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Paclitaxel Versus Sirolimus Stents in Diabetic and Nondiabetic Patients

Maria Chiu, MSc; Dennis T. Ko, MD, MSc; Peter C. Austin, PhD; Eric A. Cohen, MD; James L. Velianou, MD; Ron Goeree, MA; Gord Blackhouse, MBA, MSc; Jack V. Tu, MD, PhD

Background—Drug-eluting stents are more effective in reducing restenosis than bare-metal stents. Less certain is the relative performance of 2 widely used drug-eluting stents—sirolimus- and paclitaxel-eluting stents—in diabetic and nondiabetic patients undergoing percutaneous coronary intervention in routine clinical practice. We therefore studied the long-term effectiveness and safety of sirolimus versus paclitaxel stents overall and stratified by the absence or presence of diabetes.

Methods and Results—We compared sirolimus and paclitaxel stents in a propensity-score matched cohort of 2054 pairs of patients (835 matched pairs of diabetic patients and 1219 matched pairs of nondiabetic patients) undergoing percutaneous coronary intervention in Ontario between December 1, 2003 and March 31, 2006. The cohort was derived from the Cardiac Care Network of Ontario percutaneous coronary intervention registry and linked to population-based administrative health databases. In the overall cohort, there was no difference in rates of target-vessel revascularization ($P=0.47$), myocardial infarction ($P=0.71$), or death ($P=0.49$). As compared with paclitaxel stents, the use of sirolimus stents was associated with a significantly lower 3-year rate of target-vessel revascularization in nondiabetic patients (8.3% versus 10.0%, $P=0.01$), but not in diabetic patients (12.7% versus 10.3%, $P=0.07$). Rates of all-cause mortality were similar in patients receiving sirolimus stents versus paclitaxel stents in both the diabetic (8.4% versus 9.2%, $P=0.91$) and nondiabetic (4.6% versus 3.0%, $P=0.22$) groups.

Conclusions—In this large observational study, patients receiving paclitaxel and sirolimus stents had similar mortality rates, but nondiabetic patients receiving sirolimus stents were significantly less likely to require repeat revascularization. **(*Circ Cardiovasc Qual Outcomes*. 2009;2:96-107.)**

Key Words: coronary disease ■ diabetes mellitus ■ revascularization ■ stents ■ real-world outcomes

Sirolimus and paclitaxel stents, the first 2 types of drug-eluting stents to be widely marketed and used in North America, have been found to be more effective than bare-metal stents in reducing the need for repeat revascularization after percutaneous coronary intervention (PCI).[1–3] Although a number of studies have compared the relative performance of these 2 drug-eluting stent systems, the results have been inconsistent. Some trials have demonstrated similar rates of repeat revascularization associated with the 2 stent types,[4,5] whereas others have reported lower rates of angiographic and clinical restenosis in patients receiving sirolimus stents.[6–8] There is also uncertainty about the relative effectiveness and safety of paclitaxel versus sirolimus stents in coronary artery disease patients with diabetes mellitus, a population at a disproportionately higher risk of atherosclerosis and in-stent restenosis than its nondiabetic counterpart.[9–13] A major limitation of earlier studies has been a lack of adequate sample size to demonstrate superiority of one drug-eluting stent over the other among diabetic patients.[14]

Clinical Perspective see p 107

In this study, we present results of a comparison of paclitaxel versus sirolimus stents in a large population-based sample of patients undergoing PCI in Ontario, Canada. Rates of target-vessel revascularization, myocardial infarction, death, and a composite of nonfatal myocardial infarction or death were examined in propensity-score matched samples of patients followed for up to 3 years. A few previous studies have suggested, but not confirmed, that the 2 drug-eluting stent types vary in their effectiveness depending on the presence or absence of diabetes.[15,16] We therefore studied patient outcomes in both the overall cohort and separately in patients with and without diabetes.

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From the Institute for Clinical Evaluative Sciences (M.C., D.T.K., P.C.A., J.V.T.); the Institute of Medical Science (M.C., J.V.T.), and the Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto (D.T.K., E.A.C., J.V.T.), Toronto, Canada; and St. Joseph's Healthcare and Programs for Assessment of Technology in Health (PATH) Research Institute (R.G., G.B.) and the Hamilton Health Sciences, McMaster University (J.L.V.), Hamilton, Canada.

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Correspondence to Jack V. Tu, MD, PhD, Institute for Clinical Evaluative Sciences G106-2075 Bayview Ave, Toronto, ON M4N 3M5, Canada. E-mail tu@ices.on.ca

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SUMMARY

- Little is known about the relative performance of sirolimus- and paclitaxel-eluting stents in diabetic and nondiabetic patients with coronary artery disease in routine clinical practice.
- This study examined the long-term effectiveness and safety of sirolimus versus paclitaxel stents in patients who underwent percutaneous coronary intervention in Ontario between December 1, 2003 and March 31, 2006.
- Rates of target-vessel revascularization, myocardial infarction, and death were compared in the propensity-score matched cohort of 2054 pairs of patients and separately among the 835 matched pairs of diabetic patients and the 1219 matched pairs of nondiabetic patients.
- In the overall cohort, there was no significant difference in 3-year rates of target-vessel revascularization ($P=0.47$), myocardial infarction ($P=0.71$), or death ($P=0.49$).
- Rates of all-cause mortality were similar in patients receiving sirolimus stents versus paclitaxel stents in both the diabetic (8.4% versus 9.2%, $P=0.91$) and nondiabetic (4.6% versus 3.0%, $P=0.22$) groups.
- A key finding of this study was the interaction between diabetes status and the effectiveness of sirolimus versus paclitaxel stents, where sirolimus stents were significantly more effective in reducing the need for target-vessel revascularization in nondiabetic patients (8.3% versus 10.0%, $P=0.01$) but not in diabetic patients (12.7% versus 10.3%, $P=0.07$).
- Greater awareness of these findings may lead to better choice of drug-eluting stents in patients and reduced need for repeat revascularization in the future.

Methods

Study Population

Our study cohort was derived from the prospective clinical registry of the Cardiac Care Network of Ontario, which includes all patients undergoing cardiac procedures in the 12 PCI centers in Ontario. All procedures are funded under the government's universal health insurance plan. Cardiac-procedure referral forms and patient charts are reviewed by Cardiac Care Network nurse coordinators to gather registry information, including patient demographic characteristics, cardiac history, and medical conditions, as well as PCI procedure data, such as lesion location and stent type, length, and diameter. Data from the Cardiac Care Network registry were supplemented by linking to population-based administrative databases, including the Canadian Institute for Health Information's hospital-discharge abstract database[17] for patient's comorbidities, and Statistics Canada's census data[18] for median household income from which patient-level income quintiles were derived. Diabetes status was verified using the Ontario Diabetes Database, a registry that has been validated against primary care health records and has been shown to identify patients with diabetes with high sensitivity (86%) and specificity (97%).[19,20]

For the current study, we identified patients who underwent a PCI between December 1, 2003 and March 31, 2006 with placement of a single sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson), a single paclitaxel-eluting stent (Taxus, Boston Scientific), or multiple drug-eluting stents of the same type. For each patient, the first PCI within the study period was chosen as the index procedure. Individuals with coexisting conditions (ie, dementia, secondary cancer, and moderate or severe liver disease), missing information on potentially important prognostic factors (eg, age, socioeconomic status, lesion location, or Canadian Cardiovascular Society angina classification), and those who had undergone a PCI in the past year were excluded from the cohort. Because linkages with multiple databases were performed using unique encrypted health card numbers, patients with invalid Ontario health card numbers were also excluded.

The study cohort was linked to clinical and administrative databases to ascertain clinical outcomes. Target-vessel revascularization was defined as a follow-up PCI performed on the same vessel as the index PCI (with or without stent implantation), or coronary-artery bypass grafting. Admissions for myocardial infarction (codes I21 and I22 in the International Classification of Diseases, 10th Revision) were identified from the Canadian Institute for Health Information discharge abstract database,[21] and all-cause mortality was identified from the Ontario Registered Persons Database. Data on all outcomes were available up to and including March 31, 2007, providing at least 1 year of follow-up for every patient in our cohort.

Choice of Drug-Eluting Stent Type

In Ontario, during the study period, each hospital received a fixed amount of funding from the government that allowed it to purchase drug-eluting stents for ≈40% of all patients undergoing PCI procedures at their institution.[1] Individual institutions then negotiated contracts with the 2 stent manufacturers. Because paclitaxel stents had a lower price than sirolimus stents in Ontario, most institutions purchased more paclitaxel stents. The choice of drug-eluting stent for each patient, however, was left to the discretion of individual operators at each institution.

Ethics Approval and Role of Funding

Ethics approval for this study was granted by the Research Ethics Board at Sunnybrook Health Sciences Centre. Written consent from patients was not required because participation in the Cardiac Care Network registry is mandated under Ontario's health information privacy legislation. This study was conducted using the funding entirely from public sources. There was no industry involvement in the study design, data collection, data analysis, or writing of the report.

Statistical Analysis

Using univariate analysis, we identified a total of 22 factors (Table 1) that were significantly associated with at least 1 of the 3 main study outcomes, ie, target-vessel revascularization, myocardial infarction, or death. We used t tests for means and χ^2 tests for proportions to compare the prevalence of risk factors in the paclitaxel versus sirolimus stent groups before propensity-score matching.

Propensity-score matching methods[22–24] used in this study are described in detail elsewhere.[1] Briefly, a propensity score was derived for each patient using the 22 factors listed in Table 1. A greedy, nearest neighbor 1:1 matching algorithm was used to match subjects on the logit of the propensity score (using calipers of width equal to 0.2 times the standard deviation of the logit of the propensity score) and on diabetes status. Standardized differences were used to compare the measured baseline characteristics between the 2 groups. A standardized difference of <0.1 was considered indicative of good balance.[25] Event-free survival curves for all clinical end points were constructed by means of the Kaplan-Meier method. The Kaplan-Meier survival curves were compared using a test proposed by Klein and Moeschberger that is similar in form to the McNemar test for comparing correlated binary proportions.[26]

We performed a sensitivity analysis using multivariate Cox proportional-hazards regression models on the entire unmatched sample of patients who met study eligibility. Hazard ratios and 95% CIs were adjusted for the 22 clinically relevant characteristics listed in Table 1, and the potential interaction between diabetes status and the effectiveness of the 2 stent types was tested.

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Table 1. Baseline Characteristics of Patients With Paclitaxel- or Sirolimus-Eluting Stents Before Propensity-Score Matching*

	All Patients			Diabetic Patients Only			Nondiabetic Patients Only		
Characteristics	PES (n=7964)	SES (n=2125)	*P*	PES (n=2999)	SES (n=865)	*P*	PES (n=4965)	SES (n=1260)	*P*
Age, y	62.0±11.5	62.1±11.5	0.75	63.1±10.9	63.3±10.6	0.63	61.3±11.8	61.2±12.0	0.83
Male sex, %	70.3	71.1	0.47	67.6	68.1	0.77	71.9	73.2	0.38
Income quintile, %†									
1	19.2	18.5	0.21	21.8	20.3	0.22	17.6	17.3	0.55
2	20.9	18.8		22.5	20.1		19.9	17.9	
3	19.9	21.1		20.0	22.2		19.9	20.4	
4	21.0	21.6		19.8	19.4		21.7	23.1	
5	19.0	19.9		15.9	17.9		21.0	21.3	
Cardiac condition or procedures, %									
Hypertension	41.0	31.3	<0.001	47.2	35.6	<0.001	37.2	28.3	<0.001
Myocardial infarction									
Same day as index PCI	8.1	6.7	0.004	6.5	6.6	0.20	9.1	6.8	0.002
1 to 7 d before index PCI	18.8	19.6		17.3	15.6		19.7	22.4	
8 to 365 d before index PCI	11.4	9.4		11.8	9.8		11.2	9.0	
None within 365 d before index PCI	61.7	64.3		64.4	68.0		60.0	61.7	
CCS angina classification‡									
0	6.3	7.4	<0.001	6.9	7.4	0.01	5.9	7.4	<0.001
I	5.5	4.9		5.6	4.7		5.4	5.1	
II	15.5	20.6		15.5	20.9		15.5	20.3	
III	26.4	25.6		27.7	24.9		25.6	26.0	
IVA	24.6	24.8		25.2	25.3		24.2	24.5	
IVB	11.5	8.3		10.4	8.2		12.2	8.4	
IVC	9.4	7.7		7.9	7.5		10.4	7.8	
IVD	0.7	0.7		0.7	1.0		0.7	0.5	
Congestive heart failure	5.3	4.9	0.40	8.5	7.4	0.29	3.4	3.2	0.66
Previous coronary-artery bypass surgery	10.9	10.2	0.35	14.2	13.5	0.60	8.9	7.9	0.27
PCI >1 yr before index PCI	6.1	4.5	0.004	7.0	4.7	0.02	5.6	4.3	0.07
Coexisting conditions, %									
Diabetes	37.7	40.7	0.01	100	100	n/a	0	0	n/a
Peripheral vascular disease	5.9	6.5	0.27	8.8	9.2	0.69	4.1	4.6	0.40
Chronic obstructive pulmonary disease	4.1	3.9	0.62	5.4	4.3	0.19	3.4	3.7	0.64
Cerebrovascular disease	5.1	4.8	0.52	5.5	6.0	0.54	5.0	4.0	0.14
Primary cancer	0.8	1.0	0.25	0.8	0.9	0.65	0.8	1.1	0.26
Renal failure requiring dialysis	1.3	1.4	0.81	2.8	2.4	0.52	0.4	0.7	0.22
Index PCI									
Ad hoc PCI§	57.1	40.8	<0.001	53.1	36.9	<0.001	59.6	43.4	<0.001
Stent length, mm	27.7±16.3	32.5±20.3	<0.001	28.2±17.0	32.3±20.9	<0.001	27.4±15.8	32.7±19.9	<0.001
Stent diameter, mm	2.8±0.4	2.8±0.3	0.02	2.8±0.4	2.8±0.3	0.18	2.8±0.4	2.8±0.3	0.05
No. stents per patient	1.5±0.8	1.5±0.8	0.03	1.5±0.8	1.5±0.9	0.24	1.5±0.7	1.5±0.8	0.07
No. vessels stented	1.1±0.4	1.1±0.4	0.43	1.1±0.4	1.1±0.4	0.85	1.1±0.3	1.1±0.3	0.17
ACC-AHA lesion type, %									
A	4.9	5.8	<0.001	5.1	6.4	0.16	4.8	5.5	<0.001
B1	25.4	23.4		25.0	24.9		25.6	22.4	
B2	39.1	34.8		38.2	34.8		39.6	34.8	
C	30.6	36.0		31.6	34.0		30.0	37.3	
No. days of follow-up	766.4±248.4	699.7±249.2	<0.001	767.9±245.1	687.5±245.2	<0.001	765.5±250.5	708.0±251.6	<0.001

PES indicates paclitaxel-eluting stents; SES, sirolimus-eluting stents; ACC-AHA, American College of Cardiology–American Heart Association.

*Plus-minus values are means±SD.

†The first income quintile is the group with the lowest socioeconomic status.

‡The Canadian Cardiovascular Society (CCS) angina classifications range from 0 (no symptoms) to IVD (shock).

§PCI performed at the same sitting as the diagnostic catheterization.

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In all analyses, the rates of outcome between paclitaxel and sirolimus stents were compared in the overall cohort and then separately for diabetic and nondiabetic patients.

All statistical tests were 2-sided, and probability values of <0.05 were considered statistically significant. Statistical analyses were performed with the use of SAS software, version 9.1 (SAS Institute, Inc) and the R programming language.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Characteristics of Patients and Procedures

Before Propensity-Score Matching

From December 2003 to March 2006, a total of 13 797 patients received either a sirolimus-eluting stent or a paclitaxel-eluting stent in PCI procedures in Ontario. After applying the study's exclusion criteria, 10 089 patients were included in the unmatched cohort. Table 1 shows the characteristics of 2125 patients with sirolimus stents and 7964 patients with paclitaxel stents. Paclitaxel-eluting stents were selectively implanted in patients who were hypertensive, more likely to have had a recent acute myocardial infarction, and more likely to have undergone a previous PCI more than a year before the index stent procedure. The mean stent length was 4.8 mm longer in patients with sirolimus stents than in those with paclitaxel stents; however, mean stent diameter differed by less than one tenth of a millimeter between the 2 groups.

The overall percentage of patients in our unmatched cohort who received the sirolimus stent was 21.1%; however, the percentage ranged from 10.1% to 34.8% during the 28 months of cohort accrual (Appendix Figure 1A). The mean follow-up period was 67 days longer in the paclitaxel-stent group than in the sirolimus-stent group ($P<0.001$).

After Propensity-Score Matching

Matching on the propensity score and diabetes status resulted in the formation of 2054 matched pairs of patients in the overall cohort. All 22 characteristics, including the mean number of days of follow-up (Appendix Figure 1B), were well balanced between the paclitaxel- and sirolimus-stent groups (standardized differences <0.04; Table 2). The mean duration of follow-up was 708 days and 707 days in the paclitaxel- and sirolimus-stent groups, respectively. All variables were also well balanced among the 835 matched pairs of diabetic patients (standardized differences <0.09) and among the 1219 matched pairs of nondiabetic patients (standardized differences <0.07; Table 2).

Rates of Target-Vessel Revascularization

The median duration of follow-up for revascularization was 619 days in the sirolimus-stent group and 618 days in the paclitaxel-stent group. Overall, in the propensity-score matched sample, the rates of target-vessel revascularization were similar in the sirolimus-stent and paclitaxel-stent groups throughout the 3-year follow-up period ($P=0.47$; Figure 1, Table 3). However, in the diabetic and nondiabetic groups, the 2 drug-eluting stent types differed in their impact on repeat procedures. Among the diabetic patients, the 3-year rate of target-vessel revascularization was higher in the sirolimus-stent group (12.7%) than in the paclitaxel-stent group (10.3%) but did not approach statistical significance at the 5% level ($P=0.07$). In contrast, among the nondiabetic patients, the rate was significantly lower in the sirolimus-stent group (8.3%) than in the paclitaxel-stent group (10.0%, $P=0.01$; Figure 1, Table 3).

Rates of Myocardial Infarction and Death

In the overall matched sample, the 3-year rates of myocardial infarction after PCI did not differ significantly between the sirolimus-stent (4.6%) and paclitaxel-stent (5.7%) groups ($P=0.71$; Table 3). As shown in Figure 2, the 3-year rates of mortality were also similar between the sirolimus-stent (6.1%) and paclitaxel-stent (5.5%) groups ($P=0.49$), as were the rates observed for the composite outcome of nonfatal myocardial infarction or death ($P=0.79$). In diabetic patients, paclitaxel stents showed favorable myocardial infarction–free survival in the first 2.6 years, but this trend did not continue throughout the 3-year study period. Among nondiabetic patients, the rates of myocardial infarction were similar in the 2 stent groups throughout the follow-up period ($P=0.17$). Death rates did not differ significantly in patients with sirolimus versus paclitaxel stents in either the diabetic (8.4% versus 9.2%, $P=0.91$) or nondiabetic (4.6% versus 3.0%, $P=0.22$) groups. Rates of the composite end point, myocardial infarction or death, were also similar between the sirolimus-stent and paclitaxel-stent groups in the patients with ($P=0.47$) and without ($P=0.71$) diabetes (Figure 2, Table 3).

Sensitivity Analysis

Table 4 displays the results of the multivariate Cox proportional-hazards regression analysis of the unmatched sample of 10 089 patients. The results of this sensitivity analysis were generally consistent with the Kaplan-Meier survival analysis of the propensity-score matched cohort, with some differences in the results for myocardial infarction in diabetic patients. The all-patient cohort showed nonsignificant relationships between drug-eluting stent type and clinical outcomes. A significant interaction ($P<0.01$), however, emerged between diabetes status and risk of target-vessel revascularization associated with the 2 stent systems. When sirolimus and paclitaxel stents were compared in diabetic and nondiabetic groups, sirolimus stents were associated with a hazard ratio (95% CI) of 1.31 (1.01 to 1.69) among diabetic patients and a hazard ratio (95% CI) of 0.72 (0.56 to 0.93) among nondiabetic patients. The hazard ratios for the remaining analyses were nonsignificant (Table 4).

Discussion

In this population-based study, we compared the long-term effectiveness and safety of sirolimus and paclitaxel stents in a propensity-score matched sample of 2054 pairs of patients (835 pairs of diabetic patients and 1219 pairs of nondiabetic patients). There was no major difference between paclitaxel and sirolimus stents in the overall cohort. An important observation in our study was that the 2 types of drug-eluting stents differed in their impact on clinically important restenosis among patients with and without diabetes. Sirolimus stents were more effective in reducing target-vessel revascularization in nondiabetic patients, but trended toward being

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Table 2. Baseline Characteristics of Patients With Paclitaxel- or Sirolimus-Eluting Stents After Propensity-Score Matching*

	All Patients			Diabetic Patients Only			Nondiabetic Patients Only		
Characteristics	PES (n=2054)	SES (n=2054)	Standardized Difference of the Mean	PES (n=835)	SES (n=835)	Standardized Difference of the Mean	PES (n=1219)	SES (n=1219)	Standardized Difference of the Mean
Age, y	61.9±11.4	62.0±11.5	0.009	63.2±10.7	63.2±10.7	0.000	61.0±11.7	61.2±12.0	0.015
Male sex, %	71.5	71.3	0.003	68.5	68.3	0.005	73.5	73.4	0.002
Income quintile, %†									
1	18.0	18.5	0.015	22.0	19.9	0.053	15.2	17.6	0.066
2	19.0	18.9	0.001	19.3	20.4	0.027	18.8	18.0	0.021
3	20.9	21.1	0.005	21.7	22.4	0.017	20.3	20.2	0.004
4	21.5	21.7	0.004	18.8	19.5	0.018	23.4	23.1	0.006
5	20.6	19.8	0.022	18.2	17.8	0.009	22.3	21.1	0.030
Cardiac condition or procedures, %									
Hypertension	31.4	32.1	0.016	36.8	36.4	0.007	27.7	29.2	0.033
Myocardial infarction									
Same day as index PCI	7.1	7.0	0.006	8.1	6.8	0.050	6.4	7.1	0.026
1 to 7 d before index PCI	19.9	19.7	0.006	18.1	15.6	0.067	21.2	22.5	0.032
8 to 365 d before index PCI	9.1	9.5	0.015	9.6	10.1	0.016	8.8	9.2	0.014
None within 365 d before index PCI	63.9	63.8	0.001	64.2	67.5	0.071	63.7	61.3	0.049
CCS angina classification‡									
0	7.3	7.2	0.006	9.2	6.9	0.083	6.0	7.3	0.053
I	5.0	5.0	0.002	4.7	4.8	0.006	5.3	5.1	0.007
II	19.5	20.1	0.013	18.6	20.5	0.048	20.2	19.8	0.010
III	24.9	26.0	0.026	24.2	25.6	0.033	25.3	26.3	0.021
IVA	25.8	24.7	0.026	26.6	25.0	0.036	25.3	24.4	0.019
IVB	8.7	8.5	0.005	8.5	8.3	0.009	8.8	8.7	0.003
IVC	7.9	7.9	0.000	7.2	7.8	0.023	8.4	8.0	0.015
IVD	0.9	0.7	0.021	1.1	1.1	0.000	0.8	0.5	0.041
Congestive heart failure	5.2	4.8	0.016	8.3	7.4	0.031	3.0	3.0	0.000
Previous coronary-artery bypass surgery	10.4	10.3	0.005	12.0	13.7	0.050	9.4	8.0	0.050
PCI >1 yr before index PCI	4.5	4.6	0.005	5.0	4.8	0.011	4.1	4.4	0.016
Coexisting conditions, %									
Diabetes	40.7	40.7	0.000	100	100	n/a	0	0	n/a
Peripheral vascular disease	6.2	6.3	0.002	8.7	9.0	0.008	4.5	4.4	0.004
Chronic obstructive pulmonary disease	4.6	3.9	0.034	5.9	4.3	0.071	3.8	3.7	0.004
Cerebrovascular disease	4.1	4.4	0.015	4.3	5.5	0.055	3.9	3.6	0.017
Primary cancer	0.9	1.0	0.015	0.7	1.0	0.026	1.0	1.1	0.008
Renal failure requiring dialysis	1.5	1.3	0.017	3.1	2.0	0.068	0.3	0.7	0.056
Index PCI									
Ad hoc PCI§	42.5	41.9	0.012	41.4	37.8	0.073	43.2	44.6	0.030
Stent length, mm	31.0±18.6	31.4±19.2	0.024	29.9±17.9	31.3±20.0	0.075	31.7±19.1	31.5±18.6	0.011
Stent diameter, mm	2.8±0.4	2.8±0.3	0.009	2.8±0.4	2.8±0.3	0.037	2.8±0.4	2.8±0.3	0.011
No. stents per patient	1.5±0.8	1.5±0.8	0.014	1.5±0.7	1.5±0.9	0.075	1.5±0.8	1.5±0.8	0.029
No. vessels stented	1.1±0.3	1.1±0.4	0.004	1.1±0.4	1.1±0.4	0.045	1.1±0.3	1.1±0.3	0.028
ACC-AHA lesion type, %									
A	6.8	6.0	0.032	7.7	6.6	0.042	6.2	5.7	0.024
B1	23.3	23.9	0.014	23.7	25.4	0.039	23.1	22.9	0.004
B2	35.0	35.0	0.001	35.8	34.7	0.023	34.4	35.2	0.017
C	34.9	35.1	0.003	32.8	33.3	0.010	36.3	36.3	0.002
No. days of follow-up	707.9±253.7	706.9±249.3	0.004	698.8±251.2	694.7±245.1	0.017	714.0±255.4	715.3±251.8	0.005

PES indicates paclitaxel-eluting stents; SES, sirolimus-eluting stents; ACC-AHA, American College of Cardiology–American Heart Association.

*Plus-minus values are means±SD.

†The first income quintile is the group with the lowest socioeconomic status.

‡The Canadian Cardiovascular Society (CCS) angina classifications range from 0 (no symptoms) to IVD (shock).

§PCI performed at the same sitting as the diagnostic catheterization.

inferior in diabetics. Our observation regarding diabetic patients is consistent with results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital registries that reported 2-year target-vessel revascularization rates in diabetic patients that favored paclitaxel stents, albeit statistically nonsignificantly.[15] Our study findings are also supported by evidence from a previous indirect meta-analysis in which sirolimus stents outperformed paclitaxel stents with respect to preventing restenosis and target-lesion revascularization in nondiabetic patients but showed no superiority over paclitaxel stents in patients with diabetes.[16]

Despite differences in the effectiveness of paclitaxel and sirolimus stents in reducing revascularization in patients with or without diabetes, the 2 devices conferred similar risks of major adverse outcomes irrespective of diabetes status. The 2 drug-eluting stent types were comparable in terms of all-cause mortality and a composite of myocardial infarction and

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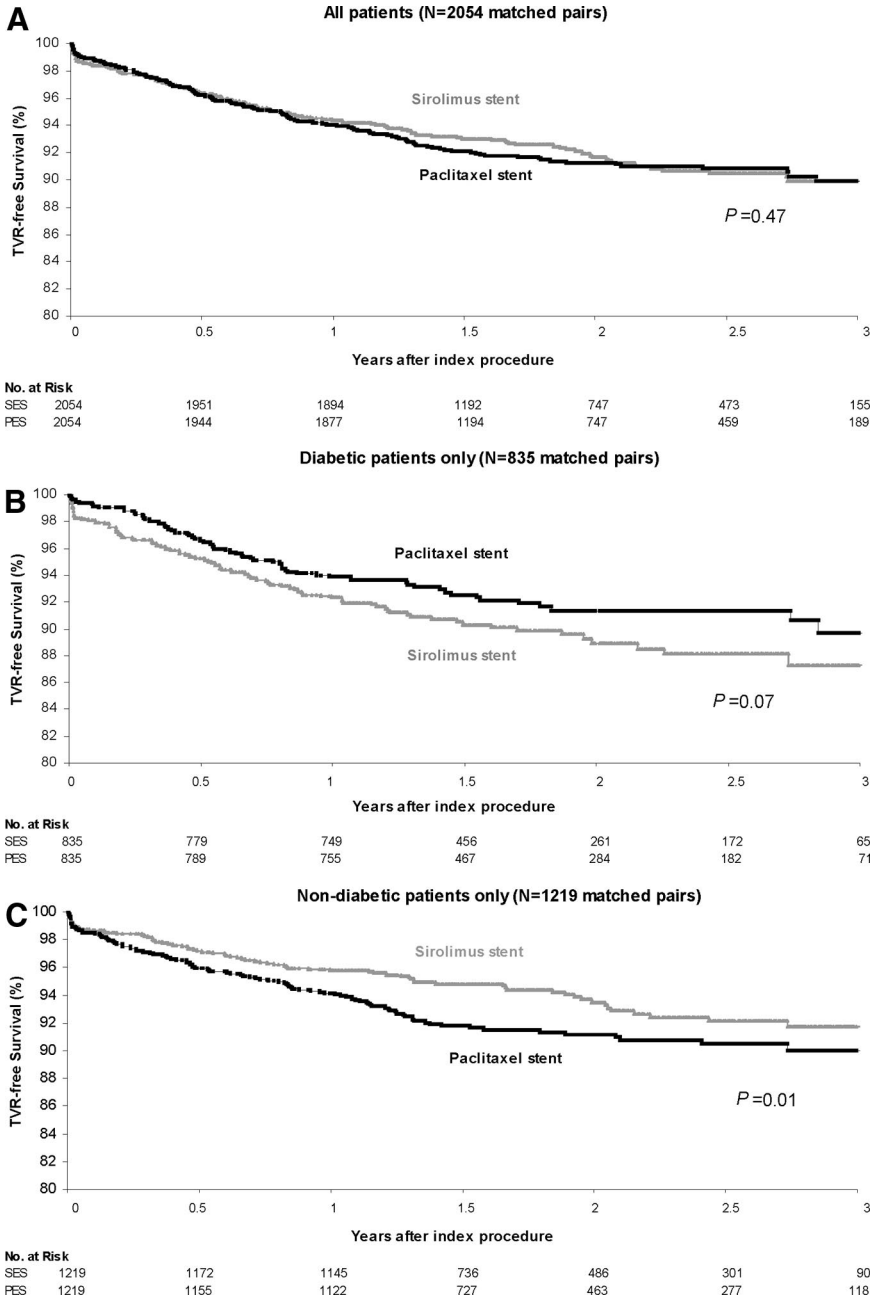

Figure 1. Target-vessel revascularization (TVR)–free survival curves for propensity-score–matched cohort of patients in the overall cohort and in diabetic and nondiabetic groups separately. *P* values are for the comparisons of the paired Kaplan-Meier curves. SES indicates sirolimus-eluting stents; PES, paclitaxel-eluting stents.

death throughout the 3-year period after stent implantation. These findings are consistent with data from the Danish Organization on Randomized Trials With Clinical Outcome II (SORT OUT II) randomized trial, which followed patients for ≈18 months,[4] as well as a meta-analysis of 16 randomized trials with a median follow-up period of 24.3 months,[7] thus reaffirming that the 2 drug-eluting devices are similar with regard to safety outcomes up to 3 years.

The results from our propensity-score matched analysis were verified by applying multivariate Cox proportional hazards regression analysis on the large unmatched cohort. In particular, when rates of target-vessel revascularization were compared in the 2 drug-eluting stent systems, we found a significant interaction between diabetes and stent type. Sirolimus stents were associated with a significant 31% increased risk in diabetic patients, but a significant 28% decreased risk in nondiabetic patients. The fact that 2 independent statistical methods, namely covariate-adjusted Cox proportional hazards modeling of unmatched samples of diabetic and nondiabetic patients and Kaplan-Meier analysis on propensity-score matched cohorts, produced analogous results provides credence to our study findings.

Of interest are the potential biological and pharmacological explanations for the apparent differences in efficacy of the 2 drug-eluting stent types among diabetic and nondiabetic patients. Sirolimus- and paclitaxel-eluting stents provide local delivery of drugs that inhibit vascular smooth muscle cell proliferation, which in turn reduces neointimal hyperplasia and restenosis. Sirolimus is a cytostatic agent that has the ability to inhibit the mammalian target of rapamycin regula-

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Table 3. Outcome Rates After Implantation of Paclitaxel- or Sirolimus-Eluting Stents in the Propensity-Score Matched Cohort*

		Years After Index Procedure						
	Stent Type	0.5	1	1.5	2	2.5	3	*P*†
All patients								
Target-vessel revascularization	PES	3.8	6.0	7.9	8.7	9.2	10.1	0.47
	SES	3.6	5.6	7.0	8.3	9.5	10.1	
Myocardial infarction	PES	1.4	2.2	3.4	4.2	4.9	5.7	0.71
	SES	1.9	2.7	3.0	3.7	4.4	4.6	
Death	PES	1.6	2.3	3.3	4.1	4.4	5.5	0.49
	SES	1.6	2.3	3.3	4.8	5.0	6.1	
Myocardial infarction or death	PES	3.0	4.3	6.3	7.9	8.8	10.6	0.79
	SES	3.2	4.5	5.7	7.8	8.7	9.7	
Diabetic patients								
Target-vessel revascularization	PES	3.4	6.1	7.4	8.6	8.6	10.3	0.07
	SES	4.7	7.7	9.7	11.1	11.9	12.7	
Myocardial infarction	PES	1.0	1.7	3.3	4.6	5.9	7.3	0.04
	SES	2.7	4.0	4.5	5.9	6.3	6.3	
Death	PES	2.2	3.2	4.8	6.4	7.2	9.2	0.91
	SES	2.2	3.1	4.4	6.4	6.7	8.4	
Myocardial infarction or death	PES	3.1	4.9	7.8	10.4	12.4	15.8	0.47
	SES	4.3	6.2	7.9	11.2	11.9	13.0	
Nondiabetic patients								
Target-vessel revascularization	PES	4.1	5.9	8.2	8.8	9.5	10.0	0.01
	SES	2.8	4.2	5.2	6.5	7.9	8.3	
Myocardial infarction	PES	1.7	2.5	3.4	4.0	4.3	4.7	0.17
	SES	1.4	1.7	2.0	2.3	3.1	3.4	
Death	PES	1.2	1.6	2.3	2.6	2.6	3.0	0.22
	SES	1.2	1.8	2.6	3.7	3.9	4.6	
Myocardial infarction or death	PES	2.9	3.9	5.4	6.3	6.5	7.3	0.71
	SES	2.5	3.3	4.2	5.7	6.6	7.5	

PES indicates paclitaxel-eluting stents; SES, sirolimus-eluting stents.
*Outcome rates were derived from paired Kaplan-Meier curves.
†*P* values are for the comparisons of the paired Kaplan-Meier curves.

tory protein kinase and block the cell cycle at the G1-S checkpoint. Mammalian target of rapamycin is regulated by growth factors via the phosphoinositide 3-kinase insulin signal transduction pathway,[27] which is degraded in people with diabetes.[28] Paclitaxel, on the other hand, stabilizes microtubules and arrests the cell cycle at the G1 and G2/M junctions.[29,30] The mechanism by which paclitaxel prevents restenosis is independent of the phosphoinositide 3-kinase pathway[31] and is not affected by insulin resistance. This would suggest that sirolimus may be less effective in diabetic patients than an agent independent of this pathway. A phosphoinositide 3-kinase–related attenuation of sirolimus' effect would not be expected in the nondiabetic population, in which sirolimus-eluting stents have been shown, in this and other studies,[16] to be superior to paclitaxel stents in preventing repeat revascularization. Sirolimus has also been shown to enhance agonist-induced platelet aggregation and secretion, which might impede the drug's effect in diabetic patients, who typically have more complex and diffuse lesions.[9,10]

The current investigation represents the largest population-based comparison of long-term outcomes in patients receiving paclitaxel versus sirolimus stents and is among the first studies to examine the real-world effectiveness and safety of the 2 types of drug-eluting stents in diabetic and nondiabetic patients. Previous studies, including registry reports, have not had adequate sample size to test differences in rates of clinical restenosis and adverse outcomes among diabetic patients with coronary artery disease.[14,32–34] Although a large, real-world randomized, controlled trial of the 2 stent types in diabetic and nondiabetic patients would be the best method to confirm our study findings, it would be expensive and time-consuming to conduct, and it would be many years before the results of such a trial might be completed and the results available.

Study Limitations

We recognize that this study suffers from the inherent limitations of any observational study. To account for the imbalances in characteristics of the treatment groups, the propensity-score matching technique was applied; however, there may still be some residual confounding by unmeasured

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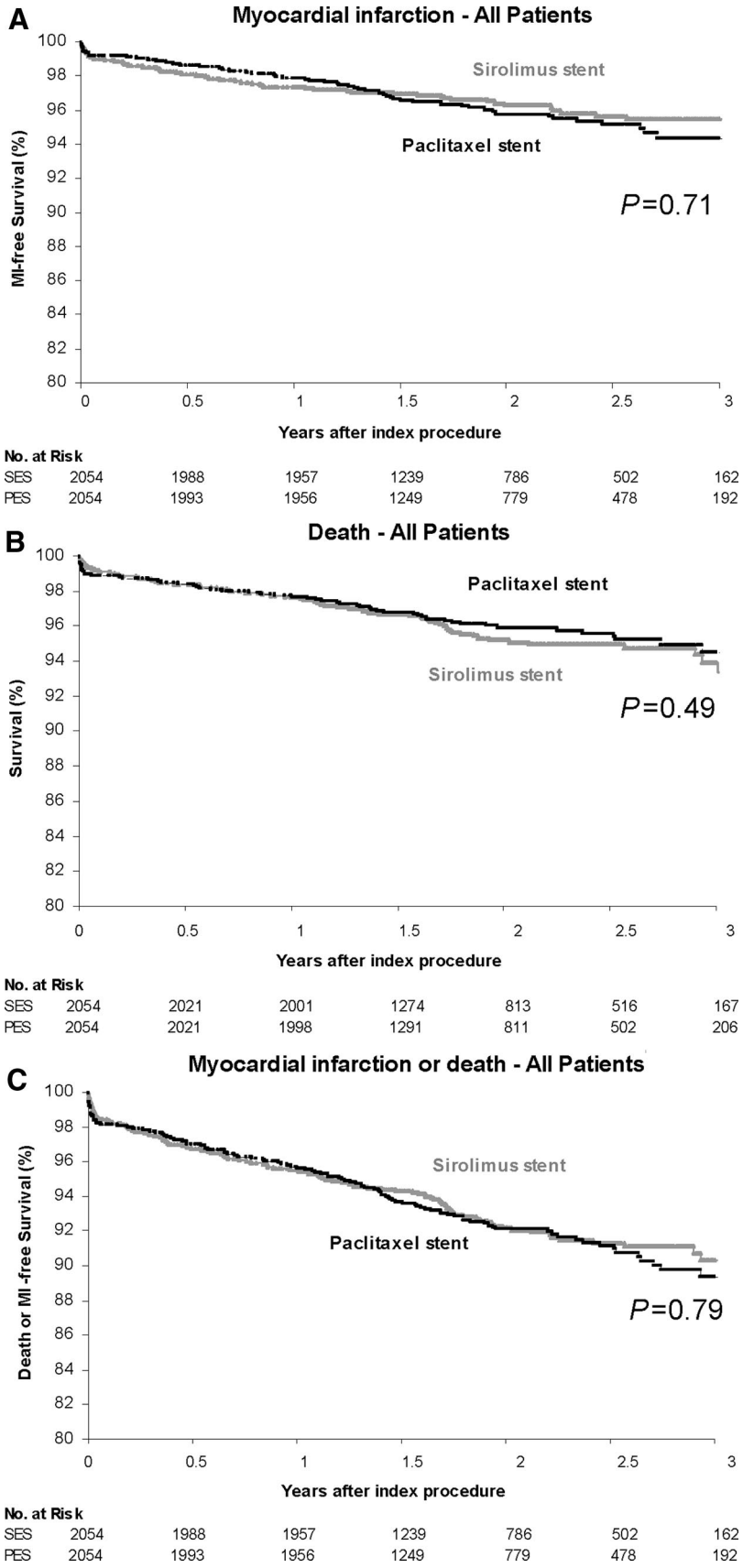

Figure 2. Event-free survival curves for propensity-score–matched cohort of patients in the overall cohort and in diabetic and nondiabetic groups separately. *P* values are for the comparisons of the paired Kaplan-Meier curves. SES indicates sirolimus-eluting stents; PES, paclitaxel-eluting stents.

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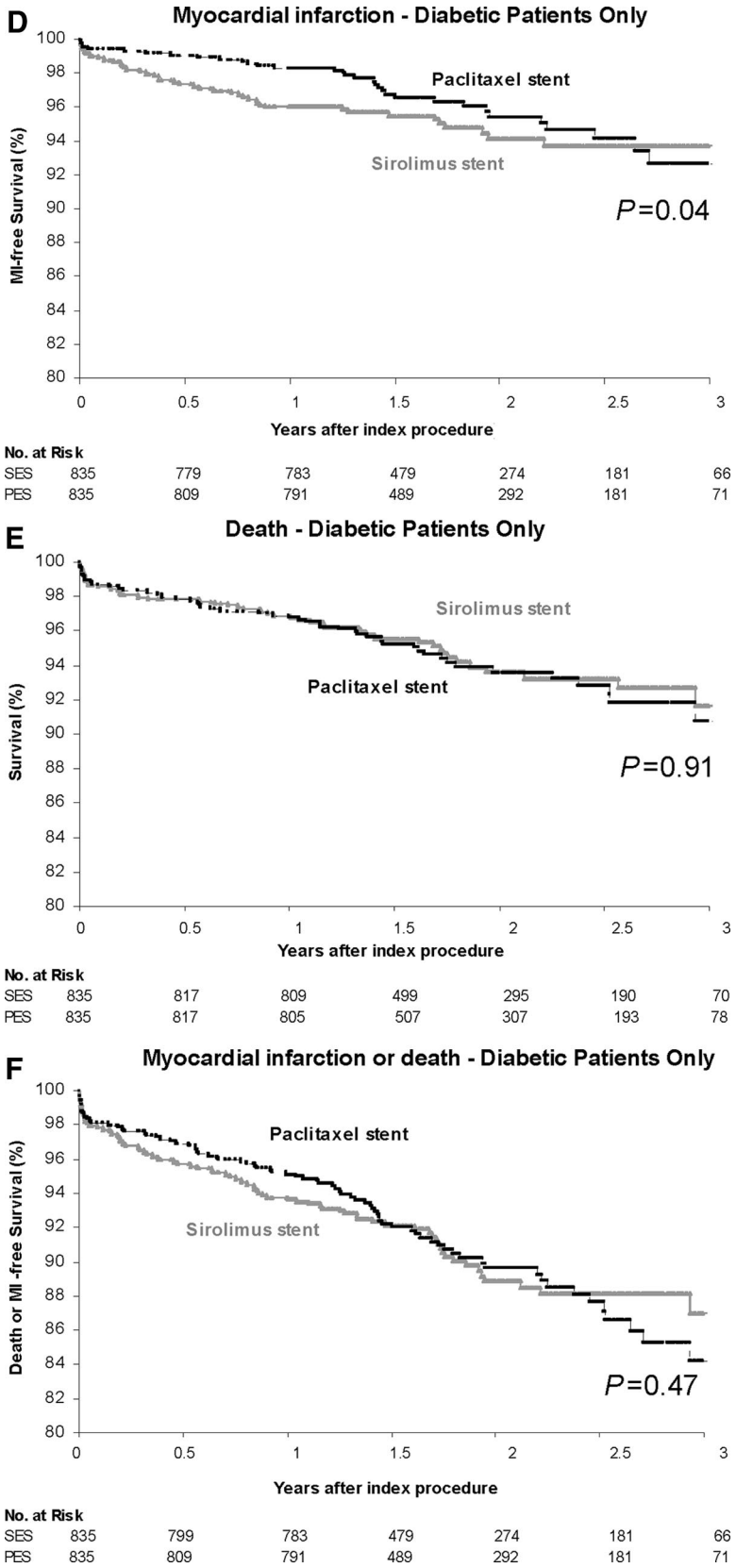

Figure 2. (*Continued*)

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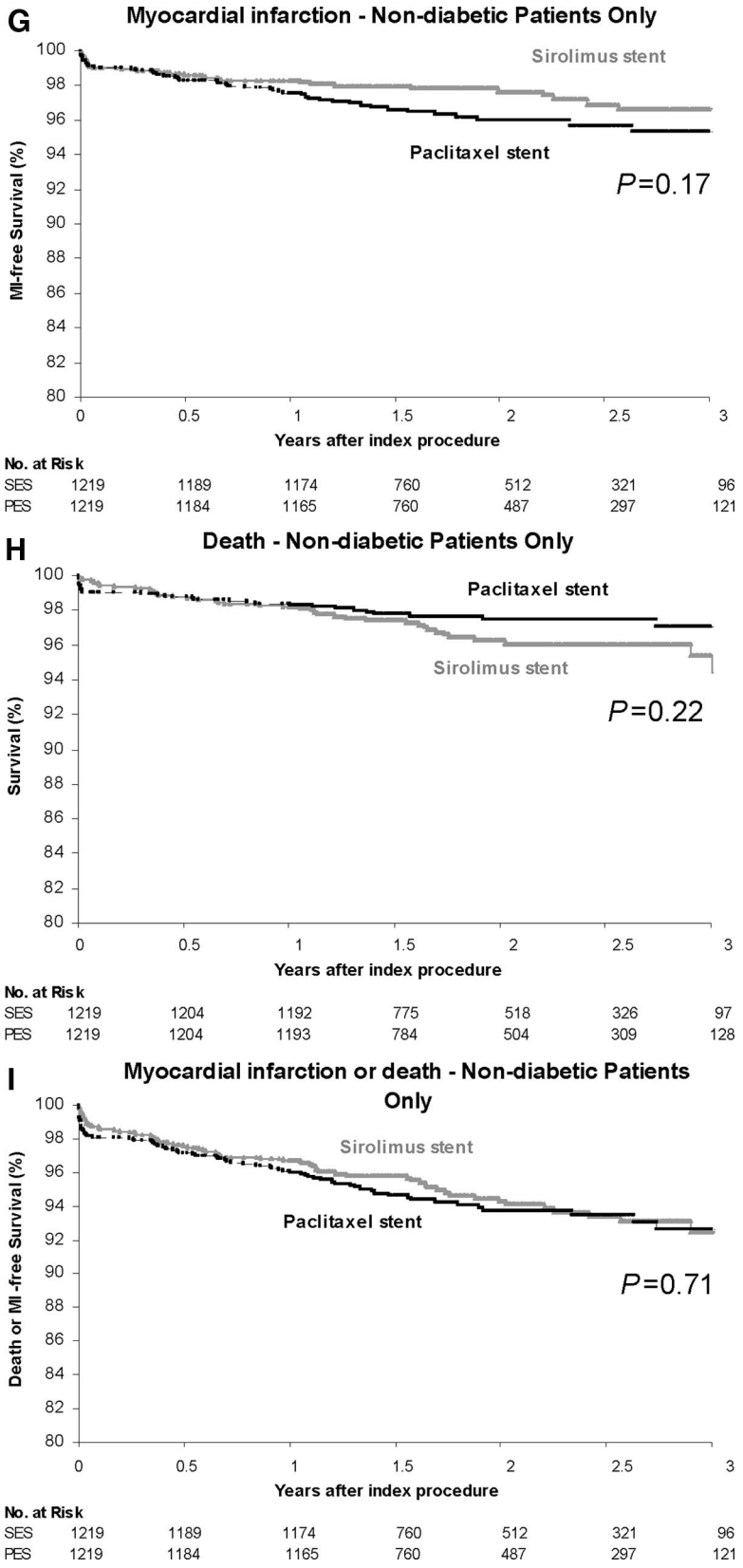

Figure 2. (*Continued*)

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Table 4. Hazard Ratios of Clinical Outcomes in Sirolimus-Eluting Versus Paclitaxel-Eluting Stent Groups Using Multivariate Cox Proportional Hazards Model*

	All Patients (n=10 089)		Diabetic Patients Only (n=3864)		Nondiabetic Patients Only (n=6225)	
Outcomes	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Target-vessel revascularization	0.94 (0.78–1.12)	0.48	1.31 (1.01–1.69)	0.04	0.72 (0.56–0.93)	0.01
Myocardial infarction	0.86 (0.66–1.11)	0.24	1.03 (0.73–1.45)	0.88	0.69 (0.47–1.03)	0.07
Death	1.14 (0.90–1.46)	0.28	1.08 (0.78–1.50)	0.65	1.27 (0.88–1.82)	0.20
Nonfatal myocardial infarction or death	0.99 (0.82–1.19)	0.91	1.07 (0.83–1.37)	0.62	0.92 (0.70–1.21)	0.55

*Each model was adjusted for age, sex, income quintile, hypertension, prior or concurrent myocardial infarction, Canadian Cardiovascular Society angina classification, congestive heart failure, previous coronary-artery bypass surgery, previous PCI >1 year before index PCI, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, cerebrovascular disease, primary cancer, renal failure requiring dialysis, ad hoc PCI, stent length, stent diameter, No. of stents per patient, No. of vessels stented, American College of Cardiology–American Heart Association lesion type, and No. of days of study follow-up.

factors. Nevertheless, this study provides important information on a highly representative sample of patients who underwent PCI in routine clinical practice. Another limitation of this study is that we lacked information on in-stent lumen loss and in-stent thrombosis. However, clinically important safety end points such as myocardial infarction and death were analyzed. Finally, we did not formally assess the cost effectiveness of the 2 different stent types and associated outcomes.

Conclusion

In conclusion, in this large observational study of paclitaxel and sirolimus stents in a real-world clinical setting, we found that although the 2 drug-eluting stent types were similarly safe in both diabetic and nondiabetic patient populations, sirolimus stents were more effective in reducing the need for target-vessel revascularization in patients without diabetes. Greater awareness of these findings may lead to better choice of drug-eluting stents in patients and reduced need for repeat revascularization in the future. Increased use of sirolimus stents in nondiabetic patients and increased use of paclitaxel stents in diabetic patients might be a strategy for enhancing the real-world effectiveness of drug-eluting stents.

Acknowledgments

M.C. conceived the study in collaboration with the other authors. M.C., J.V.T., D.T.K., and P.C.A. were responsible for conception and design of the study. M.C. and P.C.A. did the analysis and all authors interpreted the data. E.A.C., R.G., G.B., and J.V.T. assisted in the acquisition of data. The first draft was written by M.C. and all authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript. J.V.T. obtained funding for the study and provided overall supervision. Administrative, technical, and logistic supports were provided by all authors.

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Disclosures

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CLINICAL PERSPECTIVE

Differences in the effectiveness of sirolimus-eluting versus paclitaxel-eluting stents in patients with or without diabetes have been suggested but not confirmed in previous research, due in large part to the limited sample sizes of earlier studies. This large observational study compares paclitaxel and sirolimus stents in propensity-score matched samples of 2054 matched pairs of patients: 1219 pairs of nondiabetic patients and 835 pairs of diabetic patients, derived from a population-based registry of percutaneous coronary intervention patients in Ontario, Canada. In the overall cohort, the 2 stent types showed no difference in their effectiveness (rates of target-vessel revascularization) or safety (rates of myocardial infarction and rates of death). A key finding of our study was a statistically and clinically significant interaction between diabetes status and the effectiveness of sirolimus versus paclitaxel stents. Sirolimus stents were significantly more effective in reducing the need for target-vessel revascularization in nondiabetic patients, but not in diabetic patients, where paclitaxel-eluting stents trended toward a lower rate of target-vessel revascularization. The modifying effect of diabetes on the effectiveness of drug-eluting stents is supported by biological evidence and has important implications for the use of paclitaxel and sirolimus stents and their analogs. The study results could potentially inform physicians' choice of stents and help to enhance the "real-world" effectiveness of drug-eluting stents in reducing the need for repeat revascularization.

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SUPPLEMENTAL MATERIAL

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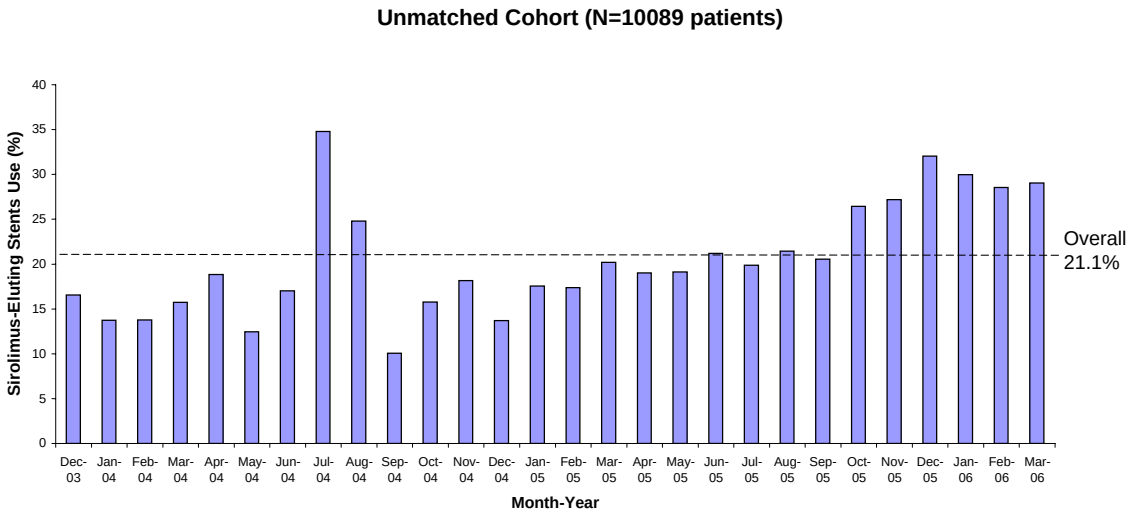
A



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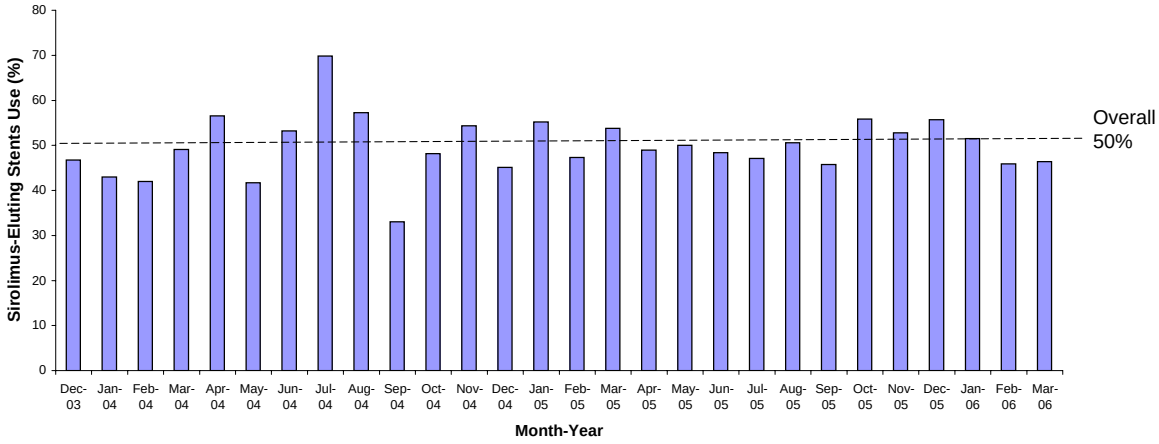

Appendix Figure 1: Temporal Trends in the Proportion of Sirolimus Stent (versus Paclitaxel Stent) Use in the Unmatched Cohort (A) and Propensity-Score Matched Cohort (B).

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