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Intracoronary Brachytherapy for Recurrent Drug-Eluting Stent Failure

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ABSTRACT

OBJECTIVES The study sought to report safety and long-term clinical efficacy of intravascular brachytherapy (VBT) for recurrent drug-eluting stent in-stent restenosis (DES-ISR).

BACKGROUND Recurrent DES-ISR remains a therapeutic challenge, and VBT has been used selectively in recurrent DES failure.

METHODS Patients undergoing VBT for recurrent DES-ISR were enrolled from a percutaneous coronary intervention registry. Clinical, procedural, VBT, and outcome data were collected for DES-ISR treated with radiation. Follow-up was obtained by phone call and clinic visits.

RESULTS A total of 186 patients (283 lesions) were included. Mean age was 65 ± 11 years, and 115 (61.8%) were men. Mean time to failure from last failed DES implantation was 450.65 ± 50 days. Majority (95%) had >2 episodes of target lesion revascularization (TLR). Commonest presentation of DES-ISR was unstable angina (68, 30%). All lesions were treated with balloon angioplasty followed by VBT using Beta-Cath system (Best Vascular Inc., Springfield, Virginia) with a dose of 23 to 25 Gy at 2 mm from source center. Radiation was delivered to site of ISR, without procedural adverse events, in 99% cases. Incidence of TLR was 3.3% at 6 months, 12.1% at 1 year, 19.1% at 2 years, and 20.7% at 3 years. No subacute thrombosis event was noted. One patient had late thrombosis during a 3-year follow-up.

CONCLUSIONS VBT for recurrent DES-ISR is safe, with low recurrence rates at 12 months post-procedure, and can be safely used as an effective short-term strategy. Overtime, there is a gradual attrition in patency requiring repeat intervention. (J Am Coll Cardiol Intv 2016;9:1259–65) © 2016 by the American College of Cardiology Foundation.

Coronary stents are a mainstay of therapy in percutaneous coronary intervention (PCI). Stents act as scaffolds and eliminate elastic recoil and late vessel contraction. However, stents are associated with a proliferative response with neointimal hyperplasia of smooth muscle cells that results in renarrowing of the stent lumen, a phenomenon described as in-stent restenosis (ISR) (1–3). Drug-eluting stents (DES) have reduced rate of ISR compared with bare-metal stents (BMS) (3). However, even with newer generations of DES, the hazard of DES-ISR remains 4% to 8% in first year and, thereafter, up to 2% per year (3).

Causes of DES-ISR are multifactorial and are related to stent, procedure, or patient characteristics. Mechanical and biological factors lead to neointima formation, resulting in narrowing of stent lumen. Patient-specific factors include, but are not limited to, resistance to the drug and the inflammatory reaction to the polymer. Recurrent episodes of DES-ISR are more common in patients with diabetes, chronic kidney disease, and in long, calcified and complex lesions, such as bifurcation lesions and vein grafts and chronic total occlusions (2–6).

Due to its recurrent and recalcitrant nature, DES-ISR remains a challenge (1). Conventional modalities for recurrent DES-ISR, including plain old balloon angioplasty (POBA); cutting balloons; atherectomy devices, such as excimer laser; and repeat DES. Even newer modalities such as drug-coated balloons result

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

DES = drug-eluting stent(s)

ISR = in-stent restenosis

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

POBA = plain old balloon angioplasty

TLR = target lesion revascularization

TVR = target vascular revascularization

VBT = vascular brachytherapy

in failure rates of up to 20% within the first year of treatment (2–4,6–11). Thus, the optimal management strategy for DES-ISR remains undefined.

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Intracoronary vascular brachytherapy (VBT) inhibits cell proliferation via cell cycle inhibition. VBT was approved for clinical use in the United States for the treatment of BMS-ISR over a decade ago but falls short to treatment with DES and drug-coated balloons. However, over past years, the main indication for VBT has been recurrent DES-ISR (10,11,12,13). Logistical issues have limited use of VBT to only a few centers in the United States. Due to this, data on efficacy and safety of VBT for recurrent DES-ISR is sparse (12,13).

This study aimed to report the clinical experience of treatment of recurrent DES-ISR with VBT and to follow the outcomes up to 3 years.

METHODS

STUDY POPULATION. The study cohort was selected from an ongoing clinical PCI registry at our institution between 2004 and 2012. Patients with recurrent failure of DES were referred to our center from a wide referral base. Consecutive patients with angina and angiographic evidence of DES-ISR undergoing VBT were included. Patients presenting acutely with ST-segment elevation myocardial infarction (MI), cardiogenic shock, or angiographic evidence of stent thrombosis were excluded. Patients with <3 years of follow-up were also excluded for this analysis. All patients provided written consent for PCI and VBT procedure. This study was conducted under local Institutional Review Board approval.

BASELINE DEMOGRAPHIC, CLINICAL, AND PROCEDURAL DATA. Baseline data were collected from prospective VBT registry records, including medical history, medications, and details of previous PCI, including type and size of DES used.

All PCI procedures were performed using standard technique via femoral approach. Patients were treated with aspirin 325 mg prior to PCI and loaded with thienopyridine. During PCI, patients received anticoagulation with either bivalirudin (intravenous bolus of 0.75 mg/kg, followed by infusion at 1.75 mg/kg/h) or unfractionated heparin (intravenous bolus of 70 to 100 U/kg and additional heparin as needed) to achieve an activated clotting time of 250 to 300 seconds. Intravenous platelet glycoprotein IIB/IIIA inhibitors were used when deemed appropriate by the operator. Adjunctive mechanical devices, such as atherectomy, cutting balloons, and intravascular imaging with intravascular ultrasound, were used in selected cases. All patients received dual antiplatelet therapy for a minimum of 12 months post-procedure.

DETAILS OF VASCULAR BRACHYTHERAPY. Radiation system used in this study was the Beta-Cath system of Novoste (Best Vascular Inc., Springfield, Virginia). A 40- and 60-mm train of strontium-90/yttrium-β source was used for delivering VBT to target sites of DES-ISR. The catheter system consisted of 3 components: 1) delivery catheter; 2) transfer device; and 3) radiation source. The triple lumen rapid exchange catheter is closed end, coronary catheter used for delivering the train of radiation source, a lumen for fluid delivery and a lumen for guidewire. Prescription dose ranged from 23 to 25 Gy at 2 mm from center of the source based on vessel diameter. For large vein grafts, a dose of 25 Gy at 2 mm was applied (13). VBT was performed following conventional PCI with either POBA or cutting balloons. A BMS or DES was rarely used in combination with VBT. Coverage length of radiation therapy consisted of the treated segment with ~5 mm of segments both proximally and distally to sufficiently cover from the healthy proximal to healthy distal segments both side of the ISR lesion.

CLINICAL ENDPOINTS AND DEFINITIONS. The primary endpoint of the study was clinically driven target lesion revascularization (TLR) at 30 days and 1, 2, and 3 years of follow-up. TLR was defined as percutaneous revascularization for a stenosis within a stent or in the 5-mm segments proximal or distal to the stent. Target vessel revascularization (TVR) was defined as either percutaneous or surgical revascularization of the stented epicardial vessel. Procedural angiographic success was defined as a residual stenosis <30% with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. MI was defined per Universal definition (14). Acute coronary syndrome was defined as either MI or unstable angina arising from a de novo culprit lesion. Acute coronary syndrome presentations in the absence of biomarker elevations were defined as unstable angina. A major adverse cardiac event (MACE) was defined as composite of death, MI, and TLR. Time to failure was defined as time from DES implantation to subsequent failure treated with VBT. ISR was defined as >50% luminal stenosis within the stent or 5 mm proximal or distal to stent. Focal ISR was defined as a restenotic lesion length <10 mm, intermediate ISR as restenotic

lesion length between 10 and 20 mm, diffuse ISR as restenotic lesion >20 mm, and proliferative ISR as lesion >20 mm extending outside the stent.

Angiographic success was defined as a residual stenosis <30% on final angiogram with TIMI flow grade 3. Stent thrombosis was adjudicated as angiographic or autopsy documentation of partial or total stent occlusion with presence of thrombus. Stent thrombosis was classified as subacute (end of procedure up to 30 days) and late (>30 days) according to the Academic Research Consortium definition of stent thrombosis (15).

FOLLOW-UP. Data management and analyses were performed by a dedicated data coordinating center (Data Center, Cardiovascular Research Institute, Washington, DC). Clinical follow-up data were recorded at 1 month and 1, 2, and 3 years by research staff to determine post-VBT events either by phone contact or an office visit. A committee independently adjudicated all clinical events.

STATISTICAL ANALYSIS. Statistical analyses were performed using the Statistical Analysis System version 8.2 (SAS Institute, Inc., Cary, North Carolina). Continuous variables were expressed as mean ± SD and categorical variables as percentages. Student *t* test or analysis of variance was used to compare continuous variables. Categorical variables were compared using the chi-square test or Fisher exact test. A p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. A total of 186 patients were included in the analysis (Table 1). Mean age of study population was 65 ± 11 years; 115 patients (61.8%) were men, and 147 (79%) were Caucasian. Mean time to failure from last failed DES implantation was 450.65 ± 50 days. The majority (95%) had >2 episodes of TLR. Significant cardiovascular risk factors were prevalent in the study population with high prevalence of hypertension (95.2%), diabetes (46.5%), hyperlipidemia (94.1%), chronic smoking (62.4%), and chronic kidney disease (20.5%). A total of 101 (55%) patients had a history of prior coronary bypass surgery. The most common clinical presentation of DES-ISR was unstable angina (68, 30%), and 7 (3%) presented with ST-segment elevation MI.

LESION CHARACTERISTICS/PROCEDURAL DATA. Lesion and procedural data are depicted in Table 2. A total of 283 lesions were treated. The majority (266, 96%) of lesions had >2 episodes of TLR. Failed stent was first-generation DES in 191 (67.6%) of lesions. Mean length of DES was 21.61 ± 6.7 mm with a mean

TABLE 1 Baseline Characteristics of Patients Undergoing Vascular Brachytherapy for Recurrent Drug-Eluting Stent Failure (N = 186)

Age, yrs	65 ± 11
Male	62
Body mass index, kg/m^2	30.1 ± 6.2
Hypertension	95
Smoking	62
Diabetes	46.5
Dyslipidemia	94
Previous CABG	55
Presentation with unstable angina	30
STEMI	3

Values are mean ± SD or %.
CABG = coronary artery bypass grafting; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Angiographic and Lesion-Specific Characteristics of Study Population

Lesion location	
Left anterior descending	21
Left circumflex	23
Right coronary	35
Venous graft	17
Ostial	7
Proximal	29
Mid	36
Distal	26
Lesion type (ACC/AHA Class)	
Type A	7
Type B1/B2	50
Type C	43
Number of previous ISR episodes	
1–2	4
3–4	63
>4	25
Unknown	8
Previous DES information	
First generation	64
Second generation	36
DES length, mm	21.61 ± 6.7
DES diameter, mm	3.08 ± 1.7
Time of failure of DES, days	450.65 ± 50.0
Pattern of restenosis	
Focal	73
Diffuse	23
Proliferative	4
Last treatment for DES-ISR	
BA alone	40
Restenting	28
Unknown	32

Values are % or mean ± SD.
ACC/AHA = American College of Cardiology/American Heart Association; BA = balloon angioplasty; DES = drug-eluting stent(s); ISR = in-stent restenosis.

diameter of 3.08 ± 1.7 mm. Right coronary artery was the commonest 99 (35%) native artery to undergo VBT. Among grafts, saphenous vein graft (17%) was more common that internal mammary artery graft (2%) to undergo VBT.

The majority of DES-ISR lesions (101, 36%) occurred in mid-segments of vessels. POBA was the most commonly used PCI modality prior to VBT (80%), and 11 (4%) had a BMS placed, while 5 (2%) had a re-DES used. Intravascular ultrasound imaging was used in conjunction with VBT in 60% of procedures. Intravascular excimer laser was used in 1% of cases. Cutting balloon was utilized in 26% of cases. Angiographic success post-procedure was achieved in 100% cases (Table 3).

CLINICAL OUTCOMES AT 30 DAYS, 6 MONTHS, AND 1, 2, AND 3 YEARS. Incidence of TLR and TVR MACE was 1.1% and 2.2%, respectively, at 30 days. MI occurred in 0.5% and all-cause mortality in 0.5%.

At 6 months, incidence of TLR and TVR-MACE was increased to 6.5% and 9.7%, respectively. Rate of MI remained at 0.5% and all-cause mortality was increased at 3.8% (Table 4).

At 1 year, the rate of TLR and TVR-MACE more than doubled at 16.8% and 23%, respectively. Similarly, incidence of MI and all cause mortality was also higher at 1.6% and 5.4%, respectively.

Incidence of TLR and TVR-MACE continued to increase at 2- and 3-year follow-up and were 27.6% and 39.2% at 2 years and 31.9% and 44.1% at 3 years after VBT, respectively. The incidence of MI was 6.7%, and that of all-cause mortality was 13.2%. Occurrence of late stent thrombosis was 0.5% at 1 year, 2 years, and 3 years. Figure 1 shows the Kaplan-Meier survival estimates of TLR and TVR in the study population.

TABLE 3 Vascular Brachytherapy Procedure Details of Study Population

Activity per seed source, mCi	23.55 ± 1.42
Irradiated length, mm	26.30 ± 13.79
Device used prior to VBT	
POBA	80
Cutting balloon	27
DES	2
BMS	4
IVUS guidance during VBT	60
IVUS used pre-procedure	96
IVUS findings	
Tissue hyperplasia	100
Unexpanded stent	0

Values are mean ± SD or %.
BMS = bare-metal stent(s); DES = drug eluting stent(s); IVUS = intravascular ultrasound; POBA = plain old balloon angioplasty; VBT = vascular brachytherapy.

TABLE 4 TLR, TVR, MI, LST, and Death at 30-Day, 1-Year, and 3-Year Follow-Up of Patients Undergoing Vascular Brachytherapy for Recurrent Drug-Eluting Stent Failure

	30 Days	6 Months	1 Year	2 Years	3 Years
TLR	1 (0.5)	6 (3.3)	22 (12.1)	31 (17.2)	30 (19.4)
Surgical TLR	0	0	0	3 (1.6)	5 (2.8)
TVR	3 (1.6)	13 (7.1)	35 (19.1)	54 (30)	55 (30.5)
Surgical TVR	0	0	0	3 (1.6)	5 (2.8)
MI	0	1 (0.5)	3 (1.5)	10 (5.6)	11 (6.7)
LST	0	0	1 (0.5)	1 (0.5)	1 (0.5)
Death	1 (0.5)	7 (3.8)	10 (5.4)	18 (9.8)	23 (13.2)

Values are n (%).
LST = late stent thrombosis; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

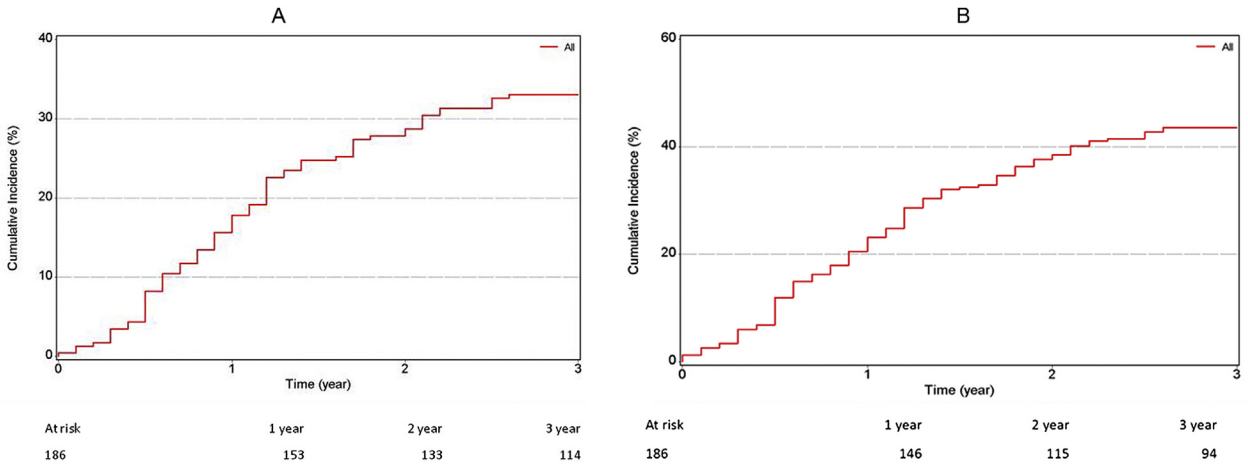
DISCUSSION

The present study is one of the largest series reporting long-term outcomes of patients with multiple recurrences (>2) of DES-ISR treated with VBT. The main findings of this study are: 1) feasibility and safety of VBT use in recurrent DES-ISR; 2) reasonable short- and medium-term outcome of VBT when adjusted for the complexity of these patients and the natural history of high recurrence rate; and 3) significant time-dependent attrition of stent patency seen on long-term follow-up.

ISR of a DES is clinically challenging and differs from BMS-ISR. Intravascular ultrasound studies have shown that the pattern of ISR in DES is focal and mostly confined to the proximal and mid-segments of the stent, and it rarely extends beyond stent edges (16). This is in contrast to the BMS-ISR, which is primarily due to diffuse intimal hyperplasia. A major pre-disposing factor for the first episode of DES-ISR is stent under expansion, while that for recurrent DES-ISR is exaggerated intimal hyperplasia response. The reported rates of DES-ISR range from 5% to 8% (2–4) in the first year depending on the complexity of the lesion and have been shown to be up to 2% per year; in patients with previous DES failure, it is up to 20% at 1 year regardless of the conventional modality used to treat the initial DES failure (2–8). This is in addition to the phenomenon of very late stent thrombosis (2).

VBT delivers ionizing radiation to the DES-ISR site, inhibiting intimal hyperplasia by interrupting the cell cycle and causing apoptosis. This is accomplished by 2 types of cell injury, direct and indirect. Direct action of ionizing radiation targets the intracellular biological molecules critical for cell division and survival while indirect injury leads to conversion of cell water into highly reactive hydroxyl free radicals. This

FIGURE 1 Kaplan-Meier Survival Estimates of Target Lesion and Vessel Revascularization at 1, 2, and 3 Years



Kaplan-Meier survival estimates target lesion **(A)** and vessel **(B)** revascularization at 1, 2, and 3 years in patients undergoing vascular brachytherapy for drug-eluting stent in-stent restenosis.

leads to cell death (17). Radiation energy also reduces leukocyte chemotaxis, cytokine induction, and matrix secretion by macrophages and other pro-inflammatory cells, reducing inflammation (17,18).

VBT is labeled for the treatment of BMS-ISR, with predominant use today for DES-ISR. However, even for DES-ISR, VBT is not the first line of therapy. Most patients presenting with DES-ISR are first treated with cutting balloon; atherectomy; re-DES; and outside of US, with drug-coated balloons. Therefore, the patients currently referred for VBT are ones who have failed at least several or all of these treatment modalities multiple times. In the present study, all subjects had at least 2 episodes of DES-ISR; some had up to 5 recurrences.

Several trials, comparing re-DES therapy with VBT in BMS-ISR, have shown that DES may be superior to VBT with similar safety profile comparing 2 modalities. The main advantage of DES was the larger acute gain with stent and higher rates of attrition over time, which seemed to be the Achilles heel of VBT (19,20).

Both re-DES and VBT have been shown to be superior to POBA alone in multiple studies of DES-ISR (21-23). On the other hand, limited head-to-head comparisons are available for VBT and re-DES for DES-ISR. When VBT was compared with repeat DES for the treatment of DES-ISR in a nonrandomized fashion, VBT had lower TLR-MACE events (24). This is especially true for recurrent DES-ISR. Usage of VBT is particularly attractive in patients with recurrent DES-ISR and those with complex lesions where re-DES may be extremely challenging and unlikely to be procedurally successful. In these patients, there are clear advantages to using VBT over another DES, as repeat stenting carries the risk of stent thrombosis and re-ISR. In addition, VBT is associated with less inflammation, no additional layers of polymers, and no further encroachment on an already narrowed lumen. Overall recurrence rate for DES-ISR with VBT has been quoted to be as high as 12% at 1 year (22); however, these rates may be acceptable in these complex patients with multiple stent failure.

There was high rate of procedural success and low rate of complications in the present study with rate of angiographic success close to 100%, confirming that VBT can be safely performed with no additional procedural complications. Rate of late thrombosis was very low at <1% over 3-year follow-up in this complex population and did not increase with time. This is contrary to previous studies in which there was an increase in late thrombosis seen in the VBT group (25). This could partially be due to the use of more effective pharmacotherapies in PCI in the current era. Late thrombosis events are related to delayed re-endothelialization after VBT and can be prevented by prolonged antiplatelet therapy. In the RESCUE (Radiation for Eluting Stents in Coronary Failure) trial, the overall recurrence rate of DES-ISR with VBT was 12% at 1 year. The trial also showed that VBT is a safe strategy in these

highly complex patients and had good procedural success (21).

There is a "late catch-up" phenomenon consistently observed in VBT studies on long-term follow-up, leading to late lumen loss (18-20). Results of the present study are consistent with those of the existing literature (19,20). In the WRIST (Washington Radiation for In-stent Restenosis Trial) trial, angiographic restenosis and TVR were reduced at 6 months in patients treated with VBT. However, between 6 and 60 months, patients treated with VBT had more TLR (21.6% vs. 4.7%) and TVR (21.5% vs. 6.1%) compared with placebo. However, at 5 years, MACE was significantly reduced with VBT (46% vs. 69%) (26). Similarly, in the SCRIPPS (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) study, there was a reduction of minimal luminal diameter in VBT group at 3 years, which was not seen in the placebo group (27). These findings suggest that brachytherapy may delay the vascular pathology in ISR but with a late catch-up phenomenon seen to emerge after 1 year (24).

STUDY LIMITATIONS. The major strength of this study is the large population of patients undergoing VBT for recurrent DES-ISR with long-term follow-up. However, it suffers from limitations of a retrospective design. Patients were not randomized to other strategies. However, due to the complex nature of DES-ISR, it would be difficult to conduct such a randomized study. Again, there was no control group of balloon angioplasty alone. In addition, due to the nature of referral, many patients were lost to follow-up. This may have led to over-reporting of recurrences. Another limitation of this study is the highly selected population, as a majority of them were specifically referred to our center for VBT, and the referring physician had decided that conventional therapy was not an option. Therefore, it is difficult to extrapolate these data to all patients with DES-ISR.

The present study is unique with respect to study population who had recurrent DES-ISR, especially given that success of other modalities in this complex population is not known. While it may be reasonable to treat the first DES-ISR with any of the conventional modalities, it is appealing to use VBT for those who failed more than once and with multiple DES layers. With lack of availability of coronary drug-coated balloons in the United States, there is growing interest of VBT in these patients, and indeed, there has been an increase in catheterization labs in the United States offering VBT. We believe that data from this registry support use of VBT for these complicated patients and provide prognostic information.

CONCLUSIONS

Treatment of recurrent DES-ISR remains challenging. VBT offers a high rate of procedural success with an excellent safety profile. Although acceptable patency rates following VBT are seen at 1 year, there is a time-dependent decline in stent patency at follow-up. Yet, given the few options available for patients with recurrent DES-ISR, VBT should be considered.

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PERSPECTIVES

WHAT IS KNOWN? DES have revolutionized the percutaneous management of coronary artery disease. However, even with newer generations of DES, the hazard of ISR remains high. Treatment of DES-ISR remains challenging in those with recurrent episodes, as is the case with complex lesions in patients with diabetes and chronic kidney disease and in long calcified and complex lesions, such as bifurcation lesions and vein grafts and chronic total occlusions. As such, optimal management of recurrent DES-ISR is unknown with options including re-DES, balloon angioplasty, drug-coated balloon, or VBT. Currently, the main indication for VBT is for recurrent DES-ISR in this complex population.

WHAT IS NEW? This is one of the largest series reporting long-term outcomes of patients with multiple recurrences (>2) of DES-ISR treated with VBT. The study showed feasibility and safety of VBT use in recurrent DES-ISR with reasonable short- and medium-term outcome of VBT, considering the complexity of these patients and the natural history of a high recurrence rate in this cohort. However, significant time-dependent attrition of stent patency was seen on long-term follow-up following VBT.

WHAT IS NEXT? Additional prospective studies are needed to better understand the pathophysiology of DES-ISR and to prospectively evaluate head to head various strategies used for treatment of DES-ISR in this complex population, which is usually excluded from large trials.

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