Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 10, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.04.077

5-Year Clinical Outcomes After Sirolimus-Eluting Stent Implantation

Insights From a Patient-Level Pooled Analysis of 4 Randomized Trials Comparing Sirolimus-Eluting Stents With Bare-Metal Stents

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Objectives Five-year clinical follow-up has been scheduled per protocol by the 4 Cypher (Cordis/Johnson & Johnson, Warren, New Jersey) sirolimus-eluting stent (SES) versus bare-metal stent (BMS) randomized trials.

Background A delayed arterial healing response after drug-eluting stent implantation has raised concerns about the long-term safety of drug-eluting stents.

Methods In a pooled analysis of 4 randomized trials, 1,748 patients were assigned to receive either an SES (n = 878) or BMS (n = 870).

Results At 5 years, there was no significant difference in the rate of death, myocardial infarction (MI), or the composite of death/MI between the 2 groups (15.1% in the SES group vs. 13.6% in the BMS group; p = 0.36). The 5-year incidence of stent thrombosis by the Academic Research Consortium definition did not differ between SES and BMS (definite/probable stent thrombosis, 2.1% vs. 2.0%; p = 0.99). The incidence of very late stent thrombosis was also similar between the SES and BMS groups (1.4% vs. 0.7%; p = 0.22). The annualized rates of definite/probable stent thrombosis after 1 year were 0.4% for SES and 0.2% for BMS. The 5-year incidence of target vessel revascularization was significantly lower in the SES group (15.2% vs. 30.1%; p < 0.0001).

Conclusions In this patient-level pooled analysis, overall use of SES compared with BMS demonstrated persistent superior efficacy at 5 years in terms of a reduction in target vessel revascularization, without an increase in rates of death, MI, or stent thrombosis. (The Initial Double-Blind Drug-Eluting Stent vs Bare-Metal Stent Study, NCT00233805; The Study of the BX Velocity Stent in the Treatment of De Novo Artery Lesions, NCT00381420; Study of Sirolimus-Coated BX VELOCITY Balloon-Expandable Stent in Treatment of de Novo Native Coronary Artery Lesions [SIRIUS], NCT00232765; The Study of the BX VELOCITY Stent In Patients With De Novo Coronary Artery Lesions, NCT00235144) (J Am Coll Cardiol 2009;54:894–902) © 2009 by the American College of Cardiology Foundation

Sirolimus-eluting stents (SES) dramatically reduce the incidence of restenosis and rates of target lesion revascularization (TLR) (1). Soon after approval, SES were enthusiastically adopted even beyond the on-label, U.S. Food and Drug Administration-approved indications. However, the theoretical thrombogenicity of drug-eluting stents (DES)

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Manuscript received November 4, 2008; revised manuscript received April 6, 2009, accepted April 7, 2009.

and the delayed arterial healing response seen with DES use raised concerns that these devices might be associated with an increase in the incidence of very late stent thrombosis (2,3).

Although 4-year clinical outcomes in a pooled analysis of data from the 4 double-blind SES versus bare-metal stent (BMS) trials have been published recently (4), the SES manufacturer was required by the U.S. Food and Drug Administration to follow patients for 5 years (5). To further address the issue of long-term safety and efficacy of SES, we investigated 5-year clinical outcomes in a pooled analysis of the 4 SES versus BMS randomized trials.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
MI = myocardial infarction
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

Methods

Patient population and study procedure. We performed a patient-level pooled analysis of the 4 multicenter, double-blinded, randomized SES versus BMS trials, including the RAVEL (Randomized Study With the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions), SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions), E-SIRIUS (European–SIRIUS), and C-SIRIUS (Canadian–SIRIUS) trials, in which patients with single de novo lesions were treated with either a Cypher SES or an uncoated Bx Velocity BMS of identical design (both Cordis/Johnson & Johnson, Warren, New Jersey). The protocol and principal results of each trial have been published elsewhere (1,6–8).

Definitions and clinical end points. The primary safety end point of this analysis was death or myocardial infarction (MI). The secondary safety end point was stent thrombosis using the Academic Research Consortium (ARC) definition up to 5 years (9). The primary efficacy end point was target vessel revascularization (TVR) up to 5 years. Follow-up information was collected by the investigating sites, including telephone contact at 1 year and annually for 5 years thereafter. Five-year follow-up was completed in 87.1% of patients. To be included in the analysis, patients must have had at least 1,800 days of follow-up.

We pre-specified that we would compare the clinical outcomes between the SES and BMS groups in patients with diabetes, because the mortality rate was signifi-

Table 1 Baseline Clinical and Procedural Characteristics

	SES	BMS	p Value
Age (yrs)	61.85 ± 11.12	61.91 ± 10.67	0.91
Male sex	71.6% (629/878)	71.5% (622/870)	0.96
Hypertension	63.8% (557/873)	63.3% (548/866)	0.84
Hyperlipidemia	70.8% (613/866)	71.8% (617/859)	0.67
Current smoking	21.2% (183/862)	24.5% (210/858)	0.12
Diabetes mellitus	22.2% (195/878)	26.8% (233/868)	0.03
Prior myocardial infarction	33.2% (287/865)	35.7% (308/862)	0.27
Prior percutaneous revascularization	22.9% (201/878)	21.2% (184/869)	0.39
Prior coronary artery bypass graft	7.5% (66/878)	7.4% (64/870)	0.93
Multivessel disease	38.6% (338/876)	38.8% (337/868)	0.92
Clinical presentation			
Stable exertional angina	23.1% (202/875)	25.0% (217/869)	0.37
Worsening exertional angina	36.6% (277/757)	33.3% (250/751)	0.19
Rest angina	21.9% (166/757)	21.8% (164/751)	1.00
Ejection fraction (%)	56.99 ± 11.02 (726)	57.34 ± 10.99 (717)	0.55
Location of target lesion			
Left anterior descending artery	46.6% (408/875)	46.7% (407/872)	1.00
Left circumflex artery	20.7% (181/875)	20.8% (181/872)	1.00
Right coronary artery	29.0% (254/875)	29.1% (254/872)	1.00
Modified ACC/AHA lesion classification			
A	7.0% (61/875)	7.0% (61/871)	1.00
B1	33.9% (297/875)	36.4% (317/871)	0.29
B2	36.6% (320/875)	38.1% (332/871)	0.52
C	22.5% (197/875)	18.5% (161/871)	0.04
Pre-reference vessel diameter, mm	2.72 ± 0.45 (871)	2.72 ± 0.48 (868)	0.98
Total implanted stent length, mm	22.87 ± 9.03 (877)	22.45 ± 8.13 (869)	0.31
Number of total implanted stents	1.42 ± 0.69 (878)	1.39 ± 0.61 (870)	0.38
Glycoprotein IIb/IIIa inhibitors during procedure	44.2% (388/878)	43.4% (377/869)	0.74

ACC = American College of Cardiology; AHA = American Heart Association; BMS = bare-metal stent(s); SES = sirolimus-eluting stent(s).

cantly higher in the SES group at 4 years in the published report (4).

Definitions of major adverse cardiac events were consistent across the trials (1,6–8). Members of the independent Clinical Events Committee retrospectively readjudicated all clinical and angiographic data based on the ARC definition of stent thrombosis (9).

Statistical analysis. Patient-level data were pooled from the 4 randomized trials comparing SES and BMS. Interactions between trial and stent on 5-year death, MI, TLR, TVR, protocol thrombosis, and ARC-defined thrombosis were not statistically significant, justifying pooling of the 4 studies. Binary variables are summarized as counts and percentages and compared using chi-square tests or the Fisher exact test where appropriate. Continuous variables are summarized as means and standard deviations and compared using *t* tests. Five-year outcomes are summarized as Kaplan-Meier estimates and compared using log-rank tests and hazard ratios. Kaplan-Meier event curves are presented and compared using log-rank tests. To assess events occurring between years 4 and 5, a landmark analysis was performed. Cox proportional hazards models using stepwise selection were used to determine multivariate predictors of clinical events. All statistical tests were 2-tailed. A p value <0.05 denoted significance.

Results

Baseline and procedural characteristics. Between August 2000 and April 2002, 1,748 patients at 115 international centers were assigned to either SES (n = 878) or BMS (n = 870). The 2 groups were well matched for all baseline and procedural characteristics except for a lower prevalence of diabetes in patients randomized to SES and a lower rate of type C lesions in patients randomized to BMS (Table 1).

Clinical outcomes up to 5 years. The 5-year rates of all-cause death, cardiac death, and MI were similar between the 2 groups (Table 2). There were no significant differences in the composite end point of death or MI at 5 years and from 1 to 5 years between the 2 groups. The 5-year cumulative incidence of TVR was nearly doubled in patients randomized to BMS. The striking difference in the TVR

Table 2 Cumulative Clinical Outcomes Up to 5 Years and Between 1 and 5 Years

	SES	BMS	Hazard Ratio (95% CI)	p Value
0–5 yrs				
Death	8.9% (76)	8.2% (69)	1.10 (0.79–1.52)	0.57
Cardiac death	4.4% (37)	3.9% (32)	1.16 (0.72–1.85)	0.55
Noncardiac death	4.7% (39)	4.5% (37)	1.05 (0.67–1.65)	0.83
MI	7.9% (67)	6.8% (58)	1.15 (0.81–1.63)	0.44
Q-wave	2.5% (21)	1.6% (13)	1.62 (0.81–3.23)	0.17
Non–Q-wave	5.7% (48)	5.4% (46)	1.03 (0.69–1.55)	0.87
TLR	9.6% (80)	24.7% (207)	0.34 (0.27–0.44)	<0.0001
TVR	15.2% (127)	30.1% (252)	0.44 (0.36–0.55)	<0.0001
Death/MI	15.1% (130)	13.6% (115)	1.12 (0.88–1.45)	0.36
Cardiac death/MI	11.1% (94)	9.8% (83)	1.13 (0.84–1.51)	0.43
Death/Q-wave MI	10.7% (91)	9.4% (79)	1.15 (0.85–1.56)	0.35
Cardiac death/Q-wave MI	6.2% (52)	5.0% (42)	1.24 (0.83–1.86)	0.29
Death/MI/TLR	21.5% (185)	34.1% (289)	0.56 (0.47–0.68)	<0.0001
Death/MI/TVR	26.2% (225)	38.5% (327)	0.60 (0.50–0.71)	<0.0001
>1 yr				
Death	7.7% (65)	7.5% (62)	1.05 (0.74–1.48)	0.79
Cardiac death	4.0% (33)	3.4% (28)	1.18 (0.71–1.95)	0.52
Noncardiac death	3.9% (32)	4.2% (34)	0.94 (0.58–1.52)	0.80
MI	4.2% (34)	2.7% (22)	1.55 (0.90–2.64)	0.11
Q-wave	1.3% (10)	0.9% (7)	1.43 (0.54–3.76)	0.46
Non–Q-wave	3.2% (26)	2.0% (16)	1.62 (0.87–3.02)	0.12
TLR	5.3% (43)	4.1% (30)	1.44 (0.90–2.29)	0.13
TVR	9.6% (78)	8.3% (64)	1.22 (0.87–1.69)	0.24
Death/MI	11.0% (92)	9.5% (79)	1.17 (0.86–1.57)	0.32
Cardiac death/MI	7.5% (62)	5.6% (46)	1.35 (0.92–1.98)	0.12
Death/Q-wave MI	8.6% (72)	8.1% (67)	1.08 (0.77–1.50)	0.67
Cardiac death/Q-wave MI	4.9% (40)	4.0% (33)	1.21 (0.77–1.93)	0.40
Death/MI/TLR	14.4% (121)	13.1% (106)	1.14 (0.88–1.48)	0.33
Death/MI/TVR	18.1% (152)	16.8% (137)	1.10 (0.88–1.39)	0.40

CI = confidence interval; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

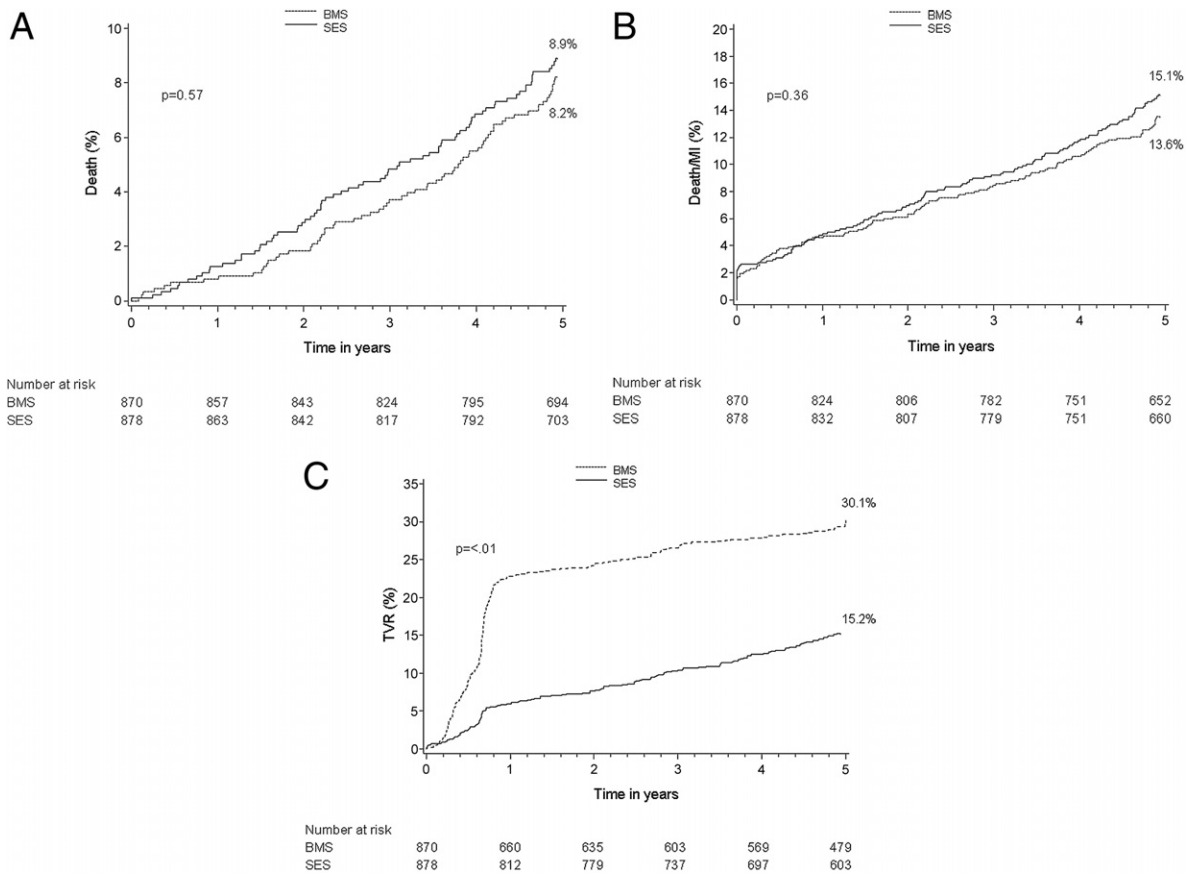

Figure 1 Kaplan-Meier Event Curves for Patients Treated With SES or BMS

Five-year cumulative event curves for **(A)** death, **(B)** death or myocardial infarction (MI), and **(C)** target vessel revascularization (TVR). BMS = bare-metal stent(s); SES = sirolimus-eluting stent(s).

Table 3 Incidence of ST According to Academic Research Consortium Definition

Definition	SES	BMS	Hazard Ratio (95% CI)	p Value
All (0–5 yrs)				
Definite ST	1.6% (13)	1.0% (8)	1.62 (0.67–3.91)	0.23
Definite + probable ST	2.1% (17)	2.0% (17)	0.99 (0.51–1.95)	0.99
Any (definite + probable + possible) ST	4.6% (38)	4.4% (37)	1.02 (0–65–1.61)	0.70
Early (0–30 days)				
Definite ST	0.3% (3)	0.0% (0)	NA	0.08
Definite + probable ST	0.5% (4)	0.3% (3)	1.33 (0.30–5.93)	0.71
Any (definite + probable + possible) ST	0.5% (4)	0.3% (3)	1.33 (0.30–5.93)	0.71
Late (30 days–1 yr)				
Definite ST	0.1% (1)	0.5% (4)	0.25 (0.03–2.22)	0.18
Definite + probable ST	0.2% (2)	0.9% (8)	0.25 (0.05–1.16)	0.05
Any (definite + probable + possible) ST	0.3% (3)	1.3% (11)	0.27 (0.08–0.97)	0.03
Very late (1–5 yrs)				
Definite ST	1.1% (9)	0.5% (4)	2.25 (0.69–7.30)	0.16
Definite + probable ST	1.4% (11)	0.7% (6)	1.83 (0.68–4.95)	0.22
Any (definite + probable + possible) ST	3.8% (31)	2.8% (23)	1.35 (0.79–2.31)	0.28

NA = not applicable; ST = stent thrombosis; other abbreviations as in Tables 1 and 2.

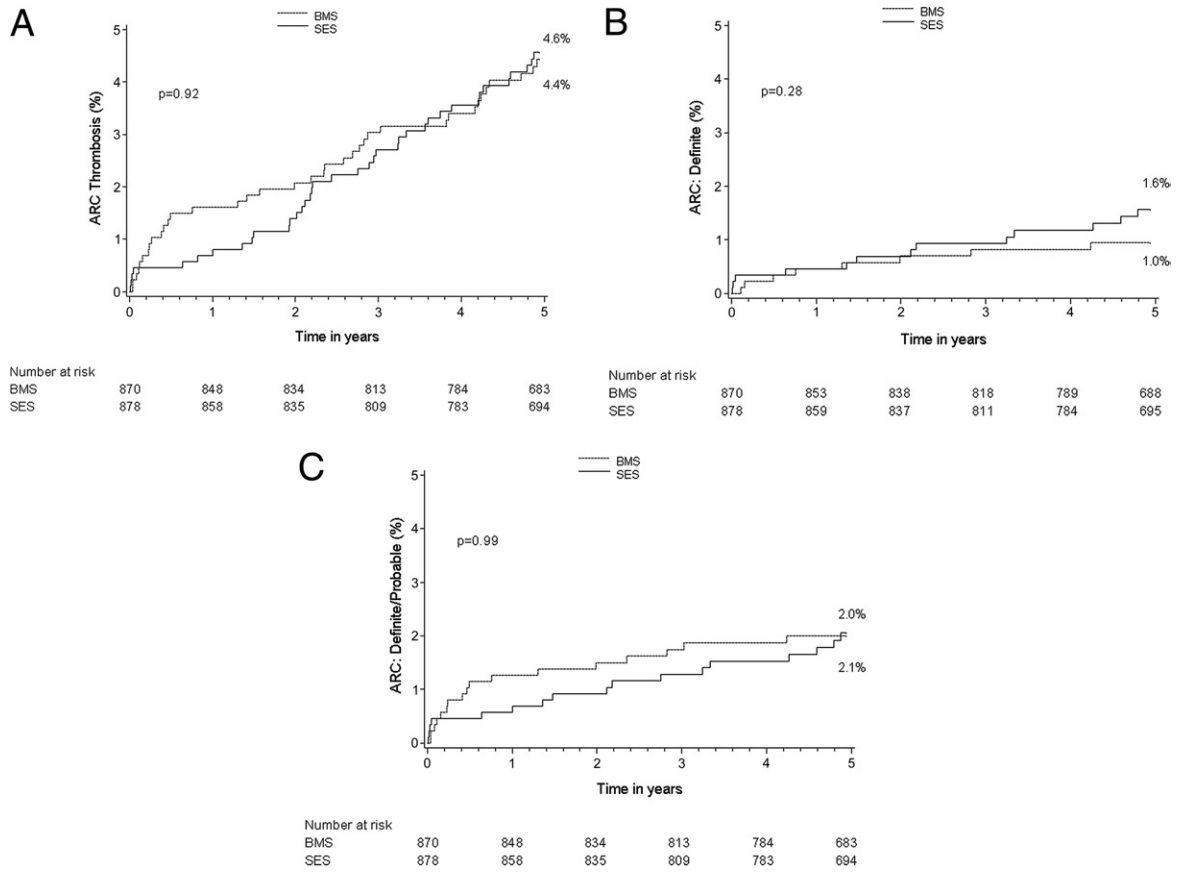

Figure 2 Kaplan-Meier Curves for Patients With Stent Thrombosis as Defined by the ARC

Five-year cumulative event curves for **(A)** any stent thrombosis, **(B)** definite stent thrombosis, and **(C)** definite and probable stent thrombosis. ARC = Academic Research Consortium; other abbreviations as in Figure 1.

rates peaked at approximately 1 year and then remained through 5 years (Fig. 1).

The incidence of any stent thrombosis did not differ between the 2 groups at 5 years (Table 3, Fig. 2). The rates of very late definite stent thrombosis (1.1% in the SES group vs. 0.5% in the BMS group; p = 0.16) and very late definite or probable stent thrombosis (1.4% in the SES group vs. 0.7% in the BMS group; p = 0.22) were also similar between the 2 groups.

Late definite or probable stent thrombosis was more frequent in the BMS group during the first year (0.2% in the SES group vs. 0.9% in the BMS group; p = 0.05), whereas very late definite or probable stent thrombosis tended to be more frequent in the SES group (1.4% vs. 0.7%; p = 0.22) (Table 3). The annual definite or probable stent thrombosis rate from 1 to 5 years was low in both groups and did not differ significantly between SES and BMS (0.4% vs. 0.2% per year) (Table 4). The annualized rates of TLR, TVR, and nontarget lesion TVR (remote TVR) after 1 year were similar for SES and BMS. In the landmark analysis, there were no significant differences in rates of the clinical end points, including stent thrombosis between years 4 and 5 in patients treated with SES versus BMS (Fig. 3).

Clinical outcomes in patients with diabetes. At 5 years, diabetic patients treated with SES versus BMS had significantly higher rates of mortality (15.9% vs. 9.0%; p = 0.03) and Q-wave MI (3.3% vs. 0.4%; p = 0.03) and had no significant differences in rates of definite, definite or probable, or any stent thrombosis either at 5 years or from 1 to 5 years (Table 5, Fig. 4). At 5 years, the use of SES compared with BMS reduced the rate of TVR from 37.1% to 17.7% (p < 0.0001).

Multivariable analysis. Independent predictors of cardiac death or MI for the entire population were smoking (hazard ratio [HR]: 1.85; 95% confidence interval [CI]: 1.34 to 2.57; p = 0.0002), congestive heart failure (HR: 1.79; 95% CI: 1.13 to 2.83; p = 0.01), diabetes (HR: 1.37; 95% CI: 1.01 to 1.86; p = 0.041), prior MI (HR: 1.49; 95% CI: 1.12 to 1.97; p = 0.006), older age (HR: 1.05; 95% CI: 1.03 to 1.06; p < 0.0001), and total number of stents implanted (HR: 1.02; 95% CI: 1.01 to 1.03; p = 0.001). In the diabetes subset, predictors of cardiac death or MI included congestive heart failure (HR: 2.33; 95% CI: 1.27 to 4.29; p =

Table 4 Annualized Hazard Ratio per 100 Patient-Years

	Year 1 Annual Hazard Rate per 100 Patient-Years			Years 2 to 5 Annual Hazard Rate per 100 Patient-Years		
	SES	BMS	p Value	SES	BMS	p Value
Death	1.3% (11)	0.8% (7)	0.35	1.9%	1.9%	0.79
Cardiac death	0.5% (4)	0.5% (4)	0.99	1%	0.9%	0.52
Noncardiac death	0.8% (7)	0.3% (3)	0.21	1%	1.1%	0.80
MI	3.8% (33)	4.1% (36)	0.70	1.1%	0.7%	0.11
Q-wave	1.3% (11)	0.7% (6)	0.23	0.3%	0.2%	0.46
Non–Q-wave	2.5% (22)	3.5% (30)	0.25	0.8%	0.5%	0.12
TLR	4.3% (37)	20.5% (177)	<0.0001	1.3%	1%	0.13
TVR	9.5% (82)	25.3% (218)	<0.0001	2.4%	2.1%	0.24
Remote TVR (non-TLR)	2.6% (23)	5.0% (43)	0.011	1.4%	1.3%	0.67
Definite ST	0.5% (4)	0.5% (4)	0.99	0.3%	0.1%	0.16
Definite + probable ST	0.7% (6)	1.3% (11)	0.22	0.4%	0.2%	0.22
Any ST (definite + probable + possible)	0.8% (7)	1.6% (14)	0.12	1%	0.7%	0.28
Death/MI	4.9% (43)	4.6% (40)	0.76	2.8%	2.4%	0.31
Death/Q-wave MI	1.3% (11)	0.8% (7)	0.35	2.2%	2%	0.67
Death/MI/TVR	13.0% (114)	27.9% (242)	<0.0001	4.5%	4.2%	0.40

Abbreviations as in Tables 1 to 3.

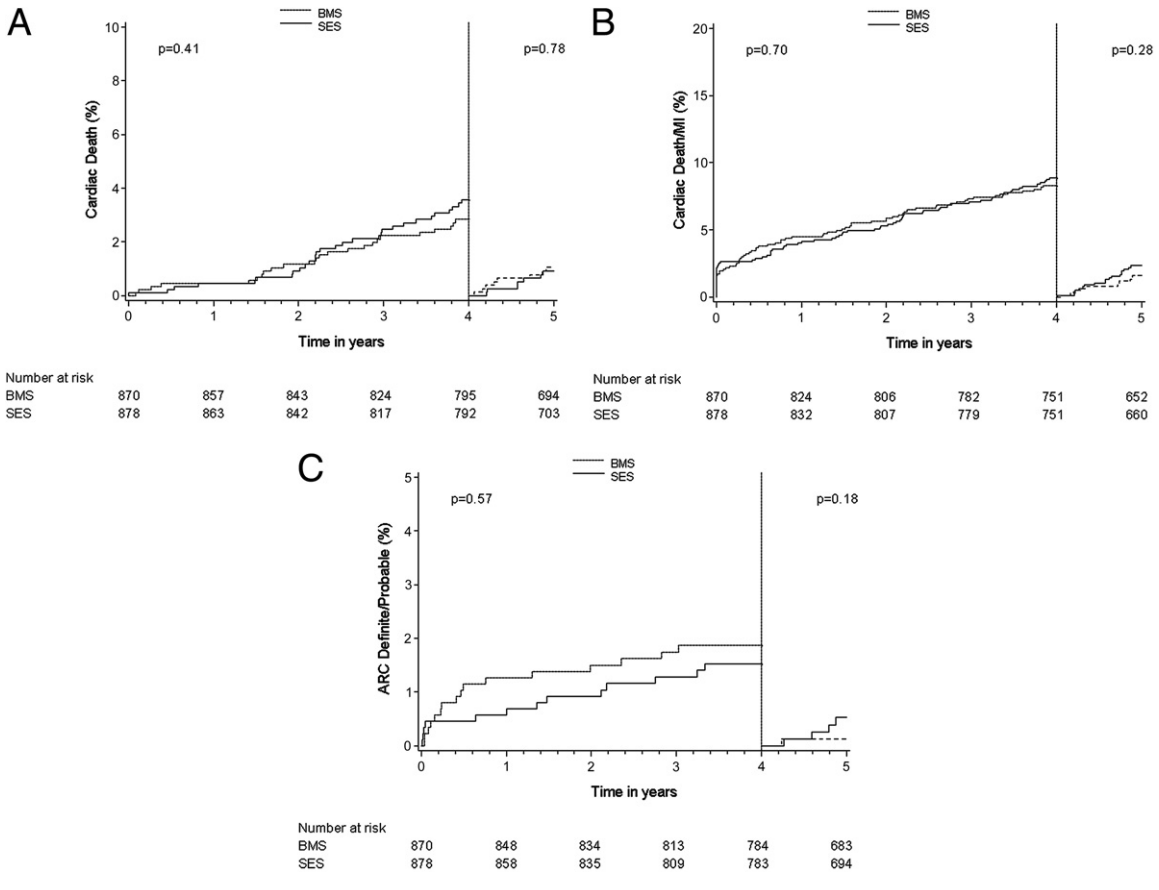

Figure 3 Kaplan-Meier Event Curves With Landmark Analysis From 4- to 5-Year Follow-Up

Landmark analyses of **(A)** cardiac death, **(B)** cardiac death or MI, and **(C)** definite and probable stent thrombosis. Abbreviations as in Figures 1 and 2.

Table 5 Clinical Outcomes in Diabetic Patients

	SES	BMS	Hazard Ratio (95% CI)	p Value
0–5 yrs				
Death	15.9% (30)	9.0% (20)	1.88 (1.07–3.32)	0.03
Cardiac death	10.5% (19)	5.0% (11)	2.17 (1.03–4.56)	0.04
Noncardiac death	6.0% (11)	4.2% (9)	1.53 (0.64–3.70)	0.34
MI	8.3% (15)	9.2% (21)	0.85 (0.44–1.64)	0.62
Q-wave	3.3% (6)	0.4% (1)	7.41 (0.89–61.54)	0.03
Non–Q-wave	5.5% (10)	8.8% (20)	0.59 (0.28–1.26)	0.16
TLR	11.9% (22)	31.9% (73)	0.32 (0.20–0.52)	<0.0001
TVR	17.7% (33)	37.1% (84)	0.41 (0.28–0.62)	<0.0001
Death/MI	21.0% (40)	16.4% (37)	1.30 (0.83–2.03)	0.25
Cardiac death/MI	16.3% (30)	12.8% (29)	1.24 (0.74–2.06)	0.41
Death/Q-wave MI	17.4% (33)	9.0% (20)	2.10 (1.20–3.65)	0.008
Death/MI/TLR	29.3% (56)	42.2% (97)	0.59 (0.42–0.82)	0.001
Death/MI/TVR	33.5% (64)	46.2% (106)	0.62 (0.45–0.84)	0.002
Definite ST	1.7% (3)	0.9% (2)	1.87 (0.31–11.16)	0.49
Definite + probable ST	2.4% (4)	2.7% (6)	0.82 (0.23–2.89)	0.75
Any ST (definite + probable + possible)	8.4% (15)	5.8% (13)	1.43 (0.68–3.00)	0.35
>1 yr				
Death	14.1% (26)	7.8% (17)	1.93 (1.05–3.56)	0.03
Cardiac death	10.0% (18)	4.2% (9)	2.52 (1.13–5.62)	0.02
Noncardiac death	4.5% (8)	3.8% (8)	1.27 (0.48–3.38)	0.63
MI	5.2% (9)	3.2% (7)	1.60 (0.59–4.29)	0.35
Q-wave	1.8% (3)	0.0% (0)	NA	0.05
Non–Q-wave	4.0% (7)	3.2% (7)	1.23 (0.43–3.52)	0.69
TLR	4.6% (8)	5.5% (12)	0.82 (0.34–2.02)	0.67
TVR	9.4% (17)	10.1% (22)	0.96 (0.51–1.81)	0.91
Death/MI	17.3% (32)	11.0% (24)	1.67 (0.98–2.84)	0.05
Death/Q-wave MI	14.6% (27)	7.8% (17)	2.02 (1.10–3.70)	0.02
Death/MI/TLR	19.9% (37)	15.9% (35)	1.30 (0.82–2.06)	0.26
Death/MI/TVR	23.1% (43)	19.5% (43)	1.24 (0.81–1.89)	0.32
Definite ST	1.2% (2)	0.5% (1)	2.55 (0.23–28.10)	0.43
Definite + probable ST	1.9% (3)	0.9% (2)	1.90 (0.32–11.38)	0.47
Any ST (definite + probable + possible)	7.9% (14)	3.3% (7)	2.52 (1.02–6.25)	0.04

NA = not applicable; other abbreviations as in Tables 1 to 3.

0.006), smoking (HR: 2.06; 95% CI: 1.11 to 3.81; p = 0.02), and older age (HR: 1.05; 95% CI: 1.02 to 1.08; p = 0.0005).

Discussion

The main findings of this analysis comparing 5-year clinical outcomes in patients treated with either SES or BMS for on-label indications were as follows: 1) the incidences of the composite of death or MI as well as ARC-defined stent thrombosis were similar up to 5 years and from 1 to 5 years between the 2 groups; 2) a significant difference in the incidence of TVR favoring the SES group versus the BMS group within the first year was maintained up to 5 years; and 3) in diabetic patients, the rates of mortality and the composite of death or Q-wave MI were significantly higher in patients receiving SES versus BMS.

Long-term safety of SES. Due to safety concerns (5), 5-year follow-up was required from the manufacturer for patients enrolled in randomized DES versus BMS trials. In 1 community-based registry, very late stent thrombosis occurred at a constant rate of 0.6% per year up to 3 years after DES implantation (2). Higher rates of very late stent thrombosis with SES rather than BMS (1.4% vs. 0%; p = 0.02) have been also shown at 4-year follow-up in another large-scale registry (10). However, despite concern initially raised about DES safety based on 3-year outcomes from the large Swedish registry, repeat analysis performed at later follow-up (at 4 years) demonstrated no differences in hard clinical end points between patients treated with DES or BMS (11). These latter results are consistent with the present study, in which rates of death and MI were similar for SES- and BMS-treated patients during 1 to 5 years of follow-up. Even though the annual incidence of definite or probable stent thrombosis after the first year was 2-fold higher in the SES group compared with the BMS group (0.4% vs. 0.2%), the difference was not statistically significant. Still, the lack of an observed difference between hard clinical end points, including stent thrombosis, for SES- and BMS-treated patients in this study may be due to inadequate statistical power.

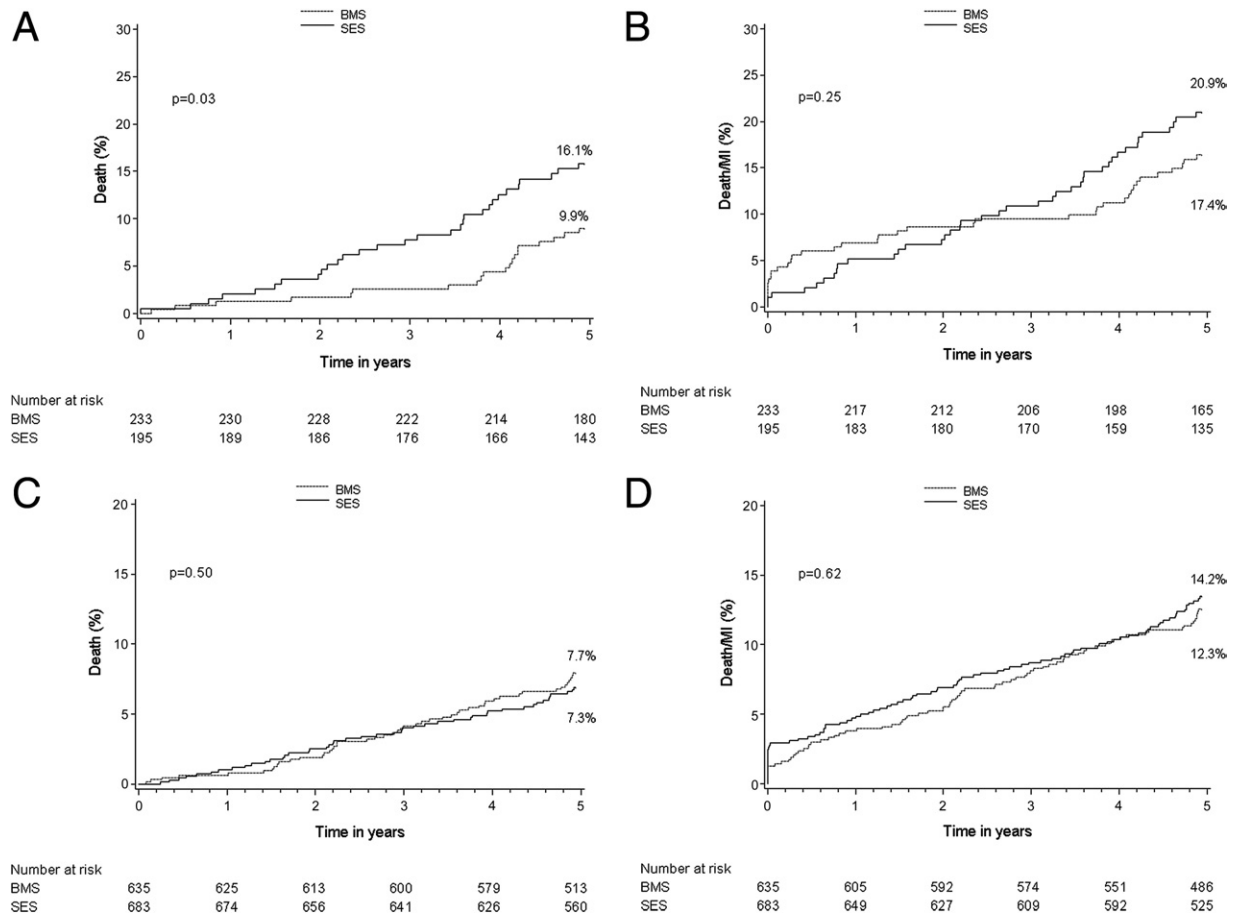

Figure 4 **Kaplan-Meier Event Curves for Patients With and Without Diabetes**

Five-year cumulative event curves for **(A)** death and **(B)** death or MI for patients with diabetes, and cumulative event curves for **(C)** death and **(D)** death or MI for patients without diabetes. Abbreviations as in Figure 1.

The current study provides information on the longest (5-year) follow-up, including an update on clinical events occurring between 4 and 5 years. After the completion of 4-year follow-up (4), patients treated with SES versus BMS had 8 versus 9 additional cases of cardiac death, 3 versus 2 cases of Q-wave MI, and 4 versus 2 cases of very late definite or probable stent thrombosis, respectively.

Clinical outcomes in diabetic patients. Mortality in diabetic patients was significantly higher in the SES group than the BMS group, mainly due to a higher rate of cardiac death beyond 1 year. Among 19 diabetic patients who experienced cardiac death in the SES group, 11 (57.9%) died of unknown causes; these cases were adjudicated as cardiac death and possible stent thrombosis. However, it is not certain that this higher mortality is in fact related to late stent thrombosis. Furthermore, the small number of diabetic patients in the current study makes it underpowered to detect differences between the 2 groups for rare events such as death and stent thrombosis. In addition, the surprisingly low event rates in the BMS group beyond 1 year may have biased the outcomes in favor of BMS. Therefore, the difference in SES versus BMS mortality seen at 5 years in patients with diabetes may be due to chance alone. Larger, more recent studies provide evidence of superior outcomes (12,13), including lower mortality and fewer MIs (12), in diabetic patients treated with DES compared with BMS.

Long-term efficacy of SES. In this pooled analysis, TVR at 5-year follow-up was reduced nearly 2-fold in the SES versus BMS group, mainly due to remarkably lower rates of TLR during the first year. The highly significant differences in rates of TLR and TVR between patients randomized to SES versus BMS persisted from 1 to 5 years. Thus, it is unlikely that the use of SES is associated with a late catch-up phenomenon.

Study limitations. The results of this analysis are hypothesis-generating. Information about patient adherence to antiplatelet therapy at follow-up was not collected. Insufficient antiplatelet therapy as a significant predictor of late stent thrombosis was not a concern in 2002, when

patient enrollment in the trials was completed. Therefore, a relationship between duration of dual antiplatelet therapy and stent thrombosis cannot be established. Finally, the results of this study cannot be generalized for the use of SES beyond the approved (off-label) indications.

Conclusions

In this pooled analysis, the use of SES compared with BMS demonstrated persistent superior efficacy in terms of a reduction in TVR without an increase in rates of death, MI, or stent thrombosis for up to 5 years and from 1 to 5 years.

Acknowledgment
The authors thank Jason Kahn for the editing of this paper.

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Key Words: drug-eluting stent ■ stent ■ restenosis ■ thrombosis ■ long term.