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Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial

Kyohei Yamaji[1†], Lorenz Räber[1†], Thomas Zanchin[1], Ernest Spitzer[1], Christian Zanchin[1], Thomas Pilgrim[1], Stefan Stortecky[1], Aris Moschovitis[1], Michael Billinger[1], Christa Schönenberger[1], Franz Eberli[2], Peter Jüni[3], Thomas F. Lüscher[4], Dik Heg[5], and Stephan Windecker[1*]

[1]Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland; [2]Department of Cardiology, Triemlispital, Zurich, Switzerland; [3]Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Department of Medicine and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada; [4]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; and [5]Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Bern, Switzerland

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Aims Compared with bare metal stents, first-generation drug-eluting stents (DES) are associated with an increased risk of late restenosis and stent thrombosis (ST). Whether this risk continues or attenuates during long-term follow-up remains unknown.

Methods and results We extended the follow-up of 1012 patients [sirolimus-eluting stent (SES): $N = 503$ and paclitaxel-eluting stent (PES): $N = 509$] included in the all-comers, randomized Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial to 10 years. Follow-up was complete in 895 patients (88.4%) at 10 years. At 1, 5, and 10 years of follow-up, rates of ischaemia-driven target lesion revascularization (ID-TLR) were 8.1%, 14.6% and 17.7%, respectively, and rates of ST were 1.9%, 4.5% and 5.6%, respectively. The annual risks of ID-TLR and definite ST were significantly higher between 1 and 5 years as compared with the 5- to 10-year period [ID-TLR: 1.8% vs. 0.7%/year, hazard ratio (HR) 0.36, 95% confidence intervals (95% CI) 0.21–0.62, $P < 0.001$; definite ST: 0.67% vs. 0.23%/year, HR 0.31, 95% CI 0.13–0.75, $P = 0.01$]. The attenuation of the risk of ID-TLR and ST beyond 5 years was independent of age. Major adverse events (cardiac death, myocardial infarction, and ID-TLR) occurred in 33.7% of SES- and 33.8% of PES-treated patients ($P = 0.72$).

Conclusions During long-term follow-up through 10 years, the annual risks of ID-TLR and definite ST significantly decreased beyond 5 years after first-generation DES implantation. These findings may have important implications for secondary prevention after percutaneous coronary intervention with first-generation DES including long-term antiplatelet therapy.

Clinical Trial Registration http://www.clinicaltrials.gov. Unique identifier: NCT00297661.

*Corresponding author. Tel: +41 31 632 44 97, Fax: +41 31 632 47 70, Email: stephan.windecker@insel.ch

†The first two authors contributed equally to the study.

Keywords Coronary artery disease • Drug-eluting stent • Restenosis • Stent • Stent thrombosis

Introduction

Compared with bare metal stents (BMS), first-generation drug-eluting stents (DES) remarkably reduce the risk of restenosis within 1 year of stent implantation. However, this benefit comes at the expense of more frequent late adverse events including target lesion revascularization (TLR) and very late stent thrombosis (ST) throughout 5 years of follow-up.[1–3] It remains largely unknown whether the risk of device-related late adverse events continues steadily or attenuates during long-term follow-up beyond 5 years.

Postmortem studies and intracoronary imaging investigations suggest a causal relationship between late adverse events and pathological evidence of chronic inflammatory reactions resulting in delayed healing and neoatherosclerosis.[4–8] New-generation DES with design iterations such as the use of more biocompatible and bioresorbable polymers, novel antiproliferative drugs and reduction in strut thickness, have improved safety and efficacy during long-term follow-up throughout 5 years compared with first-generation DES.[9–13] Direct comparisons between first- and new-generation DES beyond 5 years are not available to date. Fully bioresorbable drug-eluting vascular scaffolds were introduced with the intent to further improve upon long-term safety and efficacy.[14,15] As the potential benefits of bioresorbable scaffolds may only occur during longer-term follow-up, i.e. after full device absorption,[16] knowledge on device-related outcomes with metallic DES beyond 5 years may serve as an important benchmark. Moreover, secondary preventive measures including considerations on long-term antiplatelet therapy are governed by not only the underlying disease but also the implanted device type.

In order to elucidate the very long-term outcomes after first-generation DES, we extended the clinical follow-up of patients included in the all-comers, randomized Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial to 10 years.[17,18]

Methods

Patient population

The design and methods of this randomized, assessor-blind trial have been reported previously.[17] In brief, 1012 patients with $\geq$1 lesion in a vessel with a reference diameter between 2.25 and 4.00 mm were randomly assigned to treatment with sirolimus-eluting stent (SES) ($N = 503$) or paclitaxel-eluting stent (PES) ($N = 509$) between April 2003 and May 2004. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital and University Hospital Zurich in Switzerland. All patients provided written informed consent.

Data collection and definitions

The results of clinical and angiographic follow-up at 9 months and 5 years have been reported previously.[17,18] For the current analysis, clinical follow-up was performed at a single timepoint at 10 years. Adverse events, angina status, and cardiovascular medication intake were assessed. Methods to obtain follow-up information (letter or phone call), event documentation, event definitions, and adjudication did not differ during the present 10-year follow-up and previous annual follow-up assessments during the first 5 years. Events within 5 years after the index procedure, which were not reported at the 5-year survey but collected during the extended 10-year survey, were also included in the present analysis (see Supplementary material online, *Supplementary Results*). A clinical events committee unaware of patients' assignments adjudicated all clinical endpoints.

The primary study endpoint was a composite of major adverse cardiac events (MACE), which included cardiac death, myocardial infarction (MI), and ischaemia-driven target lesion revascularization (ID-TLR). Secondary endpoints included all components of the primary endpoint and definite ST.[19] Definitions of study endpoints are described in the Supplementary material online.

Statistical analysis

Categorical variables were compared with Fisher's exact test. Continuous variables were expressed as mean value $\pm$ standard deviation and compared with Student's *t*-test. Cumulative incidences and their 95% confidence intervals (95% CI) were estimated by the Kaplan–Meier method. All events beyond 10 years after the index procedure were censored. Cumulative incidences of events accounting for a competing risk with all-cause death were also calculated using multi-state models in which events and all-cause death were the terminal states.

Statistical analyses were performed with the use of R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). All the statistical analyses were two-tailed. *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the entire cohort have been reported previously and did not differ between stent groups (*Tables 1* and *2*).[17] A comparison of baseline and procedural characteristics according to age is provided in the Supplementary material online, *Tables S1* and *S2*. Cardiovascular medication status in patients alive at 5 and 10 years is presented in *Table 3*. Dual antiplatelet therapy was prescribed in 16% of patients at 5 years and 11% at 10 years. At 10 years, statins were administered in 65% of patients, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers in 51% of patients.

Clinical outcomes

Clinical follow-up information was obtained in 895 (88.4%) patients at 10 years without differences among patients allocated to SES ($N = 448$, 88.0%) or PES ($N = 447$, 87.8%, $P = 0.56$) and between elder ($N = 442$, 87.7%) and younger patients ($N = 453$, 89.9%, $P = 0.49$), respectively. Cumulative incidences of cardiovascular events and

Table 1 Baseline clinical characteristics

Variables	N = 1012
Patient age, years	62.3 ± 11.1
Male sex[a]	781 (77.2%)
Diabetes mellitus[a]	201 (19.9%)
Hypertension[a]	622 (61.5%)
Hyperlipidaemia[a]	597 (59.0%)
Current smoking[a]	365 (36.1%)
Previous myocardial infarction[a]	297 (29.3%)
Clinical indication[a]	
Stable angina pectoris	492 (48.6%)
Unstable angina	58 (5.7%)
Non-ST-segment elevation MI	235 (23.2%)
ST-segment elevation MI	227 (22.4%)
Time from onset of symptoms of MI to percutaneous coronary intervention (h)[a]	
<24	372 (36.8%)
24–72	68 (6.7%)
>72	22 (2.2%)
Extent of coronary artery disease[a]	
Single-vessel disease	403 (39.8%)
Two-vessel disease	346 (34.2%)
Three-vessel disease	218 (21.5%)
Left main disease	45 (4.4%)

MI, myocardial infarction.
[a]Variables included in the multivariable analysis comparing younger and older patients.

Table 2 Baseline lesion characteristics

Variables	N =1409
Target-lesion coronary artery	
Left main	22 (1.6%)
Left anterior descending	647 (45.9%)
Left circumflex	278 (19.7%)
Right	438 (31.1%)
Bypass graft	24 (1.7%)
ACC-AHA lesion class	
A	285 (20.2%)
B1	607 (43.1%)
B2	332 (23.6%)
C	185 (13.1%)
Total occlusion	262 (18.6%)
<3 months	237 (16.8%)
≥3 months	25 (1.8%)
Thrombus present	318 (22.6%)
Bifurcation lesion	116 (8.2%)
Ostial lesion	106 (7.5%)
Calcification	
None or mild	927 (65.8%)
Moderate	432 (30.7%)
Severe	50 (3.5%)

Table 3 Medication status at 5 and 10 years

	5 Years (N = 907)	10 Years (N = 794)
Dual antiplatelet therapy	141 (15.5%)	88 (11.1%)
Aspirin	749 (82.6%)	520 (65.5%)
Thienopyridine	195 (21.5%)	141 (17.8%)
Oral anticoagulants	84 (9.3%)	79 (9.9%)
Statins	769 (84.8%)	518 (65.2%)
ACE-I or ARB	624 (68.8%)	402 (50.6%)
β-Blockers	570 (62.8%)	384 (48.4%)
Calcium channel blockers	146 (16.1%)	130 (16.4%)
Insulin	59 (6.5%)	32 (4.0%)
Oral antidiabetic	125 (13.8%)	115 (14.5%)

Data on medication status were available in 859 patients (95%) at 5 years and in 635 patients (80%) at 10 years.
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

those taking the competing risk with all-cause death into account are summarized in *Table 4* and *Figure 1*.

The primary endpoint of MACE occurred in 207 patients (20.8%) at 5 years and in 313 patients (33.8%) at 10 years. The cumulative incidence of cardiac death amounted to 5.8% at 5 years and increased to 15.4% at 10 years. Of 135 patients who suffered from cardiac death throughout 10 years, only 19 patients (14.1%) had undergone ID-TLR prior to death, whereas the remainder (85.9%) did not (see Supplementary material online, *Figure S1*).

Ischaemia-driven target lesion revascularization occurred in 81 patients (8.1%) at 1 year, in 143 patients (14.6%) at 5 years, and in 166 patients (17.7%) at 10 years. Beyond 1 year, the annual risk of ID-TLR was significantly higher for the period between 1 and 5 years (1.8%/year, 95% CI 1.3–2.2%/year) as compared with the period between 5 and 10 years [0.7%/year, 95% CI 0.4–1.0%/year; hazard ratio (HR) 0.36, 95% CI 0.21–0.62, $P < 0.001$]. The cumulative incidences of definite ST were 1.9% at 1 year, 4.5% at 5 years, and 5.6% at 10 years. ST occurred following a previous TLR (secondary ST) in only 7 of 52 events. The annual risk of ST beyond 1 year was significantly higher for the period between 1 and 5 years (0.67%/year, 95% CI 0.41–0.93%/year) as compared with the period between 5 and 10 years (0.23%/year, 95% CI 0.069–0.38%/year; HR 0.31, 95% CI 0.13–0.75, $P = 0.01$).

The cumulative incidence of non-ID-TLR increased between 4 and 6 years, suggesting study mandated follow-up angiography inflated the incidence of non-ID-TLR (see Supplementary material online, *Figure S2*). Nonetheless, patients with vs. without follow-up angiography showed similar and low incidences of ID-TLR (HR 2.30, 95% CI 0.83–6.40, $P = 0.11$), and ST (HR 0.34, 95% CI 0.07–1.76, $P = 0.20$) beyond the timepoint of the 5-year angiography (see Supplementary material online, *Table S3*).

We performed a multivariable analysis to identify independent predictors during different landmarks and found age, previous MI, saphenous vein graft lesions, and left main lesions as independent predictors of MACE throughout 10-year follow-up.

Table 4 Cumulative incidences of clinical events

	1 Year	5 Years	10 Years	Between1 and 5 years	Between5 and 10 years	1–5 vs. 5–10 Years	
						HR (95% CI)	*P* value
Death	26 (2.6%)	104 (10.4%)	226 (24.2%)	78 (8.0%)	122 (15.4%)	1.45 (1.07-1.97)	0.02
Cardiac death	18 (1.8%/1.8%)	57 (5.8%/5.7%)	135 (15.4%/14.5%)	39 (4.1%/4.0%)	78 (10.2%/9.9%)	1.84 (1.23-2.77)	0.003
After ID-TLR	2 (0.2%/0.2%)	11 (1.2%/1.1%)	19 (2.2%/2.0%)	9 (1.0%/0.9%)	8 (1.1%/1.0%)	0.84 (0.30-2.36)	0.74
Without prior ID-TLR	16 (1.6%/1.6%)	46 (4.7%/4.6%)	116 (13.4%/12.5%)	30 (3.2%/3.1%)	70 (9.2%/8.8%)	2.14 (1.37-3.37)	<0.001
MI	36 (3.6%/3.6%)	68 (7.0%/6.7%)	88 (9.7%/9.0%)	32 (3.5%/3.4%)	20 (2.9%/2.7%)	0.65 (0.36-1.18)	0.16
Q wave MI	13 (1.3%/1.3%)	24 (2.5%/2.4%)	28 (3.0%/2.8%)	11 (1.2%/1.1%)	4 (0.6%/0.5%)	0.23 (0.05-1.04)	0.06
Non-Q wave MI	23 (2.3%/2.3%)	47 (4.8%/4.7%)	64 (7.1%/6.6%)	24 (2.6%/2.5%)	17 (2.4%/2.3%)	0.81 (0.42-1.54)	0.52
Death or MI	60 (5.9%)	162 (16.1%)	296 (31.3%)	102 (10.8%)	134 (18.1%)	1.28 (0.98-1.69)	0.07
Cardiac death or MI	52 (5.2%/5.1%)	117 (11.8%/11.6%)	211 (23.4%/22.3%)	65 (7.0%/6.9%)	94 (13.1%/12.7%)	1.42 (1.01-1.98)	0.04
Definite stent thrombosis	19 (1.9%/1.9%)	44 (4.5%/4.4%)	52 (5.6%/5.3%)	25 (2.7%/2.6%)	8 (1.1%/1.1%)	0.31 (0.13-0.75)	0.01
ID-TLR	81 (8.1%/8.0%)	143 (14.6%/14.2%)	166 (17.7%/16.8%)	62 (7.1%/6.9%)	23 (3.6%/3.4%)	0.36 (0.21-0.62)	<0.001
Any TLR	82 (8.2%/8.1%)	166 (17.1%/16.5%)	195 (21.0%/19.7%)	84 (9.7%/9.4%)	29 (4.6%/4.3%)	0.39 (0.25-0.61)[a]	<0.001
ID-TVR	93 (9.3%/9.2%)	175 (17.9%/17.3%)	203 (21.7%/20.5%)	82 (9.5%/9.2%)	28 (4.6%/4.3%)	0.33 (0.20-0.54)	<0.001
Any TVR	95 (9.5%/9.4%)	209 (21.6%/20.8%)	245 (26.4%/24.8%)	114 (13.4%/12.9%)	36 (6.1%/5.7%)	0.37 (0.25-0.55)[a]	<0.001
MACE	111 (11.0%/11.0%)	207 (20.8%/20.5%)	313 (33.8%/32.5%)	96 (11.0%/10.8%)	106 (16.4%/15.9%)	1.08 (0.80-1.46)	0.61
TVF	120 (11.9%/11.9%)	232 (23.3%/23.0%)	339 (36.5%/35.2%)	112 (13.0%/12.8%)	107 (17.1%/16.6%)	0.96 (0.72-1.28)	0.78

Data were presented as number of patients with event (cumulative incidence) or number of patients with event (cumulative incidence/cumulative incidence estimator accounting for competing risk with all-cause death).
ID-TLR, ischaemia-driven target lesion revascularization; MI, myocardial infarction; ID-TVR, ischaemia-driven target vessel revascularization; MACE, major adverse cardiac events; TVF, target vessel failure.
[a]Proportional assumption was not fulfilled according to the scaled Schoenfeld residuals plots.

Comparison between SES and PES

The difference in MACE was attenuated beyond 1 year (20.1% vs. 21.5% at 5 years and 33.7% vs. 33.8% at 10 years; $P = 0.72$ for the entire follow-up and $P = 0.62$ between 5 and 10 years, respectively) (*Figure 2* and *Table 5*). The risks of cardiac death, MI, ID-TLR, and ST were similar between SES and PES ($P = 0.30$, 0.55, 0.28, and 0.97 for the entire follow-up and $P = 0.22$, 0.39, 0.81, and 0.50 between 5 and 10 years, respectively).

Elder vs. younger patients

Elder patients had a higher risk of MACE as compared with younger patients at 10 years (41.1% vs. 27.0%, $P < 0.001$; adjusted HR 1.48, 95% CI 1.15–1.89, $P = 0.002$), largely driven by a higher rate of cardiac mortality (25.1% vs. 6.5%, $P < 0.001$; adjusted HR 3.45, 95% CI 2.24–5.31, $P < 0.001$) (*Figure 3*; see Supplementary material online, *Table S5*). Conversely, the adjusted risks of ID-TLR (adjusted HR 0.94, 95% CI 0.67–1.31, $P = 0.72$), and ST (adjusted HR 0.73, 95% CI 0.39–1.35, $P = 0.31$) were similar between elder and younger patients, respectively. It is noteworthy that the annual risks of ID-TLR and ST between 5 and 10 years compared with the earlier period between 1 and 5 years were similarly attenuated in young and elderly patients (*Figure 4*).

Discussion

The extension of the SIRTAX study clinical follow-up to 10 years has the following salient findings:

(1) The annual risk of ID-TLR between 5 and 10 years after first-generation DES implantation decreases by more than 50% (0.7%/year vs. 1.8%/year, $P < 0.001$) as compared with the period between 1 and 5 years.
(2) Similarly, the annual risk of very late ST is substantially reduced during the extended follow-up time period (5–10 years: 0.23%/year vs. 1–5 years: 0.67%/year, $P = 0.01$).
(3) The primary endpoint MACE occurred with similar frequency among patients allocated to SES and PES throughout the 10-year follow-up. Similarly, no differences were observed in terms of the key secondary endpoints of cardiac death, MI, ID-TLR, and ST.
(4) Although elder patients experienced a higher cardiac mortality as compared with younger patients, the risk of ID-TLR, MI, and ST was similar. Of note, the attenuation in the risk of ID-TLR and ST occurring after 5 years was independent of age.

Efficacy of first-generation DES throughout 10 years of follow-up

We and others previously reported on the steady risk of restenosis beyond the timepoint of 1 year with angiographic evidence of a continued increase of the late lumen loss throughout 5 years.[18,20] The risk of late restenosis has been attributed at least in part to a delay in healing and the phenomenon of instent-neoatherosclerosis as attested by pathology and intracoronary imaging studies.[4–8,21] To which extent these pathomechanisms may perpetuate to translate into very late occurring ID-TLR (i.e. beyond 5 years) remains largely unknown to date. An optical coherence tomography study in 88 SIRTAX patients at 5 years indicated that arterial healing was nearly complete with few stent struts remaining uncovered (1.3%) or

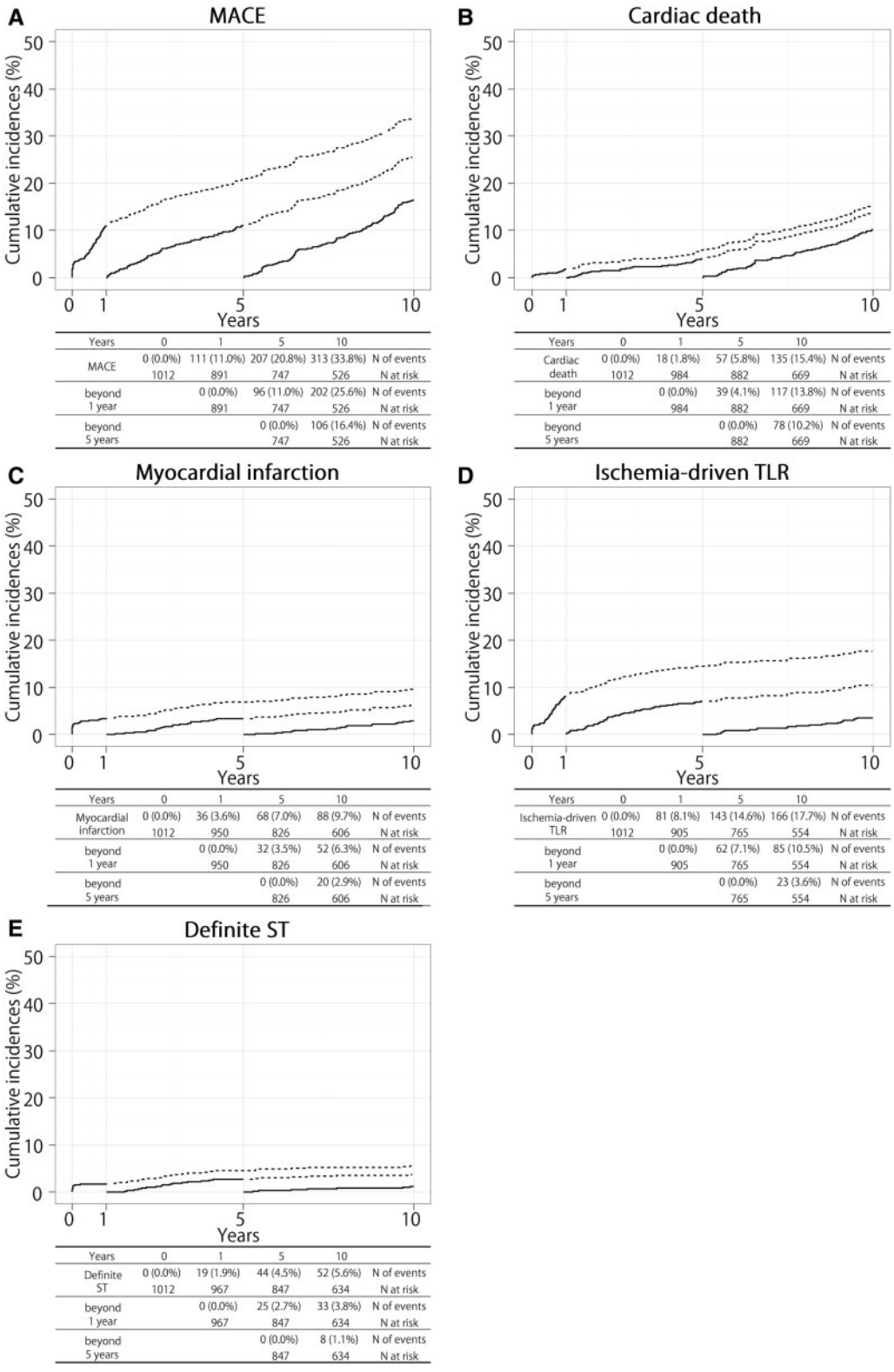

Figure 1 Cumulative incidence curves throughout 10 years and landmark analyses beyond 1 year and 5 years for (*A*) major adverse cardiac events, (*B*) cardiac death, (*C*) myocardial infarction, (*D*) ischaemia-driven target lesion revascularization, and (*E*) definite stent thrombosis. MACE, major adverse cardiac events; TLR, target lesion revascularization; ST, stent thrombosis.

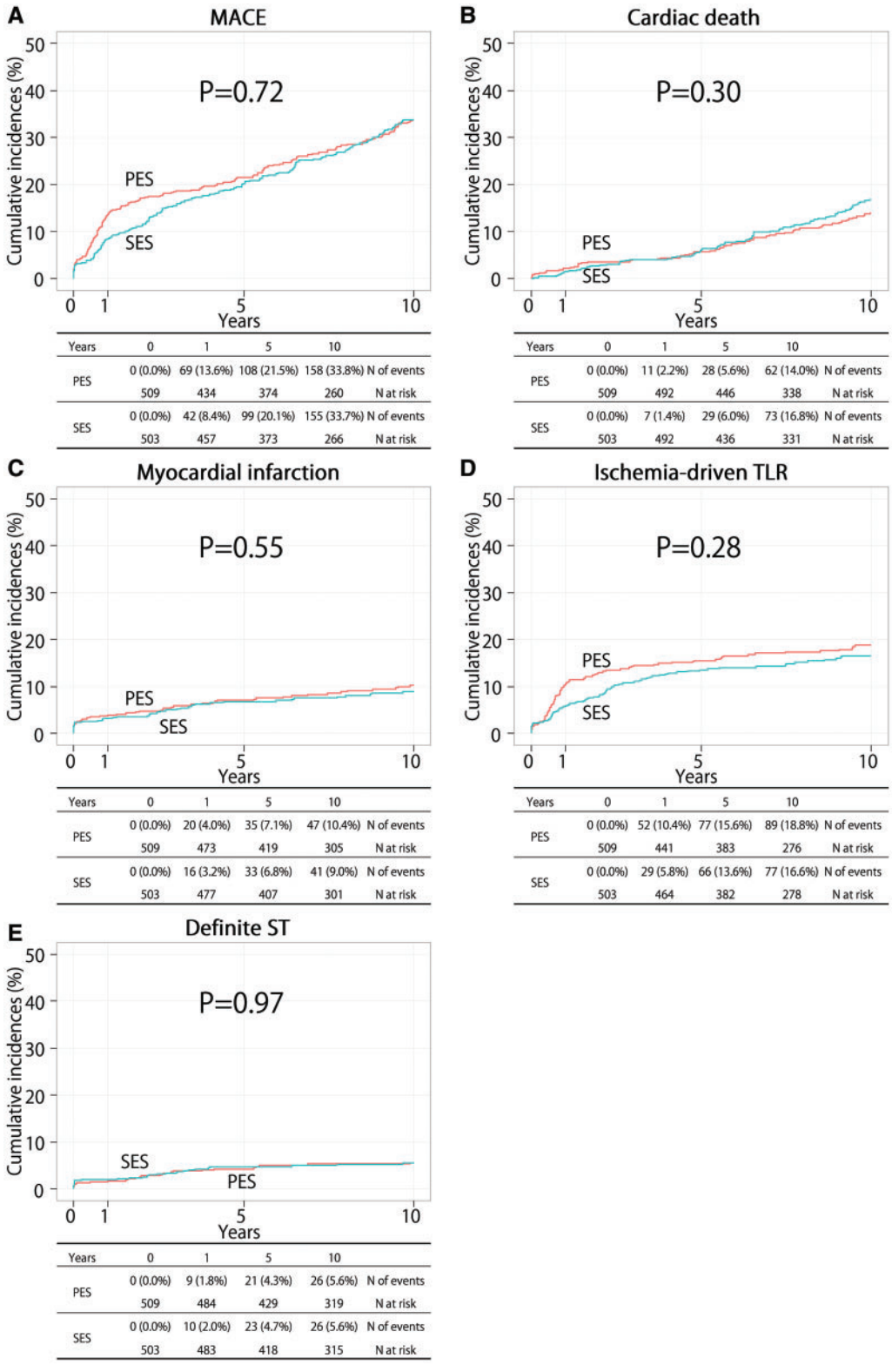

Figure 2 Cumulative incidence curves in patients allocated to sirolimus-eluting stents and paclitaxel-eluting stents for (*A*) major adverse cardiac events, (*B*) cardiac death, (*C*) myocardial infarction, (*D*) ischaemia-driven target lesion revascularization, and (*E*) definite stent thrombosis. MACE, major adverse cardiac events; TLR, target lesion revascularization; ST, stent thrombosis.

Table 5 Cumulative incidences of clinical events at 10 years in patients with sirolimus-eluting stents and those with paclitaxel-eluting stents

	SES	PES	*P* value
Death	117 (25.0%)	109 (23.4%)	0.52
Cardiac death	73 (16.8%/15.8%)	62 (14.0%/13.3%)	0.30
After ID-TLR	8 (1.9%/1.7%)	11 (2.6%/2.3%)	0.51
Without prior ID-TLR	65 (15.2%/14.1%)	51 (11.7%/10.9%)	0.17
MI	41 (9.0%/8.4%)	47 (10.4%/9.7%)	0.55
Q wave MI	17 (3.7%/3.5%)	11 (2.3%/2.2%)	0.24
Non-Q wave MI	27 (6.0%/5.5%)	37 (8.3%/7.7%)	0.22
Death or MI	153 (32.2%)	143 (30.4%)	0.50
Cardiac death or MI	110 (24.5%/23.2%)	101 (22.2%/21.3%)	0.49
Definite stent thrombosis	26 (5.6%/5.3%)	26 (5.6%/5.3%)	0.97
ID-TLR	77 (16.6%/15.6%)	89 (18.8%/17.9%)	0.28
Any TLR	88 (19.2%/17.9%)	107 (22.8%/21.6%)	0.13
ID-TVR	90 (19.3%/18.2%)	113 (24.1%/22.8%)	0.07
Any TVR	105 (22.7%/21.3%)	140 (30.0%/28.4%)	0.01
MACE	155(33.7%/32.3%)	158 (33.8%/32.8%)	0.72
TVF	164 (35.6%/34.1%)	175 (37.4%/36.2%)	0.36

Data were presented as number of patients with event (cumulative incidence) or number of patients with event (cumulative incidence/cumulative incidence estimator accounting for competing risk with all-cause death).
Abbreviations are same as in *Table 4*.

malapposed (1.0%), yet neoatherosclerotic plaques (i.e. atherosclerotic lesions extending for more than 1 mm inside the neointimal tissue) were not an infrequent finding (15.9% of lesions) suggesting a hypothetical source for subsequent events.[22]

The extended follow-up throughout 10 years suggests that ID-TLR still occurs but at a much lower rate of approximately 0.7%/year, corresponding to a 64% (95% CI 38–79%) reduction when compared with the time period 1–5 years, a finding that was notably independent of age. Palhais *et al.*[23] reported 10-year follow-up outcomes of 200 SES-treated patients, and observed a continuous risk of TLR prior and beyond 5 years (3.5% at 5 years and 8.0% at 10 years). More recently, Miura *et al.*[24] reported that TLR continued to occur beyond 5 years up to 10 years in 342 patients who received SES (18.8% and 9.7% at 5 years and 31.1% and 20.0% at 10 years), without attenuation in the frequency of TLR. Our study confirmed those single-centre observations of the ongoing risk of TLR beyond 5 years, yet at a much lower rate beyond 5 years. A potential explanation may be related to the high long-term compliance with anti-atherosclerotic drugs such as statin, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers that may not only aid in the prevention of *de novo* lesions but also limit the occurrence of clinically significant neoatherosclerosis, one of the most likely reasons for late occurring events.

At variance with our observations following first-generation DES implantation, clinical long-term outcomes after BMS implantation have been associated with a continuous risk of TLR without any attenuation.[25,26] We may hypothesize that the accelerated incidence of TLR between 1 and 5 years after the DES implantation was reduced to a level that is rather comparable with BMS beyond 5 years of follow-up.

Several considerations should be taken into account for the observed attenuation in the annual risk of ID-TLR beyond 5 years. First, the impact of age requires careful consideration when interpreting the results. Older patients may be less symptomatic and are therefore less likely to undergo late revascularization. Furthermore, the higher death rate may potentially camouflage ongoing but clinically inapparent very late stent failures. For these reasons, we investigated the effect of age on the ID-TLR frequency between 1–5 and 5–10 years. It is noteworthy that the cumulative incidences of ID-TLR and the observed reduction in the annual risk of ID-TLR between 1–5 and 5–10 years were consistent in the young and elderly patient group, suggesting that the late attenuation of ID-TLR beyond 5 years is a biological phenomenon irrespective of age. Secondly, we clarified the potential impact of the angiographic follow-up performed in a subset of study patients at 5 years and found no interaction.

Safety of early-generation DES throughout 10 years of follow-up

The annual risk of definite very late ST after the implantation of first-generation DES within 5 years has been reported in the range of 0.1–0.8%/year in several observational studies and randomized trials.[1–3,9–12] In our study, the annual risk of definite ST beyond 1 year was significantly attenuated beyond 5 years. The attenuation of the annual risk of ST was observed, despite a relatively low intake of dual antiplatelet therapy among 11.1% of patients at 10 years. Although this study was not powered to evaluate the risk of ST, the observations of a significant attenuation of very late occurring device-related events may have implications for secondary prevention including long-term antiplatelet and lipid-control therapies.

Recently, we and others investigated the mechanisms for very late ST and identified malapposition, neoatherosclerosis, uncovered stent struts, and stent underexpansion as the leading mechanisms involved.[7,27] Although persistent malapposition, uncovered stent struts and underexpansion represent obstacles that carry a continued risk for thrombus formation from the onset after stent implantation, late acquired malapposition due to positive remodelling and neoatherosclerosis may develop only late and represent a potential nidus for thrombotic events during long-term follow-up. Malapposition and neoatherosclerotic plaques were infrequently observed at 5 years in event-free patients in the SIRTAX LATE OCT substudy,[22] and subsequent ST only occurred in those patients with an extreme degree of malapposition and evidence of positive remodelling and in none with neoatherosclerotic plaques.

The underlying mechanisms of late attenuation in the risks of ID-TLR and ST beyond 5 years are unknown and difficult to unravel. Although postmortem study suggests that the prevalence of neoatherosclerosis continues to increase beyond 3 years after first-generation DES implantation,[8] lower risks of late clinical events beyond 5 years in our study imply the stabilization of chronic inflammatory reactions, delayed healing, and potentially also neoatherosclerosis beyond 5 years. Longer-term pathological analyses would

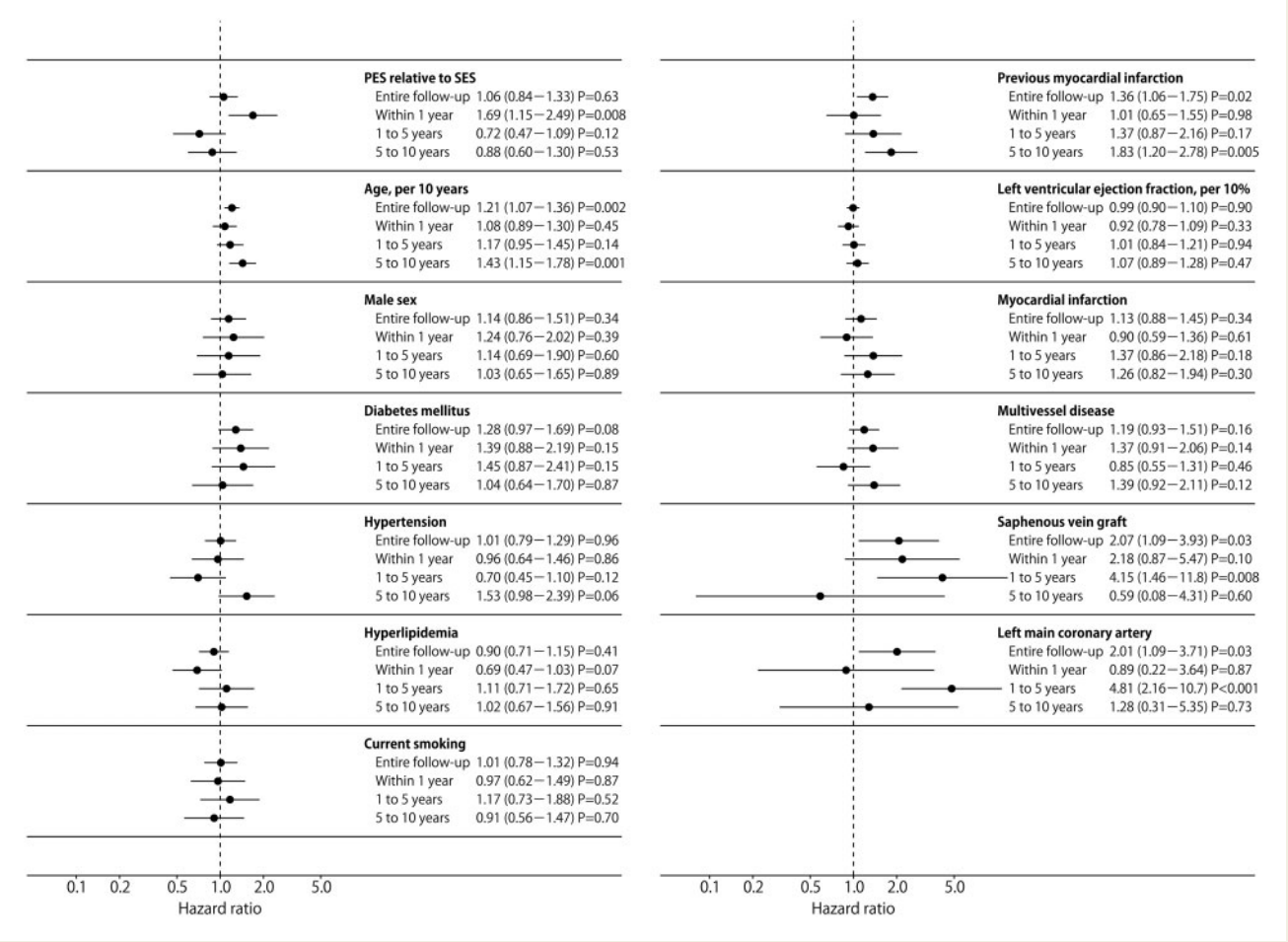

Figure 3 Hazard ratios for predictors of major adverse cardiac events during entire follow-up, within 1, 1–5, and 5–10 years.

provide relevant insights and are required to confirm our observations on a histological level.

New-generation DES have reduced the risk of late adverse events both in terms of TLR and ST as compared with first-generation DES throughout 5 years of follow-up.[9,10] No data are currently available with a further extension of the clinical follow-up to investigate whether the attenuation of events following early-generation DES may apply to newer generation DES platforms as well. Fully bioresorbable vascular scaffolds have been introduced into clinical practice to minimize the risk associated with the presence of a permanent metallic prosthesis.[14,15] Our observation of an attenuation of stent-related events beyond 5 years to an annual risk of <1%/year for ID-TLR and <0.3%/year for ST may serve as a relevant benchmark for the comparison with fully bioabsorbable scaffold platforms.

Study limitations

This study has several important limitations. First, the extended follow-up to 10 years was not pre-specified. The follow-up rate of 88.4% at 10 years was relatively high but not complete. There was no significant difference in baseline characteristics between patients with follow-up vs. those without, except for smoking status. We therefore suggest that no relevant bias was introduced by patients lost to follow-up (see Supplementary material online, *Table S6*). Second, in variance to the annual follow-up between 1 and 5 years, only one follow-up was performed at 10 years. However, cardiac events leading to hospitalization at Inselspital were continuously collected throughout the study period and complemented by a search of the hospital database at both institutions. Third, although we included patients into an all-comer trial, high-risk patients may have been excluded from our randomized controlled trial during the enrolment period of the early-DES era (2003–2004). Fourth, we did not collect data on symptom status and/or results of non-invasive stress tests. Therefore, we were unable to capture clinically relevant symptomatic restenosis, although the annual risk of ID-TLR was attenuated beyond 5 years. Fifth, among 78 cardiac deaths observed between 5 and 10 years, 36 deaths (46.2%) were regarded as unclear and thus categorized as cardiac as detail information on the cause of death was not available. Clinical information on death could hardly be obtained at the later follow-up and elderly patients may less likely to undergo surveys for reasons of death. Therefore, the incidence of cardiac death

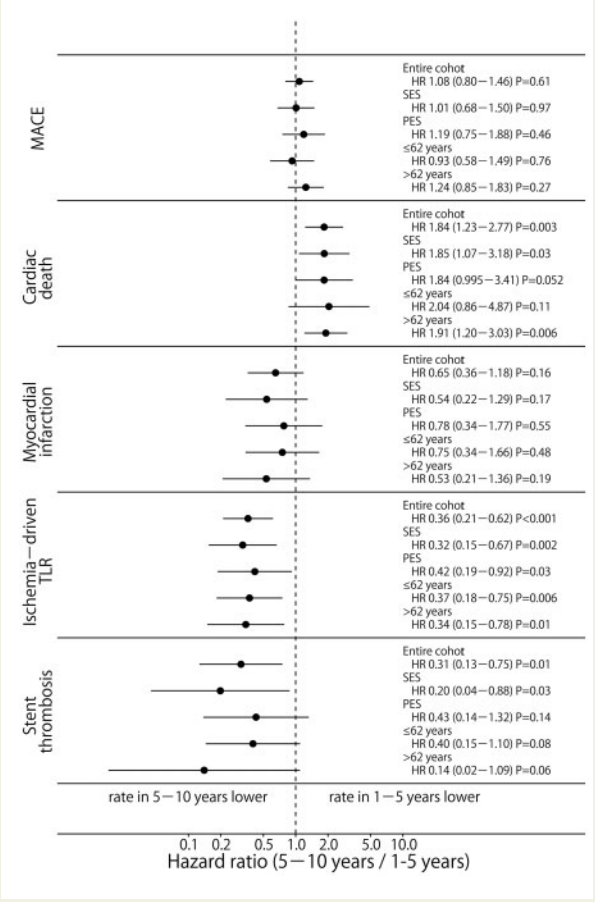

Figure 4 Hazard ratios for clinical endpoints between 5 and 10 years relative to the time period between 1 and 5 years in the entire cohort, in patients ≤62 years vs. >62 years, and in patients with sirolimus-eluting vs. paclitaxel-eluting stents. MACE, major adverse cardiac events; TLR, target lesion revascularization; HR, hazard ratio.

might be overestimated especially at the long-term follow-up. Sixth, as death without detail information was regarded as cardiac death by definition, the incidence of cardiac death might be overestimated especially at the long-term follow-up. Finally, the primary objective of this study was to compare SES and PES, both of which are no longer available.

Conclusions

During long-term follow-up through 10 years, the annual risks of ID-TLR and definite ST significantly decreased beyond 5 years after first-generation DES implantation. These findings may have important implications for secondary prevention after percutaneous coronary intervention with first-generation DES including long-term antiplatelet therapy.

Author's contribution

K.Y. and L.R. drafted the manuscript; S.W. and all other authors made critical revision of the manuscript for key intellectual content; all authors acquired the data; L.R. and S.W. conceived and designed the research; K.Y. and D.H. performed statistical analysis.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: S.W. reports to have received research contracts to the institution from Abbott, Biotronik, Boston Scientific, Medtronic, Edwards, and St. Jude. P.J. has received research grants to the institution from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, and serves as unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St. Jude Medical, and The Medicines Company. L.R. has received grants to the institution from St. Jude Medical. The other authors report no conflict with regards to the content of this manuscript.

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