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3-Year Follow-Up of the SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) Trial

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Objectives The aim of this study was to evaluate long-term outcome of patients treated for in-stent restenosis of bare-metal stents (BMS).

Background Treatment of restenosis of BMS is characterized by high recurrence rates. Vascular brachytherapy (VBT) improved outcome although late catch-up events were documented. Drug-eluting stents tested against VBT in this setting were found superior for at least the first year; superiority at longer follow-up is uncertain.

Methods We evaluated 3-year outcome of the multicenter SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial, which randomized patients with restenosis of BMS to either a sirolimus-eluting stents (SES) or VBT.

Results Target vessel failure (cardiac death, infarction, or target vessel revascularization [TVR]) at 9 months as previously reported was significantly improved with SES. Kaplan-Meier analysis at 3 years documented that survival free from target lesion revascularization (TLR) and TVR continues to be significantly improved with SES: freedom from TLR 81.0% versus 71.6% (log-rank $p = 0.018$), and TVR 78.2% versus 68.8% (log-rank $p = 0.022$), SES versus VBT. At 3 years, target vessel failure and major adverse cardiac events (death, infarction, emergency coronary artery bypass grafting, or repeat TLR) remained improved with SES, but did not reach statistical significance. There was no statistically significant difference in definite or probable stent thrombosis (3.5% for SES, 2.4% for VBT; $p = 0.758$).

Conclusions At 3 years of follow-up, after treatment of in-stent restenosis of BMS, patients treated with SES have improved survival free of TLR and TVR compared with patients treated with VBT. Stent thrombosis rates are not different between the 2 groups but are higher than reported in trials of treatment of de novo lesions. (J Am Coll Cardiol Intv 2008;1:439–48) © 2008 by the American College of Cardiology Foundation

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In patients with complex coronary anatomy who are treated with drug-eluting stents (DES), follow-up is less well described than in the patients initially treated in randomized clinical trials that included highly selected patients and lesions (1–3). Long-term follow-up of these "off-label" indications is of great interest.

A particularly high-risk group of patients/lesions include those with restenosis within a bare-metal stent. This problem was extremely resistant to conventional treatment and finally resulted in the development and approval of vascular brachytherapy (VBT) (4–12). While VBT was initially very effective, several issues emerged (7–12). These included a late catch-up phenomenon, whereby the initial benefit of reduced restenosis gradually lost significance after the first year. In the 5-year follow-up of the SCRIPPS (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) trial, there was loss in initial clinical efficacy over time so that 74% reduction in freedom from target lesion revascularization (TLR) at 6 months decreased to 48% reduction at 5 years, and the minimal lumen diameter of the treated segment decreased from 2.49 at 6 months to 2.12 at 36 months (13). In addition, the problem of stent thrombosis was raised, particularly if a new bare-metal stent was placed at the time of VBT. These problems, among others, led to the evaluation of DES to treat this problem (14–22).

Abbreviations and Acronyms

ARC = academic research consortium
DES = drug-eluting stent(s)
MACE = major adverse cardiac events
MI = myocardial infarction
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization
VBT = vascular brachytherapy

Several randomized trials of VBT versus DES were undertaken. In the 2 largest trials, SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) (14) and TAXUS V (15), patients were randomized to either a Cypher stent or to VBT. In the SISR trial (14), the 9-month primary end point of target vessel failure (TVF) was significantly reduced with sirolimus-eluting stents (SES) from 21.6% to 12.4% ($p = 0.023$). Stent thrombosis at 9 months was not reported with VBT but was 0.8% with SES (2 patients). Similarly, in the TAXUS V trial (15), a significant beneficial effect with paclitaxel-eluting stents compared with VBT was seen with a reduction in 9-month TVF from 20.1% to 11.5% ($p = 0.03$). In this latter study, target vessel thrombosis was seen in 3 patients in the paclitaxel-eluting stent group (1.5%) versus 5 in the VBT group (2.6%; $p = 0.72$).

Subsequent to these pivotal trials, there has been more attention paid to late adverse events such as death, myocardial infarction (MI), and stent thrombosis (23–29) as well as interest in whether late "catch-up" (13) with subsequent renarrowing would be observed with DES for this high-risk group of patients. This report extends the follow-up of the SISR trial to 3 years with specific attention to late mortality, MI, stent thrombosis, antiplatelet medication use, and the need for repeat target vessel intervention.

Methods

The trial design and the primary end point of the SISR trial have been previously reported (Table 1) (14). In brief, this multicenter prospective 2-arm institutional review board-approved randomized trial evaluated the safety and efficacy of SES compared with VBT for the treatment of in-stent restenosis occurring after implantation of a bare-metal stent. The primary end point was TVF defined as cardiac death, MI, or target vessel revascularization (TVR) at 9 months post-procedure. Entry criteria included patients undergoing clinically indicated revascularization of bare-metal in-stent restenotic native coronary lesions ≥15 mm but ≤40 mm in length and in vessels ≥2.5 mm but ≤3.5 mm in diameter. Patients with recent MI or unstable angina, complete occlusion of the in-stent restenotic segment, or planned intervention of another lesion within 30 days of the study procedure were excluded. All patients signed a consent form.

Vascular brachytherapy was performed with either gamma or beta sources. The lesion was pre-dilated and then radiation applied to the target lesion with a 5-mm margin on either side. Placement of a new stent in association with the VBT procedure was strongly discouraged because this had been previously shown to increase late thrombosis. In the SES arm, pre-dilation was also performed. The DES was selected to cover the initial lesion and more than 3 mm beyond both ends of the region of pre-dilation balloon angioplasty, optimizing stent coverage from the angiographically normal vessel proximal to distal. It was required that the restenotic segment be fully covered although it was not required that the entire region initially covered by the bare-metal stent be restented. Study medications included the following:

1. *Pre-procedure*: aspirin 325 mg was administered 24 h before the procedure and thienopyridine either ticlopidine or clopidogrel administered with a loading dose before or immediately after the procedure.
2. *Intraprocedure*: heparin with an intravenous bolus to achieve and maintain an activated clotting time of approximately 250 s if a glycoprotein IIb/IIIa inhibitor was administered or 300 to 350 s if no glycoprotein IIb/IIIa inhibitor was used. Administration of a glycoprotein IIb/IIIa inhibitor was at the operator's discretion.
3. *Post-procedure*: aspirin 325 mg a day and a thienopyridine ≥3 months in the sirolimus-eluting limb or ≥6 months in the VBT group if a new stent was not placed (90% of

Table 1. 9-Month Follow-Up and Primary End Point

Adverse Events	Vascular Brachytherapy (n = 125)	Sirolimus-Eluting Stent (n = 259)	Relative Risk (95% CI)	p Value
Major adverse clinical event	24 (19.2)	26 (10.0)	1.9 (1.1–3.2)	0.02
Death	0 (0.0)	0 (0.0)	*	
Myocardial infarction	0 (0.0)	6 (2.3)	*	0.18
Q-wave	0 (0.0)	1 (0.4)	*	≥0.99
Non–Q-wave	0 (0.0)	6 (2.3)	*	0.18
Emergent CABG surgery	0 (0.0)	0 (0.0)	*	
Target lesion revascularization	24 (19.2)	22 (8.5)	2.3 (1.3–3.9)	0.004
Target lesion CABG surgery	6 (4.8)	1 (0.4)	12.4 (1.5–102.2)	0.006
Target lesion PTCA	20 (16.0)	21 (8.1)	2.0 (1.1–3.5)	0.02
Target vessel revascularization	27 (21.6)	28 (10.8)	2.0 (1.2–3.2)	0.008
Target vessel failure	27 (21.6)	32 (12.4)	1.7 (1.1–2.8)	0.02
Stent thrombosis	0 (0.0)	0 (0.0)	*	
Late stent thrombosis	0 (0.0)	2 (0.8)	*	≥0.99

*Relative risk could not be calculated due to zero cell. Values are n (%) of patients.
CABG = coronary artery bypass grafting; CI = confidence interval; PTCA = percutaneous coronary angioplasty.

patients) or ≥12 months in the VBT limb if a new stent was placed. The recommendation for a thienopyridine administered for ≥3 months in the sirolimus limb was based on the initial instructions for use after product approval.

Stent thrombosis was defined per study protocol as the finding of angiographic thrombus within the stented vessel at the time of clinically driven angiographic restudy for documented ischemia with abrupt or subacute closure of the treated segment. Angiographic stent thrombosis requiring TLR during the first 30 days after the index stent placement was considered as an end point for the combined 30-day ischemic end point. Any death not attributable to a noncardiac cause or any Q-wave MI in the territory of the stented vessel within the first 30 days after stent implantation was considered a surrogate for stent thrombosis.

Stent thrombosis was also evaluated post hoc by the clinical events committee using the recently described academic research consortium (ARC) definitions (30). These definitions identify timing of the event as acute stent thrombosis 0 to 24 h after stent implantation, subacute thrombosis ≥24 h to 30 days after stent implantation, late stent thrombosis at 30 days to 1 year after stent implantation, and very late stent thrombosis ≥1 year after index stent implantation. The ARC definition includes definite stent thrombosis if there is: 1) Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 with an occlusion originating in the stent or in a segment 5 mm proximal or distal to the stent region in the presence of thrombus; or 2) TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the region with angiographic documentation of thrombus, when it occurs in the setting of either new onset of ischemic symptoms at rest, new ischemic electrocardiogram changes, or a typical rise and fall in cardiac biomarkers. The ARC definition of probable stent thrombosis is any unexplained death within the first 30 days after the index procedure, or any MI in the absence of an obvious cause, which is in the territory of the implanted stent without angiographic confirmation of a stent thrombosis. Possible stent thrombosis is defined as any unexplained death beyond 30 days.

Data collection follow-up and core laboratory analysis. Baseline and clinical data were collected on standard case report forms by the clinical investigators at the clinical sites. Data were submitted to the data coordinating center (Harvard Clinical Research Institute, Harvard Medical School, Boston, Massachusetts). Clinical end points were adjudicated by an independent clinical events committee blinded to study group assignment. A separate data and safety monitoring board not affiliated with either the study sponsor or the investigators reviewed data periodically throughout the trial to identify potential safety issues and monitor study conduct. The data presented herein represent all angiographic and clinical follow-up data available as of October 4, 2007.

Statistical analysis. Safety evaluation and effectiveness analysis was performed on an intent-to-treat basis. This study was designed to demonstrate the noninferiority or superiority of the Cypher stent (Cordis, Warren, New Jersey) compared with intracoronary VBT for the primary end point, TVF. Noninferiority was expected based on documented safety and efficacy with both approaches. Superiority was expected due to significant reduction in TLR due to an improvement in analysis segment net gain and late lumen loss in previous studies with the SES. The trial was designed and powered for the 9-month primary end point; while no specific hypothesis was pre-specified for longer-term evaluation, follow-up was pre-specified for the first year after

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 4, 2008
AUGUST 2008:439–48

treatment and then yearly thereafter to a total of 5 years. Thus, the statistics for these later time points are descriptive. No patients were censored at the time of reintervention, but rather were censored for lost-to-follow status before the analyzed event was observed or no analyzed event was observed at the end of the analysis period (i.e., 1,080 days after index procedure). If a patient had multiple repeated interventions, that patient was considered to have an analyzed reintervention event at the earliest occurrence after index procedure. All event rates are estimated using Kaplan-Meier analysis, which partially adjusts for patients lost to follow-up. The analyses at 9 months and 3 years were relatively independent of each other, and the conclusion that was drawn from the 3-year follow-up data was not conditioned to the conclusion of the 9-months results.

Since the trial was neither powered nor designed for long-term follow-up, the focus of this longer-term follow-up involved an examination of the pre-specified safety end points of death, MI, and stent thrombosis and an evaluation of the efficacy end point of TLR to determine whether any new safety issues emerged with subsequent follow-up and whether the major benefit of SES, namely reduction in TLR, was maintained. The analyzed events were adjudicated by independent Clinical Events Committee members who were blinded to the treatment assignment when the events were adjudicated, and, therefore, no other censoring method was applied.

Results

From February 12, 2003 through July 27, 2004, 384 patients were enrolled at 26 centers and randomized to treatment with VBT (n = 125) or the SES (n = 259). Compliance to follow-up at 1,080 days (3 years) was similar in both groups at 88.0% for VBT (110 of 125) and 91.9% of SES patients (238 of 259).

Examination of data to 3 years demonstrated no safety issues in either arm. No differences were observed in the frequency of death, MI, or protocol-defined stent thrombosis between the VBT and SES arms to 3 years (Tables 2 and 3). Further examination of the adjudicated end points of cardiac death, noncardiac death, Q-wave MI, non–Q-wave MI, and stent thrombosis using the ARC definitions also failed to demonstrate any significant differences between the VBT and SES groups. In total, these end points were infrequent, and the increment per year in the rates of death, MI, and stent thrombosis was similar between the 2 groups. No Q-wave MIs at 3 years were observed in the

Table 2. In- and Out-of-Hospital Complications Out to 3 Years—All Patients

Nonhierarchical Complications to 1,080 Days	Vascular Brachytherapy (n = 125)	Sirolimus-Eluting Stent (n = 259)	All Patients (n = 384 Patients, n = 384 Lesions)	Difference (95% CI)	p Value
MACE (death, Q- or non–Q-wave MI, emergency CABG, TLR)	28.0% (35/125)	23.6% (61/259)	25.0% (96/384)	4.4% (−4.6% to 14.1%)	0.379
Death	2.4% (3/125)	3.9% (10/259)	3.4% (13/384)	−1.5% (−4.9% to 3.3%)	0.560
Cardiac	0.8% (1/125)	1.5% (4/259)	1.3% (5/384)	−0.7% (−3.2% to 3.0%)	1.000
Noncardiac	1.6% (2/125)	2.3% (6/259)	2.1% (8/384)	−0.7% (−3.6% to 3.5%)	1.000
MI (Q- or WHO non–Q-wave)	3.2% (4/125)	6.2% (16/259)	5.2% (20/384)	−3.0% (−7.1% to 2.3%)	0.327
All Q-wave MI	0.0% (0/125)	1.5% (4/259)	1.0% (4/384)	−1.5% (−3.9% to 1.6%)	0.309
TV Q-wave MI	0.0% (0/125)	1.5% (4/259)	1.0% (4/384)	−1.5% (−3.9% to 1.6%)	0.309
Non-TV Q-wave MI	0.0% (0/125)	0.0% (0/259)	0.0% (0/384)	0.0% (−1.5% to 3.0%)	—
All WHO non–Q-wave MI	3.2% (4/125)	5.4% (14/259)	4.7% (18/384)	−2.2% (−6.2% to 3.0%)	0.444
TV WHO non–Q-wave MI	3.2% (4/125)	5.0% (13/259)	4.4% (17/384)	−1.8% (−5.7% to 3.3%)	0.598
Non-TV WHO non–Q-wave MI	0.0% (0/125)	0.4% (1/259)	0.3% (1/384)	−0.4% (−2.2% to 2.6%)	1.000
All TV MI (Q- or WHO non–Q-wave MI)	3.2% (4/125)	5.8% (15/259)	4.9% (19/384)	−2.6% (−6.6% to 2.7%)	0.325
All non-TV MI (Q or WHO non–Q-wave MI)	0.0% (0/125)	0.4% (1/259)	0.3% (1/384)	−0.4% (−2.2% to 2.6%)	1.000
Emergent CABG	0.0% (0/125)	0.0% (0/259)	0.0% (0/384)	0.0% (−1.5% to 3.0%)	—
TL revascularization	26.4% (33/125)	17.8% (46/259)	20.6% (79/384)	8.6% (−0.0% to −18.0%)	0.059
TL-CABG	6.4% (8/125)	3.1% (8/259)	4.2% (16/384)	3.3% (−0.9% to 9.2%)	0.171
TL-PTCA	23.2% (29/125)	15.8% (41/259)	18.2% (70/384)	7.4% (−0.8% to 16.4%)	0.091
TV revascularization not involving TL	8.8% (11/125)	6.9% (18/259)	7.6% (29/384)	1.9% (−3.5% to 8.6%)	0.540
TV/non–TL-CABG	2.4% (3/125)	0.4% (1/259)	1.0% (4/384)	2.0% (−0.4% to 6.4%)	0.103
TV/non–TL-PTCA	7.2% (9/125)	6.6% (17/259)	6.8% (26/384)	0.6% (−4.4% to 7.0%)	0.830
TV failure to 270 days (primary end point)	21.6% (27/125)	12.4% (32/259)	15.4% (59/384)	9.2% (−1.5% to −18.0%)	0.023
TV failure to 1,080 days	30.4% (38/125)	23.9% (62/259)	26.0% (100/384)	6.5% (−2.8% to 16.3%)	0.214
TV revascularization (all)	29.6% (37/125)	20.8% (54/259)	23.7% (91/384)	8.8% (−0.3% to 18.4%)	0.073

MACE = major adverse cardiac events; MI = myocardial infarction; TL = target lesion; TLR = target lesion revascularization; TV = target vessel; WHO = World Health Organization; other abbreviations as in Table 1.

Table 3. Summary of Protocol and ARC Stent Thrombosis (to 1,080 Days)—All Patients

Events to 1,080 Days	Vascular Brachytherapy (n = 125)	95% CI	Sirolimus-Eluting Stent (n = 259)	95% CI	All Patients (n = 384 Patients, n = 384 Lesions)	95% CI	Difference (95% CI)	p Value
Protocol thrombosis								
Acute thrombosis (0–1)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Subacute thrombosis (2–30)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Late thrombosis (31–360)	0.0% (0/125)	(0.0% to 2.9%)	1.2% (3/259)	(0.2% to 3.3%)	0.8% (3/384)	(0.2% to 2.3%)	−1.2% (−3.3% to 1.9%)	0.554
Very late thrombosis (361–1,080)	0.8% (1/125)	(0.0% to 4.4%)	0.8% (2/259)	(0.1% to 2.8%)	0.8% (3/384)	(0.2% to 2.3%)	0.0% (−2.1% to 3.7%)	1.000
All thrombosis (0–1,080)	0.8% (1/125)	(0.0% to 4.4%)	1.9% (5/259)	(0.6% to 4.4%)	1.6% (6/384)	(0.6% to 3.4%)	−1.1% (−3.7% to 2.6%)	0.668
Any ARC thrombosis								
Acute thrombosis (0–1)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Subacute thrombosis (2–30)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Late thrombosis (31–360)	0.8% (1/125)	(0.0% to 4.4%)	1.5% (4/259)	(0.4% to 3.9%)	1.3% (5/384)	(0.4% to 3.0%)	−0.7% (−3.2% to 3.0%)	1.000
Very late thrombosis (361–1,080)	2.4% (3/125)	(0.5% to 6.9%)	3.1% (8/259)	(1.3% to 6.0%)	2.9% (11/384)	(1.4% to 5.1%)	−0.7% (−4.0% to 4.0%)	1.000
All thrombosis (0–1,080)	2.4% (3/125)	(0.5% to 6.9%)	4.2% (11/259)	(2.1% to 7.5%)	3.6% (14/384)	(2.0% to 6.0%)	−1.8% (−5.4% to 2.9%)	0.562
Definite or probable ARC thrombosis								
Acute thrombosis (0–1)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Subacute thrombosis (2–30)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Late thrombosis (31–360)	0.8% (1/125)	(0.0% to 4.4%)	1.5% (4/259)	(0.4% to 3.9%)	1.3% (5/384)	(0.4% to 3.0%)	−0.7% (−3.2% to 3.0%)	1.000
Very late thrombosis (361–1,080)	2.4% (3/125)	(0.5% to 6.9%)	2.3% (6/259)	(0.9% to 5.0%)	2.3% (9/384)	(1.1% to 4.4%)	0.1% (−3.0% to 4.7%)	1.000
All thrombosis (0–1,080)	2.4% (3/125)	(0.5% to 6.9%)	3.5% (9/259)	(1.6% to 6.5%)	3.1% (12/384)	(1.6% to 5.4%)	−1.1% (−4.5% to 3.6%)	0.758
Definite ARC thrombosis								
Acute Thrombosis (0–1)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Subacute thrombosis (2–30)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Late thrombosis (31–360)	0.0% (0/125)	(0.0% to 2.9%)	1.5% (4/259)	(0.4% to 3.9%)	1.0% (4/384)	(0.3% to 2.6%)	−1.5% (−3.9% to 1.6%)	0.309
Very late thrombosis (361–1,080)	2.4% (3/125)	(0.5% to 6.9%)	1.5% (4/259)	(0.4% to 3.9%)	1.8% (7/384)	(0.7% to 3.7%)	0.9% (−2.0% to 5.4%)	0.687
All thrombosis (0–1,080)	2.4% (3/125)	(0.5% to 6.9%)	2.7% (7/259)	(1.1% to 5.5%)	2.6% (10/384)	(1.3% to 4.7%)	−0.3% (−3.5% to 4.3%)	1.000
Probable ARC thrombosis								
Acute thrombosis (0–1)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Subacute thrombosis (2–30)	0.0% (0/125)	(0.0% to 2.9%)	0.0% (0/259)	(0.0% to 1.4%)	0.0% (0/384)	(0.0% to 1.0%)	0.0% (−1.5% to 3.0%)	—
Late thrombosis (31–360)	0.8% (1/125)	(0.0% to 4.4%)	0.0% (0/259)	(0.0% to 1.4%)	0.3% (1/384)	(0.0% to 1.4%)	0.8% (−0.8% to 4.4%)	0.326
Very late thrombosis (361–1,080)	0.0% (0/125)	(0.0% to 2.9%)	0.8% (2/259)	(0.1% to 2.8%)	0.5% (2/384)	(0.1% to 1.9%)	−0.8% (−2.8% to 2.3%)	1.000
All thrombosis (0–1,080)	0.8% (1/125)	(0.0% to 4.4%)	0.8% (2/259)	(0.1% to 2.8%)	0.8% (3/384)	(0.2% to 2.3%)	0.0% (2.1% to −3.7%)	1.000

ARC = academic research consortium; CI = confidence interval.

VBT group while a low frequency was observed in the SES group (4 of 259 or 1.5%).

While the trial was neither designed nor powered to examine efficacy end points or composite safety and efficacy end points beyond the 9-month time primary end point period, it is instructive to examine changes in both TLR (Fig. 1) and TVR (Fig. 2) as well as TVF (Fig. 3) and major adverse cardiac events (MACE) with time. Using Kaplan-Meier analysis, survival free from TLR and TVR at 3 years demonstrates that patients treated with SES show a significant improvement as compared with patients treated with VBT (TLR: 81.0% vs. 71.6%, log-rank p = 0.018; TVR: 78.2% vs. 68.8%, log-rank p = 0.022) (Figs. 1 and 2). There were, however, no differences in survival free from TVF or MACE at 3 years (TVF: 75.1% vs. 67.9%, log-rank p = 0.087; MACE: 75.5% vs. 70.5%, log-rank p = 0.186) (Figs. 3 and 4) (SES vs. VBT).

Using the protocol definition, stent thrombosis was adjudicated in 6 patients: 1 patient in the VBT group (1 of 125 or 0.8%) and 5 patients in the SES group (5 of 259 or 1.9%, p = 0.668) (Table 2). At the time of the stent thrombosis, the VBT patient was taking clopidogrel, but not aspirin, and 4 of the 5 SES patients were taking aspirin, but not clopidogrel.

Adjudicated using the ARC definition, the total number of events increased compared with those adjudicated using

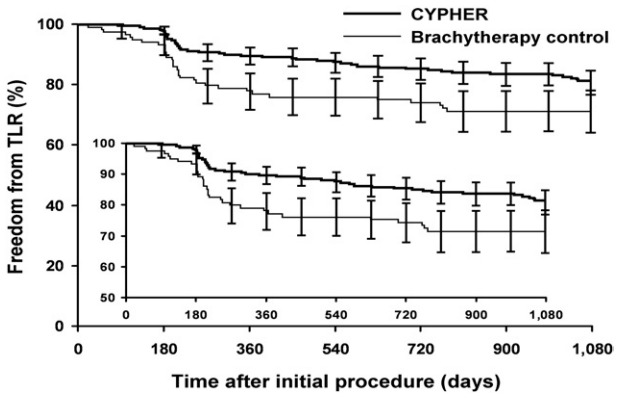

Figure 1. Kaplan-Meier Curves and Survival Table for the End Point of TLR to 1,080 Days

In patients treated with the Cypher stent (Cordis), freedom from target lesion revascularization (TLR) remains significantly better than vascular brachytherapy throughout the 3-year follow-up period (log-rank p = 0.018).

the per-protocol definition, but there was no significant difference between VBT and SES. Using the definition of "any ARC thrombosis," this occurred in 2.4% for VBT versus 4.2% for SES (p = 0.562). Using the definition of "definite or probable thrombosis," the difference was less, 2.4% versus 3.5% (p = 0.758). Irrespective of what definition was used, stent thrombosis was observed most frequently very late, after the first year of follow-up in both groups. At the time of ARC-defined stent thrombosis, 4 of 9 patients identified as having "definite" ARC stent thrombosis were taking both aspirin and clopidogrel, while 5 of those 9 patients were taking neither drug. Of the 3 patients with "probable" ARC stent thrombosis, 1 patient was taking both drugs, 1 was taking aspirin but not clopidogrel, and 1 was taking neither drug. Of the 2 patients identified as having "possible" stent thrombosis, 1 patient was on both medications, while the other was taking clopidogrel, but not aspirin. Thus, for patients with stent thrombosis identified using the protocol definition, almost all of the patients were not taking either Plavix (Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, New Jersey) or aspirin; for stent thrombosis patients identified using the ARC definitions, approximately one-half were on both antiplatelet drugs and one-half were not taking either antiplatelet drug.

In putting these data in perspective, it is useful to remember that only 6 (VBT) and 3 (SES) months of dual antiplatelet therapy were recommended per protocol. Actual medication use was more prolonged than these recommendations (Table 4). Continued dual antiplatelet medication use was high and quite similar in both arms through 3 years of follow-up (Table 4) despite these different recommended durations of treatment. At hospital discharge and during follow-up to the primary end point at 9 months, dual antiplatelet medication use was reported in >61% of patients, and more than one-half of the remaining 39% of patients received either aspirin or a thienopyridine agent as single drug therapy; only 15.2% of VBT and 7.7% of SES patients were not on any oral antiplatelet agent. From 9 months to 3 years, antiplatelet medication was not protocol mandated; use of these medications still remained fairly

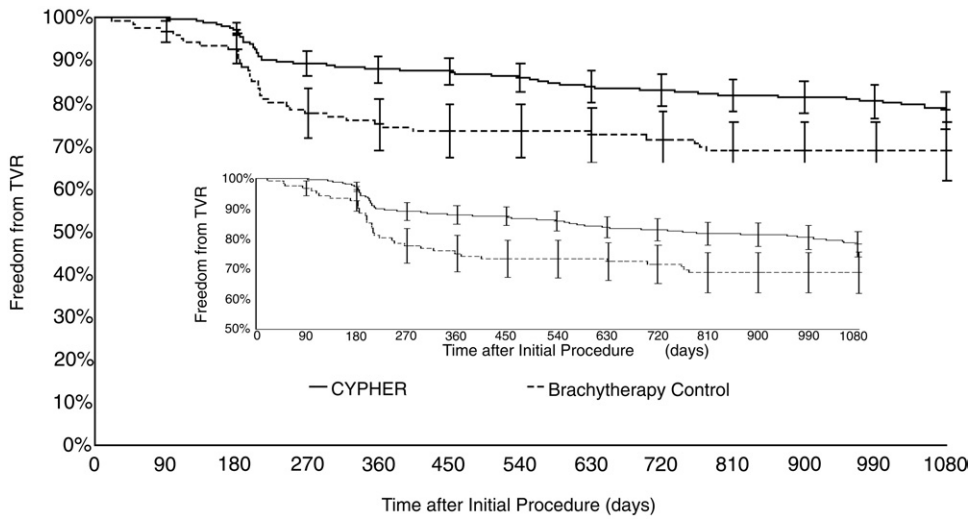

Figure 2. Kaplan-Meier Curves and Survival Table for the End Point of TVR to 1,080 Days

In patients treated with the Cypher stent (Cordis), freedom from target vessel revascularization (TVR) remains significantly better than vascular brachytherapy throughout the 3-year follow-up period (log-rank p = 0.022).

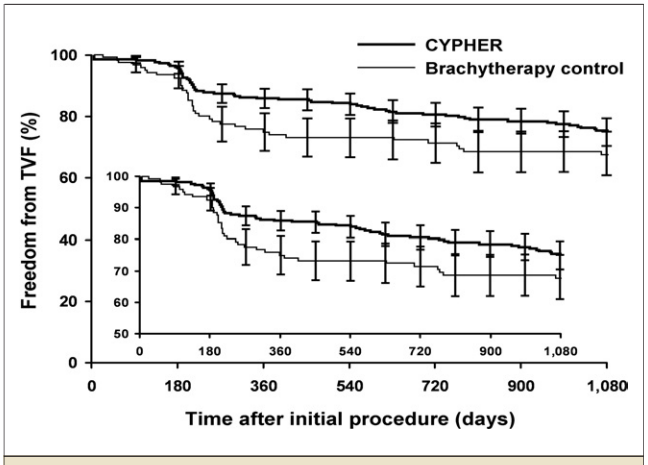

Figure 3. Kaplan-Meier Curves and Survival Table for the End Point of TVF to 1,080 Days

In patients treated with the Cypher stent (Cordis), the difference in freedom from target lesion revascularization from vascular brachytherapy is attenuated throughout the 3-year follow-up period (log-rank p = 0.087). TVF = target vessel failure.

high so that by year 3 of follow-up, approximately 56.7% of patients were on dual antiplatelet therapy whereas 19.5% of patients were not on any antiplatelet regimen.

Discussion

While trials are designed and powered to test a pre-defined primary end point, long-term follow-up is useful in identifying any late safety signals that may emerge after ascertainment of the primary end point and in providing insight into the preservation of the initially measured clinical benefit. Progression of disease and further intervention or treatment that does not follow the randomization scheme can either increase event rates and/or introduce random effects, or both, which can complicate proper interpretation of late follow-up findings.

Nevertheless, there are several important findings evident in the data generated from the intermediate 3-year follow-up of the SISR trial (14) comparing SES and VBT for the treatment of in-stent restenosis of bare-metal stents, including: 1) at 3 years, safety end points such as all death, cardiac death, all MI, Q-wave MI, and non–Q-wave MI remain infrequent and do not suggest that a safety signal has emerged in either the VBT or SES arms; 2) stent thrombosis remains relatively uncommon but is clearly increased compared with that seen in patients treated with SES for de novo lesions. There was, however, no significant difference between SES and VBT groups; 3) continued use of dual antiplatelet therapy at 3 years remains high (~60%) with only ~20% of patients receiving no oral antiplatelet agent; 4) differences in oral antiplatelet drug use were notable for patients with protocol-defined stent thrombosis, but not for patients with ARC-defined stent thrombosis; 5) superiority of SES over VBT is maintained when restricted to the efficacy end points of TLR and TVR; and 6) rates of TVF and MACE are no longer different between the control and experimental arms.

These findings have significant implications. First, both treatment modalities studied in this trial demonstrated no new safety issues of death or infarction. While VBT (7–12,31) has virtually disappeared due to its cumbersome equipment needs and due to the availability and widespread use of DES, no differences in the safety outcomes of death and infarction were observed between SES and VBT. It appears that the use of prolonged dual antiplatelet therapy and avoidance of use of stenting at the time of VBT have successfully eliminated the previously observed increased frequency of stent thrombosis with VBT. The maintenance of a clinical benefit of SES over VBT when looking only at the efficacy end points of TLR and TVR suggests both improvement of outcomes of SES over VBT but also a lack of "late catch-up" as described in the VBT literature (8,12,31). Despite the finding that stent thrombosis was not significantly different between SES and VBT, the absolute rate of 3.5% is higher than seen with treatment of de novo lesions. This could have important implications. Finally, despite a limited recommended duration of dual antiplatelet use, a majority of patients in both arms were observed to have remained on or to have been restarted on this therapy. While this might be due to the desire to allow benefits to patients with respect to the reduction in death, MI, and stroke by thienopyridine agents when used as medical therapy in patients with coronary disease, it is more likely that this treatment has been maintained or restarted due to concerns about late stent thrombosis and the recommendations of professional groups such as the American Heart Association, American College of Cardiology, Society for

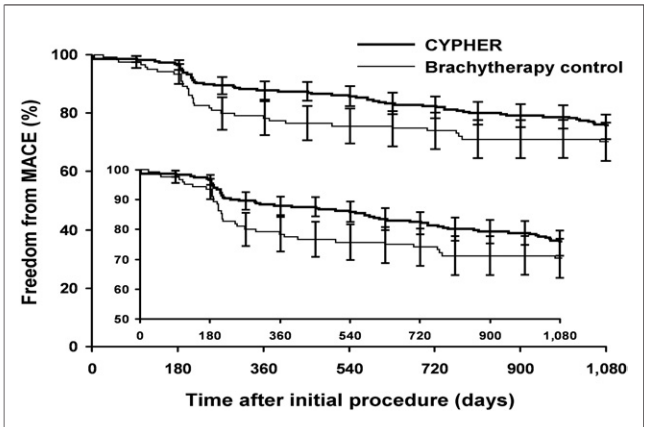

Figure 4. Kaplan-Meier Curves and Survival Table for the End Point of MACE to 1,080 Days

In patients treated with the Cypher stent (Cordis), the difference in major adverse cardiac events (MACE) from vascular brachytherapy is attenuated throughout the 3-year follow-up period (log-rank p = 0.186)

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AUGUST 2008:439–48

Table 4. Medication Usage to 3 Years

Measure	Vascular Brachytherapy (n = 125)	Sirolimus-Eluting Stent (n = 259)	All Patients (n = 384 Patients, n = 384 Lesions)	p Value
Discharge				
ASA + (clopidogrel or ticlopidine)	87.9% (226/257)	87.2% (109/125)	87.7% (335/382)	0.869
ASA only	0.0% (0/257)	0.0% (0/125)	0.0% (0/382)	—
Clopidogrel only	11.7% (30/257)	12.0% (15/125)	11.8% (45/382)	1.000
Ticlopidine only	0.0% (0/257)	0.8% (1/125)	0.3% (1/382)	0.327
None of the above	1.2% (3/259)	0.0% (0/125)	0.8% (3/384)	0.554
At 30-day follow-up				
ASA + (clopidogrel or ticlopidine)	83.3% (210/252)	86.3% (107/124)	84.3% (317/376)	0.547
ASA only	1.6% (4/252)	2.4% (3/124)	1.9% (7/376)	0.689
Clopidogrel only	14.3% (36/252)	9.7% (12/124)	12.8% (48/376)	0.251
Ticlopidine only	0.0% (0/252)	0.8% (1/124)	0.3% (1/376)	0.330
None of the above	3.5% (9/259)	1.6% (2/125)	2.9% (11/384)	0.515
At 6-month follow-up				
ASA + (clopidogrel or ticlopidine)	70.1% (176/251)	75.0% (87/116)	71.7% (263/367)	0.384
ASA only	6.8% (17/251)	5.2% (6/116)	6.3% (23/367)	0.649
Clopidogrel only	21.9% (55/251)	15.5% (18/116)	19.9% (73/367)	0.163
Ticlopidine only	0.0% (0/251)	0.9% (1/116)	0.3% (1/367)	0.316
None of the above	4.2% (11/259)	10.4% (13/125)	6.3% (24/384)	0.025
At 12-month follow-up				
ASA + (clopidogrel or ticlopidine)	52.0% (127/244)	55.7% (64/115)	53.2% (191/359)	0.571
ASA only	21.7% (53/244)	16.5% (19/115)	20.1% (72/359)	0.263
Clopidogrel only	19.7% (48/244)	20.0% (23/115)	19.8% (71/359)	1.000
Ticlopidine only	0.0% (0/244)	0.9% (1/115)	0.3% (1/359)	0.320
None of the above	12.0% (31/259)	14.4% (18/125)	12.8% (49/384)	0.516
At 2-year follow-up				
ASA + (clopidogrel or ticlopidine)	42.4% (100/236)	41.2% (47/114)	42.0% (147/350)	0.908
ASA only	25.4% (60/236)	23.7% (27/114)	24.9% (87/350)	0.792
Clopidogrel only	19.1% (45/236)	18.4% (21/114)	18.9% (66/350)	1.000
Ticlopidine only	0.0% (0/236)	0.0% (0/114)	0.0% (0/350)	—
None of the above	20.8% (54/259)	24.0% (30/125)	21.9% (84/384)	0.511
At 3-year follow-up				
ASA + (clopidogrel or ticlopidine)	56.1% (128/228)	57.8% (63/109)	56.7% (191/337)	0.815
ASA only	30.3% (69/228)	30.3% (33/109)	30.3% (102/337)	1.000
Clopidogrel only	5.3% (12/228)	3.7% (4/109)	4.7% (16/337)	0.597
Ticlopidine only	0.0% (0/228)	0.0% (0/109)	0.0% (0/337)	—
None of the above	19.3% (50/259)	20.0% (25/125)	19.5% (75/384)	0.891

Per the protocol, the Cypher patients were to take acetylsalicylic acid (ASA) indefinitely and Plavix or Ticlid (Bristol-Myers Squibb/Sanofi Pharmaceuticals) for at least 12 weeks. The radiation patients were to take ASA indefinitely. Those that received a stent during the procedure were to take Plavix or Ticlid for at least 12 months. Those patients who did not receive a stent were to take Plavix or Ticlid for at least 6 months. Patients may have more than 1 medication at each time point.

Cardiovascular Angiography and Interventions, and the European Society of Cardiology to use prolonged dual antiplatelet therapy in patients after deployment of a DES (32). Given the late stent thrombosis in this patient subset, efforts at maintaining prolonged dual antiplatelet therapy need to be emphasized.

These results have assumed increased importance due to the recent shift in stent use from ~90% DES use in recent years to the current ~60% or lower DES use. The use of DES has decreased in part because of the potential of late stent thrombosis and the recommended need for prolonged dual antiplatelet therapy (23–27,32). Some institutions and regions, as well as individual operators, have implemented a policy of the use of more frequent placement of bare-metal stents, using only DES for more "complex" lesions. Taken to the extreme, Swedish investigators (26) have recently adopted a policy that discourages DES use, and the BASKET (Basel Stent Kosten-Effektivitats Trial) stent trial investigators concluded that current DES are not cost effective in many patients (33,34). These trends have led to an increase in the use of BMS, and, thus, more BMS restenosis will probably be encountered in routine clinical practice.

The treatment of restenosis occurring after placement of bare-metal stents has been problematic. Even though restenosis after bare-metal stents occurred less frequently than after conventional percutaneous transluminal coronary angioplasty, it still resulted in clinical problems including recurrent ischemia, acute coronary syndromes, need for repeat procedures, and, infrequently, death. Grading schemes (35) were developed that could be used to assess risk of subsequent events after restenosis of bare-metal stents; using one of these algorithms, the rate of adverse subsequent events was as high as 80% to 90%.

Recently, more data have become available on the spectrum of events that occur in patients with restenosis of bare-metal stents (36–38). We recently reported on the frequency and outcome of stent thrombosis and restenosis during extended follow-up of 4,503 patients treated with at least 1 bare-metal stent (36). Restenosis in these patients may present as acute infarction, and, when it does so, the mortality is increased. In this patient cohort in the patients with restenosis at 10 years, 7.4% had experienced unstable angina and 2.1% had experienced an MI. Given the relative frequency of restenosis versus stent thrombosis, restenosis events accounted for more absolute deaths than did stent thrombosis. Williams and Abbott (39) editorialized that "one might postulate that in-stent restenosis related MI would be observed less commonly among DES treated patients than patients treated with a BMS" because DES is associated with less in-stent restenosis. Similarly, Chen et al. (38) evaluated 1,186 patients with restenosis of bare-metal stents. They found that 36% presented as an MI or unstable angina. Of these, an ST-segment elevation MI was present in 2.2%. Nayak et al. (37) evaluated longer-term outcome in 2,462 patients undergoing percutaneous transluminal coronary angioplasty with a bare-metal stent. Of patients with in-stent restenosis, 5% presented with an ST-segment elevation MI.

Thus, strategies to avoid the occurrence of restenosis are warranted. However, if restenosis is observed in the context of prior treatment with a BMS, the 3-year follow-up data from the SISR trial suggest that SES appear to provide an effective and durable therapy that is devoid of new safety issues of death and infarction and that offer several advantages over the only other approved treatment for restenosis, namely VBT. However, the increase in stent thrombosis relative to initial treatment of de novo lesions remains of concern.

Study limitations. The primary end point of this trial was TVF at 9 months. Follow-up after the primary end point was yearly. The trial was not powered for long-term follow-up. This was of particular relevance for low-frequency events such as stent thrombosis. In addition, approximately 10% of patients were lost to follow-up. This current follow-up analysis is descriptive and examines the pre-specified safety end points of death, MI, and stent thrombosis as well as the efficacy end point of TLR. In addition, antiplatelet regimens after 9 months were not mandated, and so they varied according to the clinical practice at participating sites.

Conclusions

In the randomized SISR trial of SES versus VBT for treatment of in-stent restenosis at 3 years: 1) the safety end point of death, cardiac death, and MI are infrequent and do not differ significantly between SES and VBT; 2) definite or probable stent thrombosis was not significantly different between the 2 treatment regiments but was increased relative to those rates seen with treatment of de novo lesions; and 3) SES remain superior in achieving the goal of decreasing the frequency of subsequent TLR and TVR.

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Key Words: bare-metal stent restenosis ■ vascular brachytherapy ■ Cypher stent.