5% [−8.4%, 7.4%]	1.000
Unstable Angina	21.6%	17.6%	4.0% [−4.1%, 12.1%]	0.359
Stable Angina	44.3%	45.1%	−0.8% [−10.9%, 9.4%]	0.917
Silent Ischemia	8.0%	9.3%	−1.4% [−7.1%, 4.4%]	0.713
Left ventricular ejection fraction (%)	59.3 ± 9.8	58.2 ± 7.9	1.0 [−0.8, 2.8]	0.261
Serum Creatinine (μmol/L)	86.9 ± 22.0	81.8 ± 22.1	5.1 [0.6, 9.6]	0.026
Complex patients	54.5%	57.0%	−2.4% [−12.6%, 7.7%]	0.675
Lesion characteristics				

Continued

Appendix 3 ***Continued***

Variables for Univariate analysis	E-ZES stent (N = 176 Patients)	C-SES stent (N = 193 Patients)	Difference [95% CI]	*P*-value
Vessel location (by patient)				
Left anterior descendent	55.2%	62.0%	−6.8% [−16.9%, 3.3%]	0.203
Left circumflex	28.2%	26.0%	2.1% [−7.0%, 11.2%]	0.724
Right coronary artery	31.6%	31.3%	0.4% [−9.2%, 9.9%]	1.000
Left main	0.6%	2.1%	−1.5% [−3.8%, 0.8%]	0.375
Bypass graft	0.6%	0.0%	0.6% [−0.5%, 1.7%]	0.475
In-stent restenosis	1.7%	2.1%	−0.4% [−3.2%, 2.4%]	1.000
Chronic total occlusion	4.0%	6.3%	−2.2% [−6.7%, 2.3%]	0.358
Bifurcation	19.5%	18.8%	0.8% [−7.3%, 8.9%]	0.894
Moderate/severe calcification (vs none or mild)	29.3%	33.9%	−4.5% [−14.1%, 5.0%]	0.370
Tortuosity moderate or severe (vs mild)	25.3%	23.4%	1.8% [−7.0%, 10.7%]	0.715
Presence of thrombus (vs none)	6.9%	12.0%	−5.1% [−11.0%, 0.9%]	0.111
Procedure characteristics				
Number of vessels treated per patient	1.14 ± 0.41	1.18 ± 0.51	−0.03 [−0.13, 0.06]	0.495
Number of lesions treated per patient	1.34 ± 0.76	1.28 ± 0.59	0.06 [−0.08, 0.20]	0.414
Number of stents per patient	1.43 ± 0.84	1.41 ± 0.85	0.02 [−0.16, 0.19]	0.830
Total stent length/ patient (mm)	27.45 ± 17.19	30.54 ± 20.83	−3.08 [−7.03, 0.87]	0.126
Number of stents per lesion	1.08 ± 0.37	1.13 ± 0.62	−0.05 [−0.14, 0.04]	0.291
Total Lesion length per patient	22.71 ± 14.53	24.71 ± 16.03	−2.00 [−5.15, 1.16]	0.215
≥1 stent ≤2.75 mm in diameter (%)	41.4%	44.3%	−2.9% [−13.2%, 7.4%]	0.598
≥1 lesion overlapping stent (%)	9.8%	12.5%	−2.7% [−9.3%, 3.8%]	0.507
Lesions with predilatation	66.7%	66.7%	0.0% [−9.7%, 9.7%]	1.000

C-SES, Cypher sirolimus-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent.

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