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10-Year Clinical Outcome After Randomization to Treatment by Sirolimus- or Paclitaxel-Eluting Coronary Stents

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ABSTRACT

BACKGROUND First-generation drug-eluting coronary stents (DES) were introduced in 2003 to 2004, and their use resulted in a considerable reduction in the development of in-stent restenosis at the cost of an increased risk of late stent thromboses.

OBJECTIVES This study followed clinical outcomes of patients included in a large randomized trial for 10 years to enable detection of late changes in annual event rates that could necessitate medical attention.

METHODS A total of 2,098 unselected all-comer patients (50% with acute coronary syndrome) were randomly assigned to have a first-generation DES implanted. This study recorded the occurrence of a major adverse cardiac event (MACE) assessed as the composite of cardiac death, myocardial infarction, and target vessel revascularization. Stent thromboses were also assessed.

RESULTS Of the 2,098 unselected patients, 73.1% were still alive after 10 years. During the follow-up period, MACE occurred in 346 (32.5%) in the group receiving a sirolimus-eluting stent and in 342 (33.1%) in the group receiving a paclitaxel-eluting stent (hazard ratio: 0.96; 95% confidence interval: 0.83 to 1.11; $p = 0.60$), with a steady annual rate of 2.6% after the first year. Definite, probable, and possible stent thrombosis appeared in 279 patients (13.3%), with no difference between stent types and with a steady annual rate of 1.3% after the first year.

CONCLUSIONS Among the surviving patients, the long-term annual MACE rate and the stent thrombosis rate appeared constant for both stent types, with no apparent late changes. Although there is no need for extraordinary medical attention for these patients, the absence of declines in annual event rates calls for continuous surveillance. (Danish Organization on Randomized Trials With Clinical Outcome II [SORT OUT II]; NCT00388934) (J Am Coll Cardiol 2017;69:616–24) © 2017 by the American College of Cardiology Foundation.

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The development of coronary drug-eluting stents (DES) in 2003 to 2004 resulted in a considerable reduction in the need for repeat revascularization (1–4), and millions of patients have since been treated with first-generation DES to relieve angina pectoris or improve their prognosis. It was later recognized that inflammation induced by the polymer or even by the stent material itself could evolve very late and cause stent thrombosis, myocardial infarction (MI), restenosis, target lesion revascularization (TLR), and even sudden death. Subsequent stent types with thinner struts, newer polymers, and different drugs with improved release kinetics have surpassed the first-generation DES with regard to both efficacy and safety. However, no guidelines have been provided on the handling of the large number of patients carrying the first-generation DES with regard to clinical control or modification of their antiplatelet treatment regimen in an attempt to reduce the risk of late-occurring adverse events.

SEE PAGE 625

The SORT OUT II (Danish Organization on Randomized Trials With Clinical Outcome II) study was designed to reflect everyday clinical practice by inclusion of consecutive, unselected all-comer patients treated with percutaneous coronary intervention. By recording clinically driven events, we avoided bias introduced by pre-planned scheduled repeat angiography (5–7). Many studies comparing sirolimus- and paclitaxel-eluting stents have been published and combined in meta-analyses (8,9). Nonetheless, the very long-term outcome of these patients is unknown, as is also the case with newer stents.

It was the aim of the present investigation to assess the 10-year clinical outcome of unselected patients treated with first-generation DES.

METHODS

STUDY DESIGN AND ELIGIBILITY CRITERIA. SORT OUT, the Danish Organization on Randomized Trials with Clinical Outcome, performed this study (6). The sole inclusion criterion was indication for use of a DES at the operator's discretion, and treatment of more than 1 lesion per patient was allowed. The only 3 exclusion criteria were non-Danish residency, inability to provide written informed consent (including patients in cardiogenic shock), and participation in other studies. Consecutive, unselected all-comer patients (N = 2,098) were randomized 1:1 to receive either the sirolimus-eluting stent (Cypher, Cordis, Johnson and Johnson, Miami, Florida) or the paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, Massachusetts). We conducted the study in accordance with the Helsinki Declaration, and the local biomedical research ethics committees approved the study. All study participants provided written informed consent. The patients were prescribed dual antiplatelet therapy for 1 year and lifelong acetylsalicylic acid therapy (6,7).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DES = drug-eluting stent(s)

HR = hazard ratio

MACE = major adverse cardiac event(s)

MI = myocardial infarction

TLR = target lesion revascularization

EVENT DETECTION AND CLASSIFICATION. Comprehensive event detection is possible in Denmark because Danish residents are treated free of charge

TABLE 1 Baseline Demographics

	Sirolimus-Eluting	Paclitaxel-Eluting	p Value
Total	1,065 (51)	1,033 (49)	
Age, yrs	64.5 ± 10.6	63.6 ± 10.9	0.08
Men	789 (74.1)	780 (75.5)	0.44
Diabetes			
Insulin-treated	61 (5.7)	45 (4.3)	0.31
Non–insulin-treated	101 (9.5)	107 (10.4)	
Previous myocardial infarction	282 (26.4)	268 (25.2)	0.52
Previous PCI	167 (15.7)	185 (17.4)	0.31
Previous coronary artery bypass grafting	52 (4.9)	57 (5.5)	0.52
Treatment for hypercholesterolemia	616 (57.9)	635 (59.6)	0.15
Treatment for hypertension	514 (48.3)	504 (47.3)	0.62
Smoking, current	420 (39.4)	405 (39.2)	0.32
Family history of coronary artery disease	463 (43.5)	464 (43.5)	0.94
PCI indication			0.32
ST-segment elevation myocardial infarction	194 (18.2)	174 (16.8)	
Non–ST-segment elevation myocardial infarction or unstable angina	357 (33.5)	336 (32.5)	
Stable angina	476 (44.7)	471 (45.6)	
Other	38 (3.6)	52 (5.1)	
Lesions treated			0.28
1	708 (66.5)	706 (68.3)	
2	234 (22.0)	237 (22.9)	
≥3	88 (8.3)	57 (5.6)	
Distribution of target lesions			
Left anterior descending artery	650 (44.0)	610 (43.2)	0.65
Left circumflex artery	323 (21.9)	312 (22.1)	0.86
Right coronary artery	474 (32.1)	452 (32.0)	0.95
Left main stem or saphenous vein graft	30 (2.0)	38 (2.7)	0.24
Stented length, mm			
Median (interquartile range)	18 (13–23)	18 (12–24)	0.72
Range	8–117	8–155	
Stent diameter, mm			
Median (interquartile range)	3.0 (2.5–3.5)	3.0 (2.7–3.5)	0.85
Range	2.25–4.5	2.25–4.5	
Delivery failure	73 (4.9)	59 (4.2)	0.98
Lesions with overlapping stents	276 (18.7)	283 (20.0)	0.36

Values are n (%) or mean ± SD unless otherwise indicated. Reproduced with permission from the *Journal of the American Medical Association* (6).

PCI = percutaneous coronary intervention.

TABLE 2 Clinical Events During 10 Years

	All	Sirolimus	Paclitaxel	HR (95% CI)	p Value
Randomized	2,098	1,065 (50.8)	1,033 (49.2)		
Major adverse cardiac events	688 (32.8)	346 (32.5)	342 (33.1)	0.96 (0.83–1.12)	0.60
Cardiac death	193 (9.2)	104 (9.8)	89 (8.6)	1.14 (0.86–1.51)	0.38
Myocardial infarction	380 (18.1)	193 (18.1)	187 (18.1)	0.99 (0.81–1.21)	0.99
Target lesion revascularization	327 (15.6)	158 (14.8)	169 (16.4)	0.89 (0.72–1.11)	0.31
Target vessel revascularization	394 (18.8)	190 (17.8)	204 (19.7)	0.89 (0.73–1.08)	0.23
All-cause death	564 (26.9)	292 (27.4)	272 (26.3)	1.05 (0.89–1.23)	0.60
Stent thrombosis	279 (13.3)	142 (13.3)	137 (13.3)	1.00 (0.79–1.27)	0.99
Definite	118 (5.6)	56 (5.3)	62 (6.0)		
Probable	56 (2.7)	22 (2.1)	34 (3.3)		
Possible	119 (5.7)	70 (6.6)	49 (4.7)		
Major adverse cardiac events after censoring for noncardiac death and emigration		(34.8)	(35.2)		
Annual rate from year 1 to 10		(2.6)	(2.5)		
Cardiac death after censoring for noncardiac death and emigration		(10.7)	(9.4)		
Myocardial infarction after censoring for all-cause death and emigration		(20.0)	(19.9)		
Target lesion revascularization after censoring for all-cause death and emigration		(16.5)	(18.1)		
Target vessel revascularization after censoring for all-cause death and emigration		(19.7)	(21.6)		
All-cause death after censoring for emigration		(27.6)	(26.4)		
Stent thrombosis after censoring for all-cause death and emigration		(14.7)	(14.7)		
Annual rate from year 1 to 10		(1.2)	(1.3)		
Definite stent thrombosis after censoring for all-cause death and emigration		(5.9)	(6.8)		
Probable stent thrombosis after censoring for all-cause death and emigration		(2.3)	(3.7)		
Possible stent thrombosis after censoring for all-cause death and emigration		(7.5)	(5.4)		

Values are n, n (%), or (%).
CI = confidence interval; HR = hazard ratio.

and are therefore all admitted to the hospitals. Furthermore, all hospital admissions, deaths, emigrations, outpatient coronary angiograms, and revascularization procedures are identifiable from national registries. To enable nonhierarchic endpoint analyses, all patients were followed until death or emigration.

The primary endpoint was a major adverse cardiac event (MACE), which was a composite of cardiac death, MI, and target vessel revascularization. Secondary endpoints were as follows: all-cause death; cardiac death (cardiac death is defined as sudden death when no other explanation is available, death from arrhythmias or after MI or heart failure, or death caused by heart surgery or endocarditis); MI (as defined by Cutlip et al. [10]); TLR; target vessel revascularization; and definite, probable, or possible stent thromboses (10). An independent endpoint committee adjudicated all potential events and was blinded to the randomization (6).

STATISTICAL ANALYSES. All analyses were performed according to the intention-to-treat principle. All p values were 2 sided with a significance level of 0.05. The cumulative proportion of patients experiencing a MACE was analyzed according to the date of the first event for each patient. We performed the log-rank test to assess the p value. If patients emigrated from Denmark, the date of emigration was used as the censoring date. Event rates were also given as values censored for death and noncardiac death as relevant (6,7). We have full and unrestricted access to all data in the study. The sponsors have no access to data and are not involved in data analyses or writing of the paper.

RESULTS

Between August 2004 and January 2006, a total of 2,098 patients were included. The mean age was 64 years, 75% were male, 15% had diabetes, 17% had

ST-segment elevation MI, 50% had acute coronary syndromes, 67% had 1 lesion, 22% had 2 lesions, and 10% had 3 or more lesions. The baseline characteristics of the patients and the lesions were well balanced (**Table 1**) (6). All patients were followed for 10 years or until they emigrated from Denmark (n = 17) or died (n = 564). In 19 patients (3.3% of the dead) it was impossible to collect information on the circumstances of death (suddenness) or cause.

The primary endpoint, MACE, occurred in 688 patients (32.8%): 346 patients (32.5%) in the sirolimus-eluting stent group and 342 patients (33.1%) in the paclitaxel-eluting stent group (hazard ratio [HR] 0.96; 95% confidence interval [CI]: 0.83 to 1.12; p = 0.60) (**Table 2**). After censoring for noncardiac death and emigration from Denmark, the percentages were 34.8% versus 35.2%, respectively (**Table 2**, **Figure 1**).

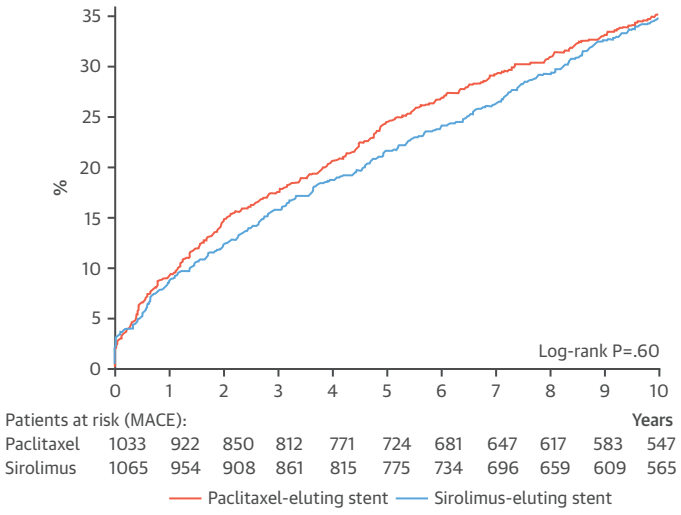
In total, 564 patients (26.9%) died, 292 (27.4%) in the sirolimus-eluting stent-group and 272 (26.3%) in the paclitaxel-eluting stent-group (HR: 1.05; 95% CI: 0.89 to 1.23; p = 0.60). Each component of the composite endpoint is reported in **Table 2** and depicted in **Figure 2**.

The efficacy of the stent treatment was estimated by the TLR. It was seen in 327 patients (15.6%), 158 (14.8%) in the sirolimus-eluting stent-group and 169 (16.4%) in the paclitaxel-eluting stent-group (HR: 0.89; 95% CI: 0.72 to 1.11; p = 0.31). There was no indication of a late increase in TLR rate because the curves for TLR were straight lines (**Figure 2**, bottom left).

The safety of the stent treatment was estimated by cardiac death, MI, or stent thromboses, and there were no statistically significant differences between the 2 stent types in any of these measures (**Table 2**). A total of 380 patients had an MI; 276 patients (13.2% of all patients) had 1 MI, 67 (3.2%) had 2 MIs, 26 (1.2%) had 3 MIs, and 12 (0.6%) had at least 4 MIs, with no difference between stent types (chi-square = 0.18, p = NS). The appearance of acute MI was predominantly early, with no indications of increased late annual rates (**Figure 2**, top right).

There was a statistically nonsignificant trend toward increased rates of definite and probable stent thrombosis with the paclitaxel-eluting stent; this trend was counterbalanced by a statistically nonsignificant trend toward increased rates of possible stent thrombosis in the sirolimus-eluting stent group. Possible stent thrombosis occurred in 70 patients (6.6%) in the sirolimus-eluting stent group versus 49 patients (4.7%) in the paclitaxel-eluting stent group (HR: 1.39; 95% CI: 0.97 to 1.97; p = 0.07). Definite, probable, and possible stent thrombosis occurred in 142 (13.3%) patients in the sirolimus-eluting stent group and in 137 (13.3%) in the paclitaxel-eluting stent group (HR: 1.00; 95% CI: 0.79 to 1.27; p = 0.99), with an annual rate of 1.3%. The annual rate of definite stent thrombosis was 0.6% to 0.7% (**Figure 3**). Cardiac death was the cause of 193 of the total 564 deaths (34%) (**Table 2**, **Figure 4**).

FIGURE 1 MACE Cumulative Incidence

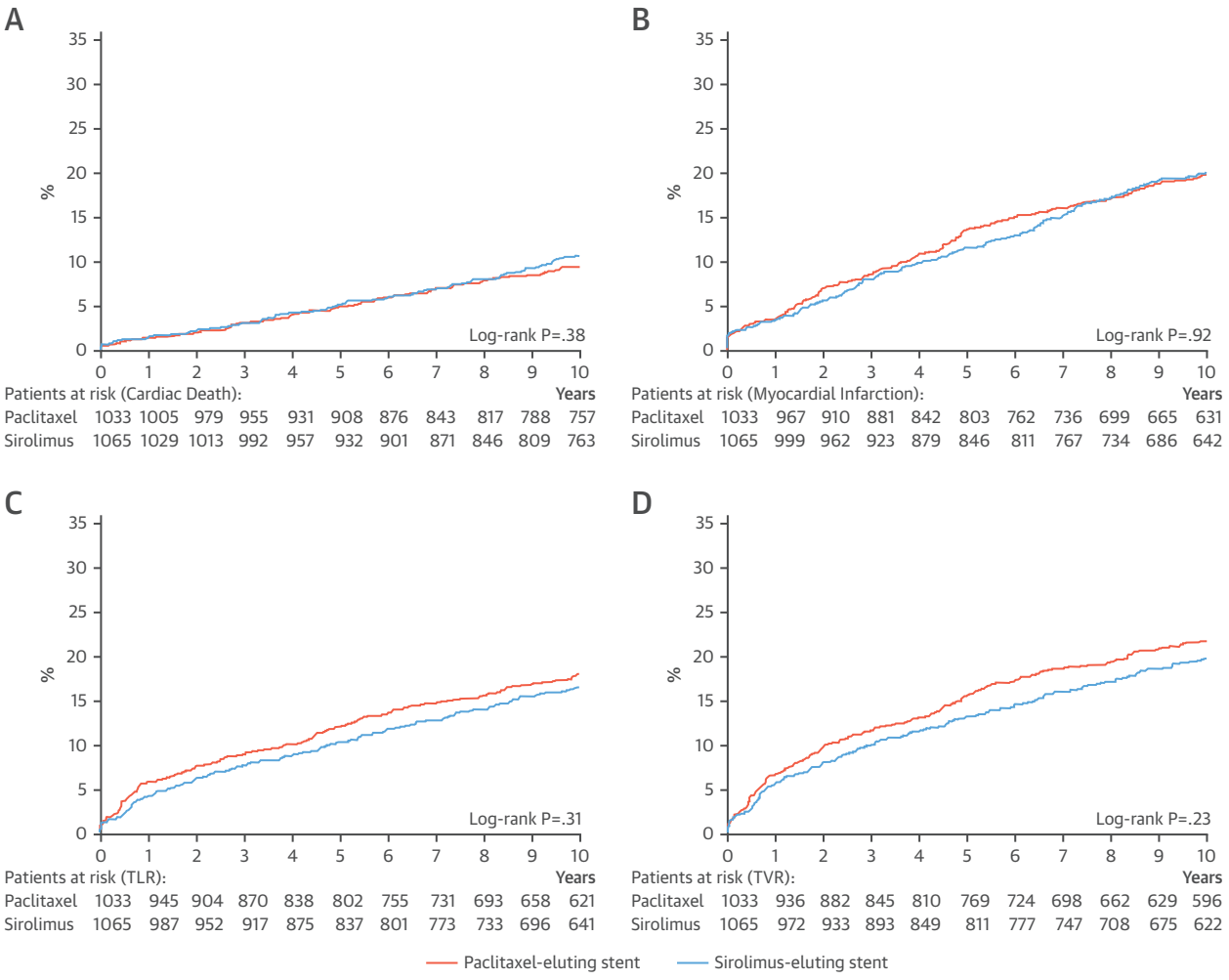


The cumulative incidence (%) of major adverse cardiac events (MACE) by time (years). The number of patients at risk each year in the 2 groups is noted below the abscissa. There is no statistical significant difference in the MACE rate between the 2 groups.

DISCUSSION

Ten years of observational data for our randomized comparison of first-generation DES are now available. Our findings are as follows: 1) the long-term event rate curves are straight lines without signs of diminishing or increasing slopes; and 2) definite, probable, and possible stent thrombosis appears to continue steadily, with an 1.3% annual rate throughout 10 years in patients who have had a first-generation DES implanted. These findings invite speculation about the rationality of prolonging the surveillance of patients treated with first-generation DES. It also raises questions about the correct use of invasive control examinations or even considerations about prescribing or reinitiating extraordinary long-term dual antiplatelet therapy to the millions of patients living with a first-generation DES in their coronary arteries. With 70% of the patients still alive, we feel obliged to continue surveillance and would recommend that this approach should be expanded to all new stent brands to ensure detection of surprising changes in event rates that could call for enhanced medical attention.

FIGURE 2 Individual Components of MACE



The cumulative incidence (%) of cardiac death **(A),** myocardial infarction **(B),** target lesion revascularization (TLR) **(C),** and target vessel revascularization (TVR) **(D)** by time (years). The number of patients at risk each year in the 2 groups is noted below the abscissa. There is no statistical significant difference in outcome between the 2 groups. MACE = major adverse cardiac events.

This study reveals that restenoses and/or stent thromboses continuously appear at a constant rate very late after stent implantation. The mechanisms of the adverse effects are multifactorial and include degeneration of the metal alloy and/or of the coating with induced inflammation, poor endothelialization, or development of neoatherosclerosis (11). Optical coherence tomography has shown heterogeneous healing to be responsible in some cases (12). Furthermore, stent malapposition, uncovered stent struts, and neoatherosclerotic intimal changes increase the thrombogenic potential after stent implantation (13,14). Neoatherosclerosis occurs more frequently in DES compared with bare-metal stents, and although the underlying mechanisms remain unclear, disturbance in the endothelial function after stent implantation seems to contribute to the formation of this condition (15). In patients developing late stent thrombosis, a hypersensitivity reaction appears to be dominant after sirolimus-eluting stents, whereas fibrin deposition occurs more frequently in paclitaxel-eluting stents (16).

Previous long-term comparisons of the clinical outcomes in patients with first-generation versus later-generation drug-eluting or bare-metal stents have generally shown better outcomes with the newer stents (17–20). The present event rates reported in this

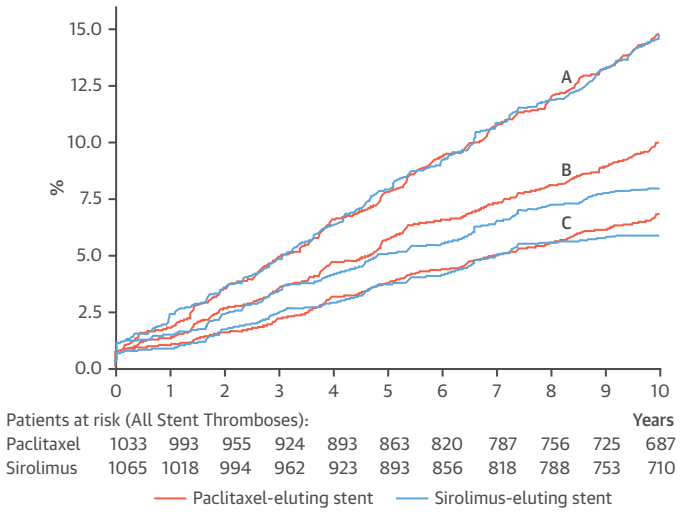
study are slightly higher than those of other studies, probably a result of the unselected patient population included in our trial (21-24). We think that this finding reflects the real long-term outcome of an all-comer population of patients treated with first-generation DES (8,25-31).

Räber et al. (32) also compared the outcome of patients who had first-generation stents implanted. These investigators found a statistically significantly higher MACE rate during the first year in patients who had the paclitaxel-eluting stent implanted, and this higher rate was apparently driven by a higher TLR rate. This difference became statistically insignificant in the following years. A similar trend was noticed in our study on a minor level (**Figure 1**), probably because we did not include mandatory repeat angiography (6). Räber et al. (32) reported an annual rate of definite stent thrombosis that was higher than that seen in our patients, a likely reflection of the slightly higher frequency of patients with diabetes and ST-segment elevation MI in their study.

Our results cannot be directly compared with other (nonexistent) 10-year randomized trials. Our previous 18-month result was part of a meta-analysis of 15,119 patients randomized to the 2 stent types. Combining 33 randomized studies with observation periods of 6 to 36 months (extractable from the Online Table 1 in Zhang et al. [25]), the HR for MACE was 0.79 (HR: 0.72 to 0.87) in favor of the sirolimus-eluting stent (25). This HR was not far from our $1^1/_2$-year HR of 0.85 (HR: 0.65 to 1.10) (6) or from our 5-year HR of 0.87 (HR: 0.72 to 1.04) (7). Traditionally, study size corresponds to reliability because size prevents outliers to determine the overall result. Our large study (N = 2,098) is 55% larger than the largest of the other studies (6,25). The third largest study, with 1,012 patients (32), had an HR of 0.60 (HR: 0.41 to 0.88) within the first year and 0.89 for the total 5-year observation period, similar to our 5-year HR of 0.87 (7).

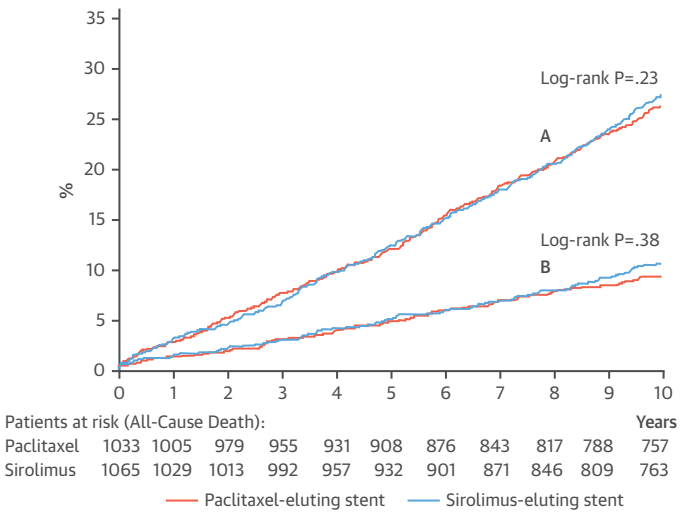
We found a constant and continuous appearance of stent thromboses in patients with first-generation DES throughout 10 years, with no signs of diminishing annual occurrence with time, as otherwise seen with newer stent types (11,18,26). The sirolimus-eluting stent seemed superior to the paclitaxel-eluting stent when solely measured by definite and probable stent thromboses, but the opposite was the case when estimated only by possible stent thrombosis. With all 3 stent thrombosis classes combined, there was absolutely no difference in stent thrombosis between the 2 stent groups. The "possible stent thrombosis" class is defined to contain death of unknown cause later than 30 days after stent implantation. We find it justified and advisable to include all subclasses of stent thromboses not only because conclusions from selected subclasses may lead to false conclusions, but also because the clinical consequence of possible stent thrombosis (death) is

FIGURE 3 Stent Thromboses



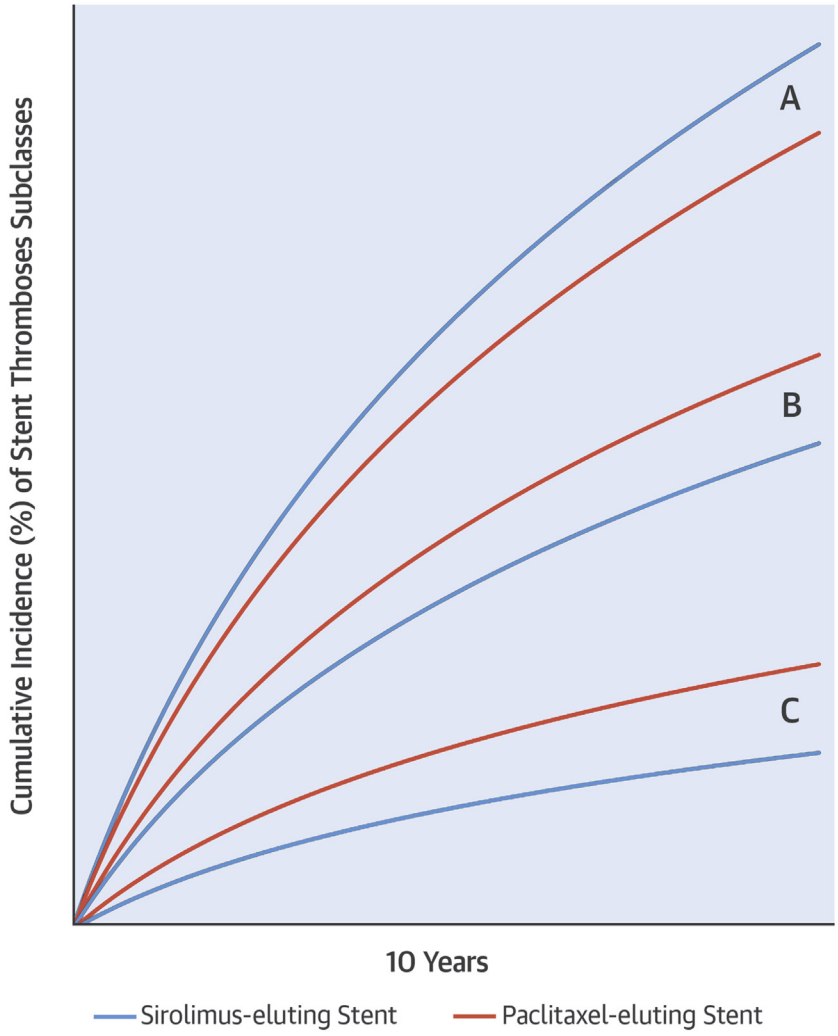
The cumulative incidence (%) of definite stent thrombosis **(C)**; definite and probable stent thrombosis **(B)**; and definite, probable, and possible stent thrombosis **(A)** by time (years). The ordinate axis is changed from 0% to 36% (as in **Figures 1 and 2**) to an ordinate axis from 0% to 16%. The number of patients at risk of definite, probable, and possible stent thrombosis in each year in the 2 groups is noted below the abscissa.

FIGURE 4 Death



The cumulative incidence (%) of all-cause death **(A)** and cardiac death **(B)** by time (years). The number of patients at risk each year in the 2 groups is noted below the abscissa.

CENTRAL ILLUSTRATION **Different Combinations of Stent Thromboses Classes**



Galløe, A.M. et al. J Am Coll Cardiol. 2017;69(6):616-24.

The cumulative incidence (%) of definite stent thrombosis (proven stent thrombosis by angiography) **(C)**; definite and probable (proven stent thrombosis and myocardial infarction in the index treated coronary vessel area or death of unexplained cause within 30 days after randomization) stent thrombosis **(B)**; and definite, probable, and possible (unexplained death later than 30 days after stent implantation) stent thrombosis **(A)**. Complete and exhaustive accounting in tables and depiction in figures of every class of stent thrombosis may enable the reader and observer to avoid being misled to wrong conclusions drawn from incomplete reporting (B curves). This is especially important when the last included endpoint is clinically more important (unexplained death) than nonlethal endpoints.

considerably more serious than the consequences of proven stent thromboses and MI in the index treated territory (which are the major components of "definite and probable stent thromboses"). Essentially, it might make a reverse result (**Central Illustration**).

The patients who have off-label indications for the use of a drug-eluting stent possess increased risk of subsequent unwanted event. With each additional off-label indication in the same patient, there is a stepwise increase in the risk of MACE (Online Figure 1). Unfortunately, patient or lesion characteristics like the presence or absence of any of the off-label indications do not predict or distinguish between an early versus late appearance of MACE (Online Table 1) or stent thromboses (Online Table 2), excepting in patients with bifurcations.

The steady annual late event rates and the absence of decline are curious and worrying, and we encourage

a debate on the appropriateness of intensified surveillance of patients who have a first-generation implanted DES. Moreover, we suggest that any new stent should be surveyed for very long time in unselected patients to procure evidence-based information on the durability of stent performance.

STUDY LIMITATIONS. In SORT OUT II, we deliberately included unselected all-comers to facilitate subsequent translation from the trial result to everyday clinical practice. We had 30-day all-cause mortality rates in the background population (all patients in Denmark who were treated with percutaneous coronary intervention), as well as cause of death in the randomized patients. This information was included to estimate whether the randomized patients were likely to be unselected all-comers. Unfortunately, the 30-day mortality rate was higher in the background population than in the randomized population, a finding indicating that some patients with a worse prognosis were not randomized.

Clinical follow-up consisted of identification of deaths and admissions, and we collected more than 18,622 journals and files. The information from these sources does not allow us to discern whether a patient was receiving and taking antiplatelet therapy on admission or whether the medication was prescribed after the patient arrived at the hospital. Consequently, we are not able to collect reliable data on this important question.

CONCLUSIONS

The majority of the patients (73%) randomized to be treated by a first-generation DES survived for 10 years. There was no statistical significant difference in MACE or stent thrombosis between the 2 stent types. The slopes of the event curves were not increasing, and the late annual event rates seemed to be steady and the same as in the second year after stent implantation. For that reason there should be no apparent need for extraordinary medical attention to these patients. At the same time, the annual event rates did not show a diminishing trend with time. This finding is worrying and may call for continuous observation. We will continue our surveillance of the population, to ensure detection of warning signals that could call for extraordinary medical attention to the millions of people who are still living with these first-generation DES.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients undergoing percutaneous coronary intervention with first-generation DES, approximately one-half in the setting of acute coronary syndromes, there were no significant differences over 10 years in survival or rates of MACE or stent thrombosis in patients receiving sirolimus- versus paclitaxel-eluting stents.

TRANSLATIONAL OUTLOOK: Future comparative studies of coronary DES types should address a granular array of clinical outcomes in large, carefully defined patient cohorts.

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APPENDIX For a supplemental figure and tables, please see the online version of this article.