Treatment of Patients With Recurrent Coronary In-stent Restenosis With Failed Intravascular Brachytherapy

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Intravascular brachytherapy (VBT) is an effective and safe treatment option for recurrent drug-eluting stent (DES) in-stent restenosis (ISR). However, the optimal therapy for patients with failed VBT is not well-defined. In this study, we sought to evaluate the optimal treatment strategy for patients after a failed VBT. Patients with recurrent ISR after an initial unsuccessful VBT were identified from our percutaneous coronary intervention database. Patients were divided into 2 cohorts (standard treatment with DES or balloon angioplasty versus repeat VBT). Baseline characteristics and clinical outcomes during follow-up were extracted. A total of 279 patients underwent PCI after an initial unsuccessful VBT at our institution. Of those, 215 (77%) patients underwent standard treatment with balloon angioplasty with or without DES, and 64 (33%) underwent balloon angioplasty followed by repeat VBT. The mean age of the cohort was 64±11 years. Overall, 71% were men, 47% had diabetes, and 22% had heart failure. The majority (64%) presented with unstable angina. The groups had similar baseline characteristics. The rate of major adverse cardiovascular events (defined as all-cause mortality, myocardial infarction, or target vessel revascularization) was significantly lower in the repeat VBT group at 1 year (31% vs 14%, p = 0.03), 2 years (51% vs 31%, p = 0.03), and 3 years (57% vs 41%, p = 0.08). Target lesion revascularization and target vessel revascularization were consistently lower in the repeat VBT group at all follow-up intervals than in the standard treatment group. Treatment of recalcitrant ISR following an initial failed VBT is associated with a high MACE rate at 3-year follow-up. Repeat VBT is safe and effective and should be considered as the preferred strategy. **(Am J Cardiol 2021;142:44−51)**

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has decreased the incidence of in-stent restenosis (ISR) when compared with bare metal stents (BMS) .[1] Despite improvements in DES technology, ISR rates remain high.[2] Patient-related characteristics such as diabetes mellitus, hypertension, and hyperlipidemia; procedure-related factors such as stent underexpansion, optimal pretreatment of lesions, and underutilization of imaging guidance; and lesion-related factors have played a role in the pathogenesis of ISR.[3] Intravascular brachytherapy (VBT) was proven to be effective and safe for the treatment of ISR of DES and recently was demonstrated to be more effective than standard therapy.[4] VBT inhibits neointimal formation within the stent by delivering radioactive energy. VBT has shown promising results in randomized trials for the treatment of BMS ISR.[5,6] Evidence for optimal treatment for recurrent ISR after an initial failed VBT in the DES era is limited to small studies with short-term follow-up.[7-9] Thus, we performed this study to evaluate the most effective treatment strategy for patients with recalcitrant ISR after an initial unsuccessful VBT.

Methods

This was a retrospective, single-center study. The MedStar Cardiovascular Research Network maintains a registry of patients who undergo PCI at our institution. We identified patients with recurrent ISR after an initial unsuccessful VBT from January 1, 2005, through July 31, 2016. Patients who met the inclusion criteria were divided into 2 cohorts depending on the type of intervention strategy: standard treatment group, which includes balloon angioplasty or DES, and the repeat VBT group, which is plain old balloon angioplasty (POBA) followed by repeat VBT.

The primary study end point was major adverse cardiovascular events (MACE), which is a composite of all-

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cause mortality, myocardial infarction, and target vessel revascularization, at 3 years. Other individual end points were myocardial infarction, cardiac mortality, target lesion and vessel revascularization, and stent thrombosis. All patients provided written consent for PCI and VBT. This study was approved by Institutional Review Board at our institution.

All PCI procedures were performed using standard technique via femoral approach. Patients were loaded with dual antiplatelet therapy before PCI. 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 70−100 U/kg and additional heparin as needed) to achieve an activated clotting time of 250−300 seconds. Intravenous glycoprotein IIB/IIIA inhibitors were used when deemed appropriate by the operator. Adjunctive mechanical devices, such as rotational atherectomy, laser atherectomy, cutting balloons, and intravascular imaging with intravascular ultrasound (IVUS), were used in selected cases. All patients received dual antiplatelet therapy for a minimum of 12 months after the procedure.

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

A dedicated data coordinating center (Data Center, MedStar Health Research Institute, Washington, District of Columbia) performed all data management and analyses. Authors (CY, CS, CZ, and RW) had full access to all the data in the study and take responsibility for the integrity of the data analysis. SAS 9.2 (SAS Institute, Cary, North Carolina) was used. Continuous variables are expressed as mean ± SD or median (25^{th}−75^{th} interquartile range), as appropriate according to the variable distribution. Categorical variables are reported as frequency and percentages. Student's *t* test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables. Paired data were assessed with the paired Student's *t* test or Wilcoxon signed rank test as appropriate. Cumulative incident function analysis was performed for MACE at maximum follow-up. The level of significance was set at $p \leq 0.05$.

Results

A total of 279 patients underwent PCI after an initial unsuccessful VBT at our institution. Of these, 215 (77%) patients underwent standard treatment with balloon angioplasty with or without DES, and 64 (23%) underwent POBA followed by repeat VBT. The majority of patients (64%) presented with unstable angina, 9% presented with acute coronary syndrome, and 2% with cardiogenic shock. All patients with cardiogenic shock underwent standard treatment with PCI. The patients' mean age was 64± 11 years. The repeat VBT group had a significantly higher percentage of patients who had previously undergone coronary artery bypass graft (CABG) surgery; otherwise, no significant differences between baseline characteristics were noted between the groups. Table 1 outlines baseline characteristics in both groups.

A total of 458 lesions were evaluated (standard treatment=361 and repeat VBT=97). No differences between procedural characteristics were noted between the groups. IVUS was used in 63% of the patients; 98% of PCI procedures were successful, with only 1 patient requiring emergent CABG in the standard treatment group. Stents were implanted in 69% of patients (55% with DES and 14% with BMS) in the standard treatment group, and 33% underwent concomitant stenting in the repeat VBT group (11.6% with BMS and 21.6% with DES). Two (0.9%) standard-treatment patients died in the hospital; no repeat VBT patients died in the hospital. The mean length of stay was 2.2±2.7 days and did not differ between the groups. Table 2 outlines major procedural details in both groups.

Overall mean follow-up was 718 ± 851 days. At 30 days and 6 months, MACE did not differ between the groups. However, from 1 year to 3 years, the MACE rate was consistently and significantly lower in the repeat VBT group than in the standard-treatment group (Figure 1). The cumulative incidence of MACE at 3 years was significantly lower in the repeat VBT group than in the standard-treatment group (57% vs 41%, $p = 0.05$) (Figure 2).

The lower MACE rate in the repeat VBT group was primarily driven by a lower target vessel revascularization (TVR) rate (14% vs 24%, $p = 0.13$ at 1 year; 21% vs 45%, $p = 0.01$ at 2 years; and 32% vs 51%, $p = 0.07$ at 3 years) when compared with standard treatment (Figure 3). The target lesion revascularization (TLR) rate showed a similar trend (Table 3). Other individual end points of MACE, myocardial infarction, and all-cause mortality were not statistically significantly different between the groups. No deaths were identified during the first year after treatment in the repeat VBT group. The stent thrombosis rate in the standard-treatment group was around 4% at 1 year and 5% at 2 years. No stent thrombosis was noted in the repeat VBT group through 3-year follow-up. Detailed clinical outcomes are outlined in Table 3.

An additional comparison of DES versus POBA versus repeat VBT was also performed. Clinical outcomes in these 3 treatment strategies are included in the supplemental appendix (Supplemental Table 1). Although nonsignificant, the MACE rate was consistently lower in the repeat VBT

Table 1
Baseline characteristics

Variable	Standard treatment (215)	Repeat VBT (64)	p-value
Age (years)	63.9 ± 11.3 (212)	64.3±10.1 (64)	0.80
Men	68.2% (146/214)	79.7% (51/64)	0.08
Body mass index (Kg/m^2)	30.46 ± 6.74 (188)	29.72 ± 6.06 (50)	0.48
White	71% (152/214)	82.8% (53/64)	0.06
Black	23.8% (51/214)	14.1% (9/64)	0.10
Prior myocardial infarction	56.1% (101/180)	57.4% (31/54)	0.87
Prior coronary artery bypass surgery	39.6% (84/212)	61.9% (39/63)	0.002
Hypertension	92.9% (197/212)	98.4% (63/64)	0.10
Diabetes mellitus	46.8% (95/203)	49.2% (29/59)	0.75
Insulin dependent Diabetes mellitus	22.2% (45/203)	11.9% (7/59)	0.08
Peripheral arterial disease	24.3% (50/206)	35.7% (20/56)	0.09
Chronic renal insufficiency	18.7% (38/203)	9.3% (5/54)	0.10
Heart failure	22.4% (45/201)	18.3% (11/60)	0.50
Smokers	54.2% (116/214)	57.8% (37/64)	0.61
LVEF	0.47 ± 0.13 (132)	0.46 ± 0.15 (42)	0.70
Number of narrowed coronary arteries	2.01 ± 0.85 (146)	2.08 ± 0.88 (50)	0.64
Number Lesions	1.66 ± 0.81 (214)	1.45 ± 0.69 (64)	0.07
Presentation			
Stable angina pectoris	23.4% (50/214)	22.2% (14/63)	0.85
Unstable angina pectoris	62.1% (133/214)	68.3% (43/63)	0.38
Acute coronary syndromes	9.8% (21/214)	7.9% (5/63)	0.65

LVEF = left ventricular ejection fraction; VBT = intravascular brachytherapy

group than in the DES and POBA-only groups. The relative increase of TVR from 6 months to 3 years was highest in the DES group (26% at 1 year, 46% at 2 years, and 51% at 3 years), followed by the POBA group (24% at 1 year, 43% at 2 years, and 51% at 3 years), and was lowest in the repeat VBT group (14% at 1 year, 21% at 2 years, and 32% at 3 years) (Figure 4). A similar trend was noted with TLR (Supplemental Table 1).

Table 2
Procedural details (lesion-based)

Variable	Standard treatment (361)	Repeat VBT (97)	p-value
Right coronary artery	35.7% (129/361)	30.9% (30/97)	0.38
Left main coronary artery	2.5% (9/361)	3.1% (3/97)	0.74
Left anterior descending artery	19.1% (69/361)	22.7% (22/97)	0.43
Left circumflex artery	25.8% (93/361)	19.6% (19/97)	0.21
Saphenous vein graft	16.3% (59/361)	21.6% (21/97)	0.22
Internal mammary artery	100% (2/2)	100% (2/2)	
IVUS Performed	60.9% (215/353)	70.5% (67/95)	0.16
Type A	5.4% (19/349)	9.9% (9/91)	0.12
Type B1 B2	57.6% (201/349)	61.5% (56/91)	0.50
Type C	37% (129/349)	28.6% (26/91)	0.14
Rotational atherectomy	1.4% (5/361)	3.1% (3/97)	0.25
Laser atherectomy	3.1% (11/359)	1% (1/96)	0.27
Cutting Balloon angioplasty	19.2% (69/360)	22.9% (22/96)	0.41
Bare metal stent	14.2% (47/332)	11.6% (11/95)	0.52
Drug eluting stent	54.7% (191/349)	21.6% (19/88)	<.001
DES Stent diameter (mm)	3.05 ± 0.35 (128)	3.02 ± 0.58 (17)	0.84
DES Stent length (mm)	18.93 ± 6.32 (128)	15.65 ± 4.81 (17)	0.04

DES = drug-eluting stent; IVUS = intravascular ultrasound; VBT = intravascular brachytherapy.

Discussion

In the quest to find the optimal treatment strategy for patients with recurrent ISR of DES who were previously treated with VBT, we found that most patients with recalcitrant ISR after an initial unsuccessful VBT presented with unstable angina (64%), and the MACE rate in this high-risk group was extremely high (54%) at 3-year follow-up. In our study, repeat VBT was safe, with no deaths observed up to 1 year and no stent thrombosis through 3-year follow-up. Repeat VBT was also effective, as it was noted to have a significantly lower MACE rate at 3 years when compared with standard treatment. The lower MACE rate was primarily driven by low TLR and TVR rates in the repeat VBT arm. In these patients, the relative increase of TLR/TVR over the years was highest in the DES group, followed by POBA, and was lowest with repeat VBT.

Although brachytherapy is an effective treatment option for multilayered DES ISR, the TLR rate at 3 years is around 30%; that is, 1 in 3 patients still present with recurrent ISR.[9,10] In this high-risk subgroup of patients with recalcitrant ISR after an initial unsuccessful VBT, adding another metallic layer of stent in this “biologically modified” environment is associated with worse outcomes. Studies have shown TLR rates of 21% at 1 year and 45% at 2 years with conventional PCI after a failed VBT.[8,11] Our study shows that in this high-risk subgroup, repeat VBT is an effective strategy, which is consistent with prior small studies of repeat VBT in the DES era.[8,11]

Along with optimization of multiple patient-related risk factors,[12] certain procedural-related changes with VBT can also potentially prolong ISR-free survival in these high-risk recalcitrant ISR patients. Two important strategies are avoiding concomitant stenting[13] and using IVUS.[10]

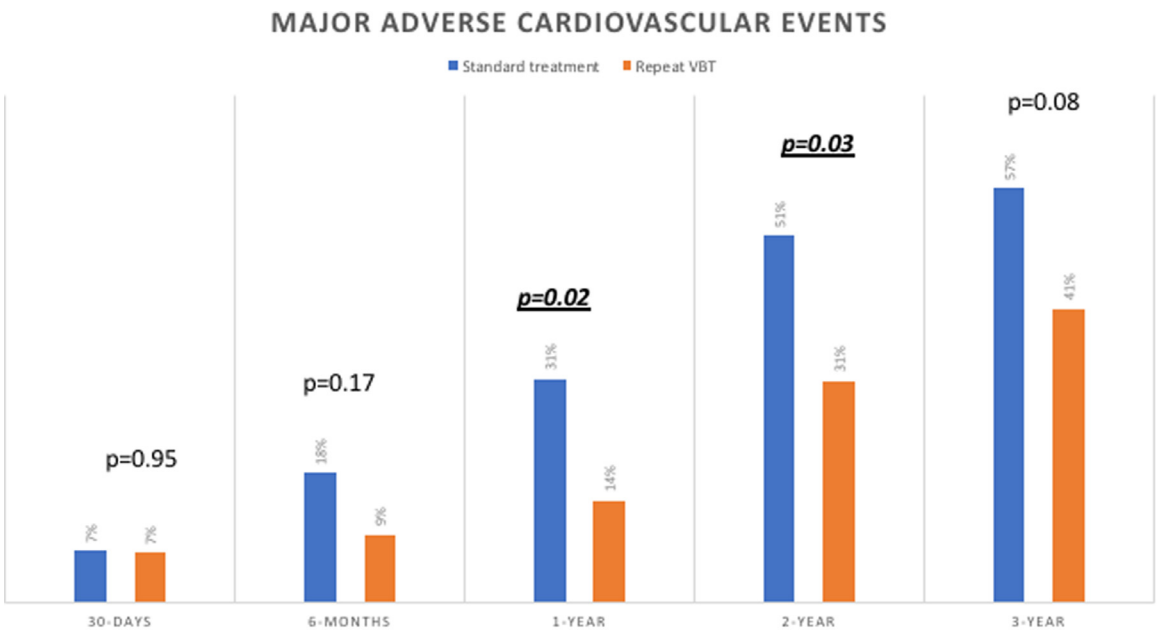

Figure 1. Major adverse cardiovascular events with 2 treatment approaches (standard treatment vs. repeat VBT) after failed intravascular brachytherapy. VBT = intravascular brachytherapy.

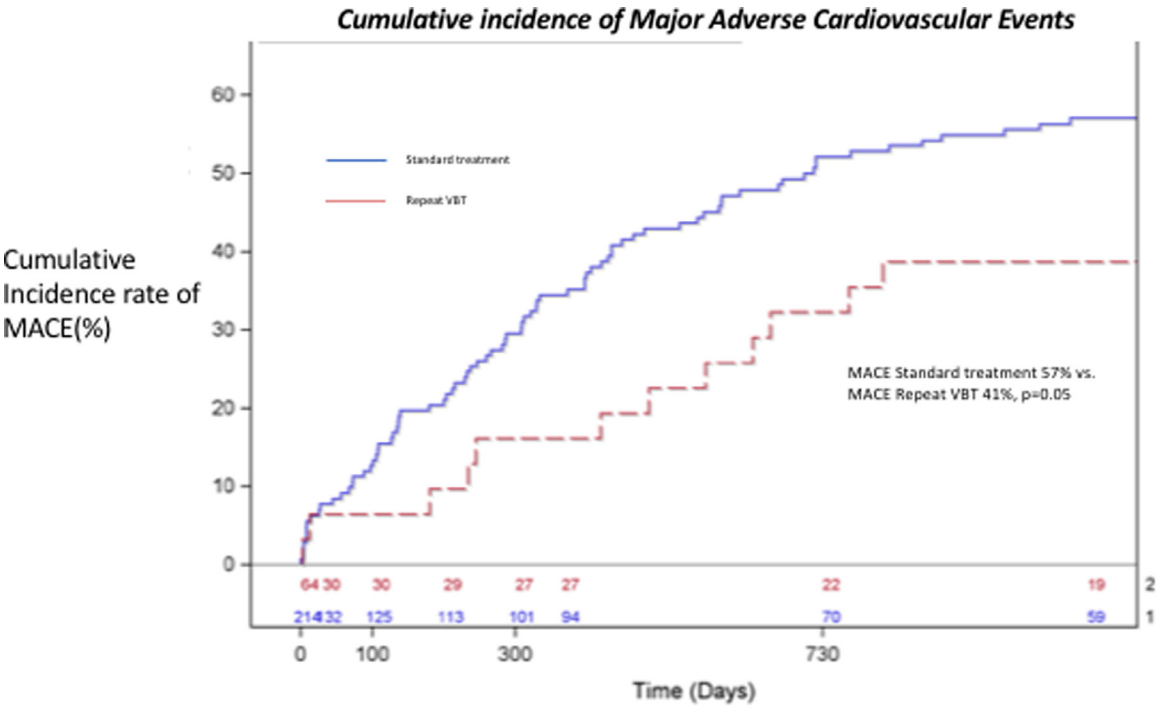

Figure 2. Cumulative incidence of major adverse cardiovascular events with standard treatment vs. repeat VBT. MACE = major adverse cardiovascular event. VBT = intravascular brachytherapy.

Concomitant stent implantation along with repeat VBT causes delayed healing of the stents due to radiation and accelerated neointimal hyperplasia at the treated segment. IVUS can accurately identify mechanical or biological causes of ISR and will help clinicians to delineate the accurate pretreatment modality based on lesion characteristics. IVUS also would be helpful for stent sizing in case of bail-out stenting.

One concern related to repeat VBT is the cumulative radiation dose and impact of the vessel to heal. To mitigate this risk, we recommend at least a 9-month interval between the initial and repeat radiation, which follows the rule of dose fractionation over time. Another concern is the lack of healing of the metallic stent with repeat radiation. In our series, we did not observe any stent thrombosis through the duration of follow-up. This can be attributed to the protocol

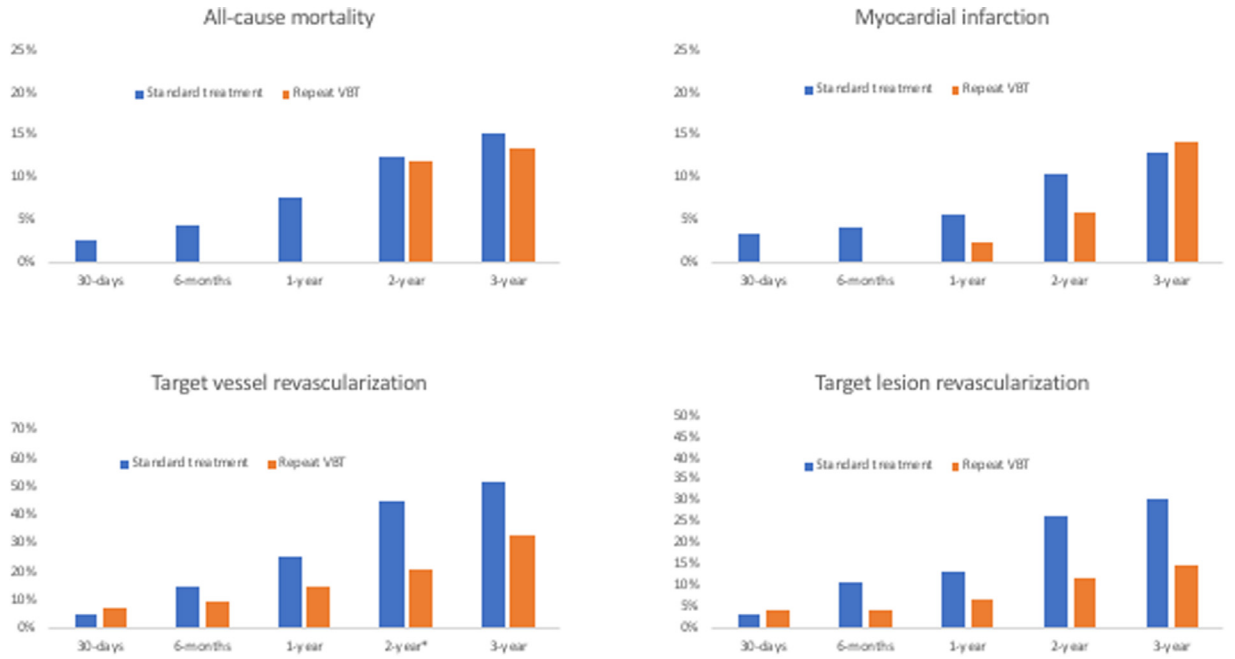

Figure 3. All-cause mortality, myocardial infarction, target lesion and vessel revascularization with 2 treatment approaches (standard treatment vs. repeat VBT) after failed intravascular brachytherapy. VBT = intravascular brachytherapy.

Table 3
Clinical outcomes between percutaneous coronary intervention with standard treatment vs. repeat intravascular brachytherapy at 30 days, 6 months, 1 year, 2 years and 3 years

30-day outcomes	Standard treatment (215)	Repeat VBT (64)	p-value
Major adverse cardiovascular events	7.1% (12/170)	6.8% (3/44)	0.96
All-cause mortality	2.4% (4/169)	0% (0/44)	0.30
Cardiac mortality	1.2% (2/167)	0% (0/44)	0.47
Myocardial infarction	3.6% (6/169)	0% (0/44)	0.21
Q wave myocardial infarction	0.6% (1/168)	0% (0/44)	0.61
Non-Q wave myocardial infarction	3% (5/168)	0% (0/44)	0.25
Target lesion revascularization	3.6% (6/167)	4.5% (2/44)	0.77
Target lesion revascularization-Coronary artery bypass surgery	0.6% (1/167)	0% (0/44)	0.61
Target lesion revascularization-percutaneous transluminal coronary angioplasty	3.6% (6/167)	6.8% (3/44)	0.35
Target vessel revascularization	4.8% (8/167)	6.8% (3/44)	0.59
Stent thrombosis	2.9% (5/171)	0% (0/44)	0.25
6-month outcomes	**Standard treatment**	**Repeat VBT**	**p value**
Major adverse cardiovascular events	17.9% (30/168)	9.3% (4/43)	0.17
All-cause mortality	4.2% (7/167)	0% (0/43)	0.17
Cardiac mortality	1.8% (3/165)	0% (0/43)	0.37
Myocardial infarction	4.2% (7/167)	0% (0/43)	0.17
Q wave Myocardial infarction	1.2% (2/164)	0% (0/43)	0.47
Non-Q wave Myocardial infarction	3% (5/166)	0% (0/43)	0.25
Target lesion revascularization	11% (18/164)	4.7% (2/43)	0.21
Target lesion revascularization-Coronary artery bypass surgery	0.6% (1/163)	0% (0/43)	0.61
Target lesion revascularization-percutaneous transluminal coronary angioplasty	11% (18/164)	7% (3/43)	0.44
Target vessel revascularization	14.6% (24/164)	9.3% (4/43)	0.36
Stent thrombosis	3.6% (6/169)	0% (0/43)	0.21
1-year outcomes	**Standard treatment**	**Repeat VBT**	**p value**
Major adverse cardiovascular events	30.9% (50/162)	14% (6/43)	0.03
All-cause mortality	7.5% (12/160)	0% (0/42)	0.07
Cardiac mortality	2.5% (4/158)	0% (0/42)	0.30
Myocardial infarction	5.7% (9/159)	2.4% (1/42)	0.39

(*continued*)

Table 3 (***Continued***)

1-year outcomes	Standard treatment	Repeat VBT	p value
Q wave myocardial infarction	1.9% (3/156)	0% (0/42)	0.37
Non-Q wave myocardial infarction	3.8% (6/158)	2.4% (1/42)	0.66
Target lesion revascularization	13.4% (21/157)	7.1% (3/42)	0.27
Target lesion revascularization-coronary artery bypass surgery	1.3% (2/155)	0% (0/42)	0.46
Target lesion revascularization-percutaneous transluminal coronary angioplasty	12.1% (19/157)	7.1% (3/42)	0.36
Target vessel revascularization	24.8% (39/157)	14% (6/43)	0.13
Stent thrombosis	3.7% (6/163)	0% (0/43)	0.20
2-year outcomes	**Standard treatment**	**Repeat VBT**	**p value**
Major adverse cardiovascular events	50.7% (75/148)	30.6% (11/36)	0.03
All-cause mortality	12.3% (17/138)	11.8% (4/34)	0.93
Cardiac mortality	3.7% (5/136)	5.9% (2/34)	0.56
Myocardial infarction	10.6% (14/132)	6.1% (2/33)	0.43
Q wave myocardial infarction	3.1% (4/128)	0% (0/32)	0.31
Non-Q wave myocardial infarction	7.7% (10/130)	6.1% (2/33)	0.75
Target lesion revascularization	26.5% (35/132)	12.1% (4/33)	0.08
Target lesion revascularization-coronary artery bypass surgery	1.6% (2/126)	0% (0/32)	0.47
Target lesion revascularization-percutaneous transluminal coronary angioplasty	25.8% (34/132)	12.1% (4/33)	0.10
Target vessel revascularization	44.5% (61/137)	20.6% (7/34)	0.01
Stent thrombosis	4.7% (7/149)	0% (0/36)	0.19
3-year outcomes	**Standard treatment**	**Repeat VBT**	**p value**
Major adverse cardiovascular events	57.3% (82/143)	40.6% (13/32)	0.08
All-cause mortality	15% (19/127)	13.3% (4/30)	0.82
Cardiac mortality	5.6% (7/125)	6.7% (2/30)	0.82
Myocardial infarction	13.1% (16/122)	14.3% (4/28)	0.87
Q wave myocardial infarction	4.2% (5/118)	0% (0/26)	0.29
Non-Q wave myocardial infarction	9.3% (11/118)	14.3% (4/28)	0.44
Target lesion revascularization	30.6% (38/124)	14.8% (4/27)	0.10
Target lesion revascularization-coronary artery bypass surgery	2.6% (3/115)	0% (0/26)	0.41
Target lesion revascularization-percutaneous transluminal coronary angioplasty	29% (36/124)	14.8% (4/27)	0.13
Target vessel revascularization	50.8% (67/132)	32.1% (9/28)	0.07
Stent thrombosis	4.9% (7/144)	0% (0/32)	0.20

VBT = intravascular brachytherapy.

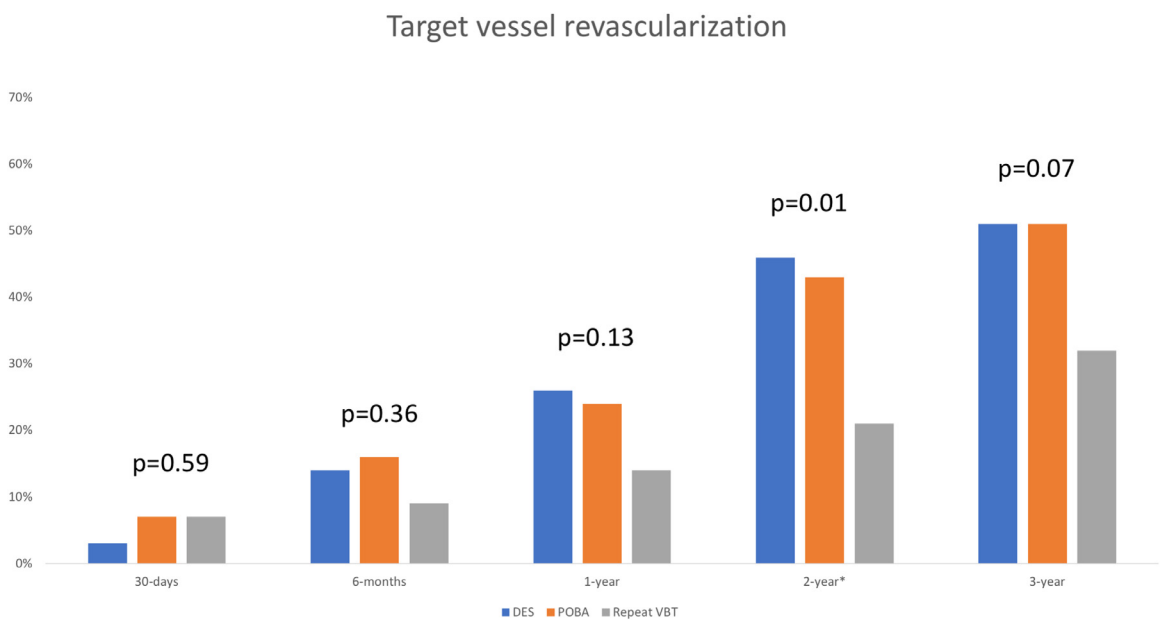

Figure 4. Target vessel revascularization with 3 treatment approaches (percutaneous coronary intervention with drug-eluting stent vs. plain old balloon angioplasty vs. repeat VBT). DES = drug-eluting stent. POBA = plain old balloon angioplasty. VBT = intravascular brachytherapy

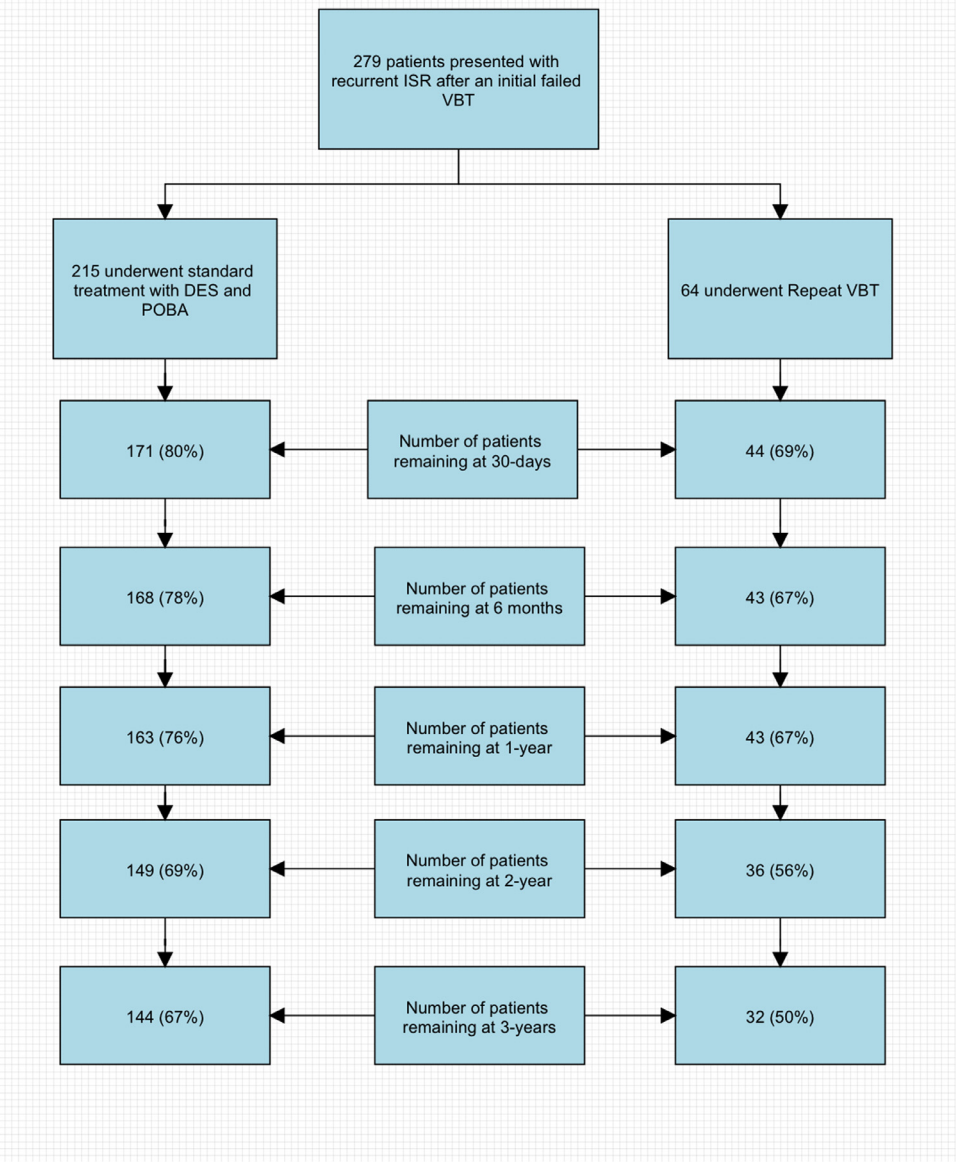

Figure 5. Flow chart outlining the number of patients at different follow-up intervals. DES = drug-eluting stent. POBA = plain old balloon angioplasty. VBT = intravascular brachytherapy.

of avoiding the combination of stent and radiation at the same setup and that the original DES was already covered with endothelium and scar tissue, which protects it from thrombosis.

We recognize that there are 2 other modalities of therapy that should be considered for the patients with an initial failed VBT: CABG or drug-coated balloon (DCB).[14] Although CABG is a viable option, nearly 62% of patients who underwent repeat VBT already had history of CABG, which would expose them to complications associated with redo CABG. The data are not sufficient to draw definitive conclusions regarding the efficacy of DCB for recurrent DES ISR, and there are no data to support the efficacy and safety of DCB following failed VBT. These kinds of studies will wait until DCB approval in the United States for the treatment of DES failure.

Major limitations of our analysis are its retrospective design, selection bias, and patients lost to follow-up. Approximately 37% of the patients in our analysis were lost to follow-up at 3 years (Figure 5). Even so, the results were still significantly better with repeat VBT at 3 years. IVUS was performed in 63% of patients, but the variables were not available for retrospective analysis, so a potential cause for TVR and stent thrombosis cannot be identified. Future studies are needed to identify patients who derive benefit with repeat VBT based on IVUS findings. Follow-up angiogram was not performed on all patients, as this was not a prospective study, which is another major limitation. Finally, the cohort was not large enough to compare in all treatment modalities (POBA, DES, atherectomy, etc.). We could not include DCB in the comparison, as it is not available for use in the USA. Nevertheless, this is the largest study to date with 3-year follow-up that shows a consistent benefit of repeat VBT when compared with other treatment approaches in high-risk recalcitrant ISR patients with initial failed VBT.

In conclusion, although VBT is an effective and safe treatment strategy for recurrent DES ISR, it is associated with recurrences of TLR beyond 1 year. Repeat VBT is a viable, safe, and effective treatment modality for these patients when compared with the standard therapy of POBA or DES and should be the preferred treatment strategy for this challenging group of patients. Future randomized studies are needed to evaluate optimal treatment strategies in this high-risk subgroup.

Authors' Contributions

Charan Yerasi, MD − Conception and design or both; drafting of the manuscript or revising. Yuefeng Chen, MD, PhD − Conception and design or both; drafting of the manuscript or revising. Brian C. Case, MD − Drafting of the manuscript or revising. Brian J. Forrestal, MD − Drafting of the manuscript or revising. Corey Shea, MS − Drafting of the manuscript or revising. Cheng Zhang, PhD − Drafting of the manuscript or revising. Rebecca Torguson, MPH − Drafting of the manuscript or revising. Itsik Ben-Dor, MD − Drafting of the manuscript or revising. Lowell F. Satler, MD − Drafting of the manuscript or revising. Ron Waksman, MD − Drafting of the manuscript or revising; final approval of the manuscript submitted.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this report.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.044.

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