Efficacy and Safety of Ultrathin, Bioresorbable-Polymer Sirolimus-Eluting Stents Versus Thin, Durable-Polymer Everolimus-Eluting Stents for Coronary Revascularization of Patients With Diabetes Mellitus

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Patients with diabetes mellitus are prone to increased adverse outcomes after percutaneous coronary intervention, even with contemporary drug-eluting stents. Randomized controlled trials have demonstrated comparable clinical outcomes between an ultrathin bioresorbable-polymer sirolimus-eluting stent (BP-SES) and a thin-strut durable-polymer everolimus-eluting stent (DP-EES) that has specific labeling for patients with diabetes. We aimed to evaluate the safety and efficacy of the BP-SES in patients with diabetes mellitus. To determine the performance of the BP-SES in diabetic patients, patient-level data from the BIOFLOW II, IV, and V randomized controlled trials were pooled. The primary end point was target lesion failure (TLF), defined as the composite of cardiovascular death, target-vessel myocardial infarction, ischemia-driven target lesion revascularization, and definite or probable stent thrombosis, at 1 year. Among 1,553 BP-SES and 791 DP-EES patients, 757 diabetic patients were identified. Of the diabetic patients included in this analysis (494 BP-SES vs 263 DP-EES), the proportion of insulin- and noninsulin-treated patients was similar between groups. The 1-year TLF rate in the diabetic population was 6.3% in the BP-SES group and 8.7% in the DP-EES group (hazard ratio 0.82, 95% confidence interval 0.047 to 1.43, p = 0.493). There were no significant differences, based on stent type or diabetes treatment regimen, in TLF hazards. In a patient-level pooled analysis of the diabetic population from randomized trials, 1-year clinical safety and efficacy outcomes were similar in patients treated with ultrathin BP-SES and thin-strut DP-EES. **(Am J Cardiol 2019;124:1020−1026)**

The prevalence of diabetes mellitus in patients with coronary artery disease who underwent percutaneous coronary intervention is increasing and affects more than 1/3 of patients undergoing revascularization.[1] The management of these patients remains challenging, with randomized clinical trials favoring coronary artery bypass grafting in diabetics with multivessel or left main disease.[2] The bioresorbable-polymer sirolimus-eluting stent (BP-SES) Orsiro (Biotronik, Bülach, Switzerland) is a CE Mark cobalt chromium stent with sirolimus-eluting bioresorbable Poly-L-Lactide polymer and a strut thickness of 60 μm that has been shown to be noninferior to current second-generation drug-eluting stents (DES).[3] Although the very-thin-strut design of BP-SES should provide an advantage over durable-polymer second-generation DES, outcomes of the BP-SES have not been specifically assessed in patients with diabetes mellitus. The present study aimed to determine whether the BP-SES is noninferior to contemporary durable-polymer everolimus-eluting stent (DP-EES) in patients with diabetes mellitus.

Methods

We performed a patient-level pooled analysis of randomized controlled trials to compare clinical outcomes for patients with diabetes who underwent placement of BP-SES and second-generation DP-EES. The study cohort included patient-level data for diabetics from the BIOFLOW II,[4] BIOFLOW IV,[5] and BIOFLOW V[6] randomized clinical trials. Each trial included in this analysis was approved by the local regulatory authorities and conducted in accordance with good clinical practice. The design and methodology of each study have been previously described.

In brief, BIOFLOW II (NCT01356888) randomized 452 patients to BP-SES or DP-EES to assess 5-year target lesion failure (TLF).[4] The investigators reported low TLF rates with BP-SES, comparable to Xience Prime DP-EES (Abbott, Santa Clara, California), with an absence of definite stent thrombosis.[4] BIOFLOW IV (NCT01939249) was a prospective, multicenter, randomized controlled trial that evaluated 579 patients from 46 international sites. Patients with de novo coronary lesions were randomized 2:1 to BP-SES and the Xience

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See page 1025 for disclosure information.

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Prime DP-EES. Three-year results from BIOFLOW IV have been reported, with 5-year follow-up planned.[5] The BIOFLOW V (NCT02389946) study randomized 1,334 patients and demonstrated reduced TLF and target vessel myocardial infarction (TV-MI) at 12-months with BP-SES compared with Xience DP-EES.[6] The BIOFLOW I and BIOFLOW III studies were not included in this analysis, as they were not randomized controlled trials.[7,8]

One-year follow-up data were available for all included trials. Patients in both the BP-SES and the DP-EES cohorts were divided into groups based on randomization to BP-SES versus DP-EES and the presence of diabetes mellitus. The main study hypothesis was that BP-SES would be noninferior to second-generation durable-polymer DES in patients with diabetes mellitus. The primary end point of the study was TLF, which was defined as the composite of cardiovascular death, TV-MI, ischemia-driven target lesion revascularization, and definite or probable stent thrombosis, at 1 year. Secondary outcomes included the individual clinical end points. Clinical events for each study were adjudicated by their respective independent clinical events committees.

Unpaired *t* Tests for continuous variables and Fisher's exact tests for categorical variables were used to make statistical comparisons between the BP-SES and DP-EES groups and were unadjusted for multiple testing. Diabetes was categorized as noninsulin-treated and insulin-treated.

Standardized differences were also calculated to compare stent groups. The standardized difference between the 2 groups is expressed in standard deviation units (the effect size) and indicates the extent of overlap between the 2 distributions. A standardized difference of 0.1, 0.2, and 0.5 indicates less than 8%, 15%, and 33% nonoverlap in the distributions, respectively. In contrast to hypothesis testing (p value), the standardized difference is not dependent on sample size.

Because of the potential of clustering of events within the 3 studies, the analyses were multilevel and included each study as a random effect. Proportional hazards regression models were used to compare BP-SES versus DP-EES TLF hazard rates based on intention to treat over 1 year of follow-up. Proportional hazards were assessed with Schoenfeld residuals. The models included "Stent" and "Diabetes" as main effects and the "Stent" by "Diabetes" interaction. The hazard distribution was modeled with Cox regression, exponentially distributed, and Weibull distributed. The choice of models was determined by Akaike's and Bayesian information criteria. On the basis of the model selected, hazards were estimated for each stent-diabetes group. Noninferiority of the BP-SES stent was assessed by computing 95% confidence intervals (CI) for the difference between the 2 stents and compared with a noninferiority margin that was 50% of the upper bound of the difference. Model-derived cumulative incidence curves were plotted for each stent-diabetes group.

Results

There were a total of 1,561 BP-SES and 794 DP-EES patients in the combined BIOFLOW II, IV, and V studies. Eleven patients (0.5%) with incomplete data pertaining to diabetes status were excluded from the analysis. These included 8 BP-SES and 3 DP-EES patients. From the pooled studies, 32.3% of patients had diabetes (n = 757). Four hundred ninety-four diabetic patients were treated with BP-SES, and 263 patients were treated with DP-EES. The study population is shown in Figure 1. Baseline demographic and clinical characteristics are similar between groups (Table 1). Insulin-treated patients comprised 8.4% of patients treated with BP-SES and 10.5% of patients treated with DP-EES (p = 0.102). Procedural characteristics, including lesion location and complexity, are presented in Table 2. One-year clinical outcomes were assessed for all patients (Table 3). There were 31 (6.3%)

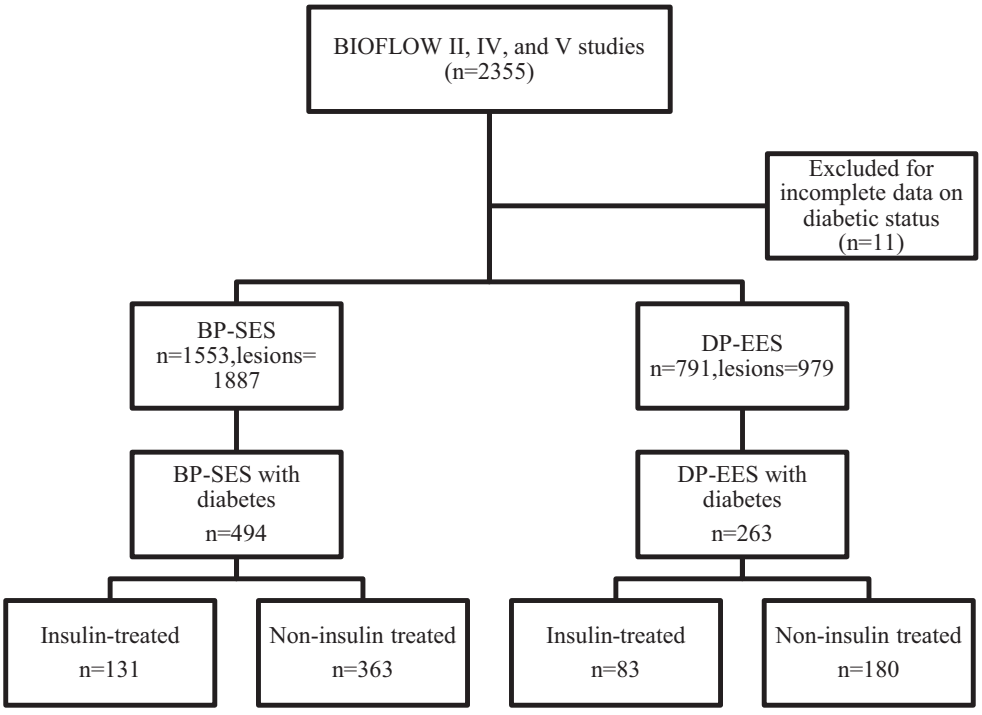

Figure 1. Study flowchart.

Table 1
Diabetic population: baseline clinical characteristics

Characteristic	BP-SES (N = 494)	DP-EES (N = 263)	Standardized difference	p Value
Age, (years)	64.9 ± 9.1	64.5 ± 9.5	0.043	0.399
Male	352 (71.3%)	196 (74.5%)	−0.074	0.338
Hypertension	434 (88.7%)	226 (86.6%)	0.057	0.385
Hyperlipidemia	401 (81.3%)	216 (82.4%)	−0.025	0.709
Diabetes mellitus				
Insulin-treated	131 (26.5%)	83 (31.6%)	−0.111	0.102
Noninsulin-treated	363 (73.5%)	180 (68.4%)	0.111	0.737
Prior myocardial infarction	146 (29.9%)	67 (25.7%)	0.091	0.226
Prior stroke or TIA	43 (8.7%)	14 (5.4%)	0.133	0.098
Renal disease	56 (11.4%)	24 (9.1%)	0.073	0.342
Prior coronary revascularization	222 (45.1%)	123 (47.3%)	−0.037	0.567
Current tobacco use	103 (20.9%)	69 (26.2%)	−0.048	0.095

Data are mean ± SD for continuous variables and n (%) for categorical variables. Standardized difference is in standard deviation units.
Negative value indicates smaller BP-SES value.
BP-SES = biodegradable polymer sirolimus-eluting stents; DP-SES = durable polymer everolimus-eluting stent; TIA = transient ischemic attack.

Table 2
Procedural characteristics

	BP-SES (N = 494)	DP-EES (N = 263)	Standardized difference	p Value
Target coronary artery	890 lesions	501 lesions		
Left main	2 (0.2%)	1 (0.2%)	0.005	0.999
Left anterior descending	369 (41.5%)	199 (39.7%)	0.035	0.532
Left circumflex	222 (24.9%)	138 (27.5%)	−0.059	0.308
Right	297 (33.4%)	163 (32.5%)	0.018	0.767
ACC-AHA lesion complexity*				
A	229 (25.8%)	121 (24.2%)	0.037	0.607
B1	332 (37.3%)	225 (44.9%)	−0.154	0.004
B2	245 (27.6%)	110 (22.0%)	0.130	0.029
C	83 (9.3%)	45 (9.0%)	0.012	0.848
No. of stents	1.30 ± 0.60	1.43 ± 0.74	−0.193	<0.001
Total stent length (mm)	19.58 ± 6.76	18.84 ± 7.43	0.104	0.007
Stent diameter (mm)	2.96 ± 0.46	2.95 ± 0.47	0.021	0.582

Data are mean ± SD for continuous variables and n (%) for categorical variables.
Standardized difference is in standard deviation units. Negative value indicates smaller BP-SES value. Lesion complexity denominator = 889 for BP-DES.
Target-lesion characteristics as assessed by the angiographic core laboratory.
*ACC-AHA, American College of Cardiology-American Heart Association.
BP-SES = biodegradable polymer sirolimus-eluting stents; DP-SES = durable polymer everolimus-eluting stent.

Table 3
One-year outcomes

Outcome	BP-SES (N = 494)	DP-EES (N = 263)	Standardized difference	p Value
Target-lesion failure	31 (6.3%)	23 (8.7%)	−0.094	0.236
Cardiac death	2 (0.4%)	4 (1.5%)	−0.114	0.190
Target-vessel myocardial infarction	19 (3.8%)	14 (5.3%)	−0.071	0.354
Clinically-driven target-lesion revascularization	16 (3.2%)	9 (3.4%)	−0.010	0.999
Stent thrombosis, definite/probable	4 (0.8%)	3 (1.1%)	−0.034	0.699
Target-vessel failure	38 (7.7%)	27 (10.3%)	−0.090	0.276
Clinically-driven target-vessel revascularization	20 (4.1%)	13 (4.9%)	−0.043	0.578
Death from any cause	2 (0.4%)	5 (1.9%)	−0.141	0.053
Any myocardial infarction	20 (4.0%)	16 (6.1%)	−0.093	0.281
Cardiac death or any myocardial infarction	22 (4.5%)	20 (7.6%)	−0.133	0.094

Data are n (%).

Table 4
Target lesion failure at 1 year by diabetic status

Diabetic status	BP-SES (N = 494)	DP-EES (N = 263)	p Value
Insulin-treated	11/131 (8.4%)	8/83 (9.6%)	0.807
Noninsulin-treated	20/363 (5.5%)	15/180 (8.3%)	0.264

Data are n/N (%).

TLFs in the BP-SES group and 23 (8.7%) in the DP-EES group at 1 year of follow-up in the diabetic population (p = 0.236). There were no significant differences in definite or probable stent thrombosis (0.8% vs 1.1%, p = 0.699). There was no difference in TLF between BP-SES and DP-EES for either insulin-treated or noninsulin-treated patients (Table 4).

There was no significant difference in TLF hazards for either stent type (BP-SES vs DP-EES, hazard ratio 0.82, 95% CI 0.047 to 1.43, p = 0.493) or diabetes treatment regimen (insulin-treated vs noninsulin-treated, hazard ratio 1.47, 95% CI 0.84 to 2.57, p = 0.182). Figure 2 plots the Kaplan-Meier TLF functions for stent-diabetes groups. The plot of the differences in hazards for noninsulin-treated and insulin-treated subgroups by BP-SES versus DP-EES is presented in Figure 3 and indicates noninferiority for both groups.

Discussion

The main findings of the pooled analysis of diabetic patients enrolled in the BIOFLOW randomized clinical trials include the following: (1) similar rates of 12-month TLF were seen between BP-SES and DP-EES; (2) no significant difference in TLF was found between patients treated with either stent type when stratified by diabetes treatment; and (3) favorably low stent thrombosis rates were seen in diabetic patients treated with either BP-SES or DP-EES.

The mechanisms that drive worse outcomes in diabetic patients are multifold. Altered inflammatory pathways as a result of hyperglycemia and insulin resistance combined with endothelial dysfunction are associated with accelerated atherosclerosis.[9] Additionally, platelet activation and reactivity are enhanced in diabetic patients.[10] These factors can lead to increased rates of in-stent restenosis and stent thrombosis in diabetics. Thin-strut stent design has been shown to result in faster endothelialization coverage, and specific coating with biodegradable polymers may reduce the overall inflammation when compared to stents with thicker struts and permanent polymers.[11]

All approved contemporary-generation DES in the United States has specific labeling for the treatment of diabetic patients. The labeling by the Food and Drug Administration is granted on the basis of meeting pre-specified performance goals that were superior to the performance of first-generation DES for the diabetic population.[12] Nevertheless, the rates of adverse events in diabetic patients remain higher than those in the nondiabetic population and are further increased in the subset of patients with diabetes who are insulin-treated.[13] Insulin-treated diabetic patients did worse than noninsulin-treated diabetics regardless of stent type in this analysis. Insulin treatment, however, suggests a longer duration of diagnosis and more advanced diabetic disease and has been associated with worse clinical outcomes.[13]

The quest for improvement in DES technology specifically for the diabetic population is ongoing. Permanent-polymer coating may contribute to chronic inflammation, which may be more pronounced in diabetic patients.[14]

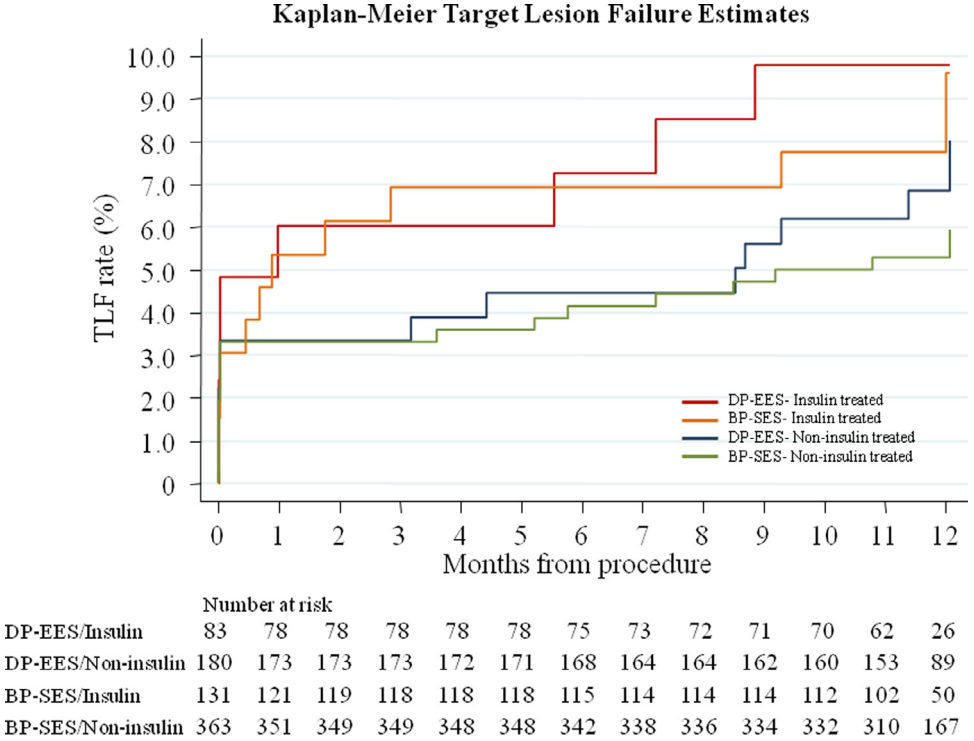

Figure 2. The Kaplan-Meier target lesion failure (TLF) functions for stent-diabetes groups.

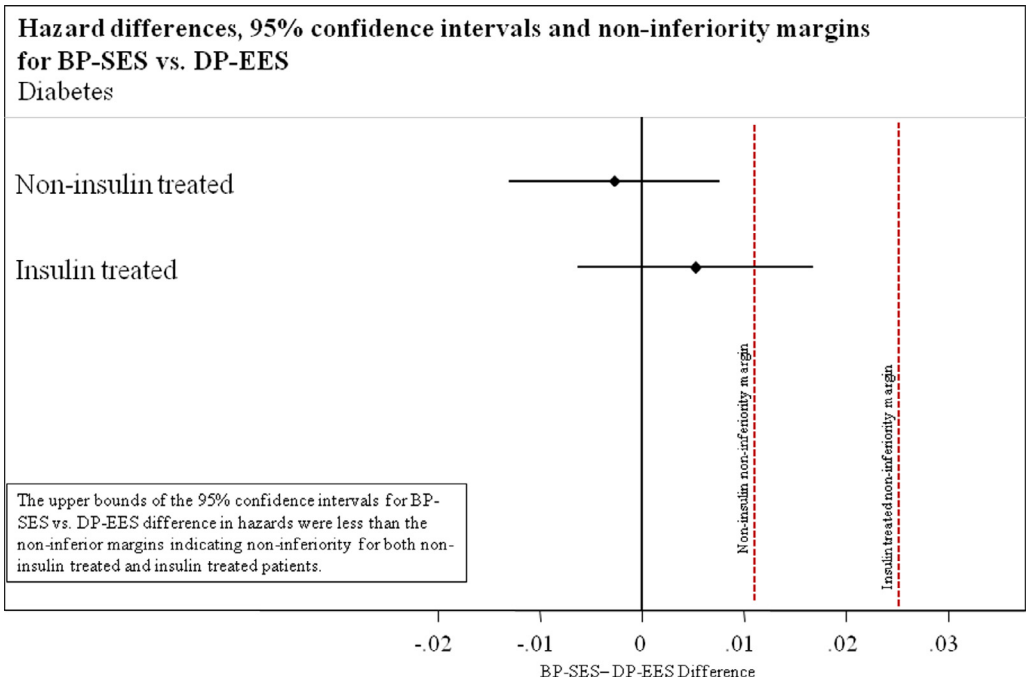

Figure 3. Hazard differences, 95% confidence intervals, and noninferiority margins for BP-SES versus DP-EES differences for noninsulin-treated and insulin-treated groups.

Thicker struts may be problematic, especially in the small-diameter vessels that are common in diabetic patients. Ultrathin-strut DES has been associated with improved clinical outcomes in an all-comer population compared with contemporary thicker-strut DES.[15]

Comparable 1-year results between BP-SES and DP-EES were reported in terms of target lesion revascularization (7.4% vs 4.9%) and TLF at 2 years (16.3% vs 16.2%, $p = 0.84$, $p_{interaction} = 0.85$) in diabetic patients enrolled in the BIOSCIENCE trial.[16,17] At 5-year follow-up in the BIOSCIENCE trial, the rates of TLF between BP-SES and DP-EES in patients with diabetes remained similar (28.8% vs 24.9%, $p = 0.244$, $p_{interaction} = 0.307$).[18] In BIOFLOW III, a prospective multicenter registry, diabetic patients treated with BP-SES had favorable clinical outcomes, with target vessel failure occurring in 6.4% of patients and TLF occurring in 3.5% at 1 year.[8] Ultrathin struts, in a meta-analysis of 69 randomized trials had significantly less stent thrombosis and MI than thick-strut DES did.[19]

Thin struts may lead to reduced arterial injury and disruption of flow, improving re-endothelialization and potentially reducing the risk of stent thrombosis or in-stent restenosis.[20] In the BIOFLOW II study, there were no stent thrombosis events in the diabetic population at 5-year follow-up.[15] A recent large network meta-analysis by Kang et al confirmed that BP-SES had similar clinical outcomes to second-generation DES.[21] Furthermore, the BP-SES was noninferior to a durable-polymer DES in a recent large randomized clinical trial that included patients with acute coronary syndromes,[22] and analysis of a separate acute coronary syndrome subgroup from a randomized clinical trial demonstrated significantly lower event rates with BP-SES.[23]

Despite further refinement of DES, including iterations in stent design, alloy composition, strut thickness, polymer biocompatibility, and bioresorption of polymers, concerns regarding incomplete endothelialization, polymer hypersensitivity, neoatherosclerosis, stent recoil, and fracture persist.[24–26] As stent technology reaches a point of equivalence between stent types, implant technique with stent optimization may be of increased importance to further reduce clinical events. Beyond 1 year after implantation, current metallic DES is associated with a 1% to 4% ongoing annual incidence of TLF events (composite occurrence of cardiac death, TV-MI, and ischemia-driven target lesion revascularization).[27] The results of the present study support labeling for the treatment of diabetic patients with BP-SES, as results are consistent with population size and event rates observed for other stents.[28,29] In addition to the noninferiority of the BP-SES to the DP-EES in this pooled analysis of randomized clinical trials, our study supports the observation that insulin-treated diabetics are prone to higher adverse event rates, but nonetheless, the performance of the BP-SES was similar to DP-EES for this group.[30]

Important limitations of the present analysis must be considered. First, these studies were not specifically designed to assess for differences in diabetic patients. The studies were not powered to detect differences in outcome by diabetic treatment regimen. Second, data on duration of diabetes and severity of diabetes, including hemoglobin A1C levels, were not available. Third, definitions of MI differed across studies. Finally, patient-level follow-up beyond 12 months was not included in this analysis.

In this post-hoc analysis of the diabetic subgroup of BIOFLOW II, IV, and V subjects, results for the primary end point of 12-month TLF in diabetics were similar between stent types regardless of diabetic treatment modality. These results support the safety and efficacy of BP-SES

compared with DP-EES in a population of subjects with baseline diabetes undergoing percutaneous coronary intervention.

Disclosures

Ron Waksman: Advisory Board: Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Consultant: Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

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