Clinical Outcomes and Treatment After Drug-Eluting Stent Failure

The Absence of Traditional Risk Factors for In-Stent Restenosis

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Background—The optimal percutaneous treatment of drug-eluting stent (DES) in-stent restenosis (ISR) and the correlates for recurrent DES ISR remain unclear.

Methods and Results—From 2003 to 2008, 563 patients presenting with recurrent symptoms of ischemia and angiographic ISR after DES implantation were included. Of these, 327 were treated with re-DES (58.1%), 132 underwent vascular brachytherapy (23.4%), and 104 were treated with conventional balloon angioplasty (18.5%). Variables associated with target lesion revascularization at 1 year were explored by individual proportional hazard models. This population presents a high prevalence of comorbidities, including diabetes (43.7%), previous myocardial infarction (MI) (45.8%), coronary bypass graft surgery (39.2%), chronic renal failure (18.8%), and heart failure (17.3%). Baseline clinical characteristics were balanced among the 3 groups; however, patients undergoing vascular brachytherapy presented with more complex lesions and a higher prevalence of prior stent/vascular brachytherapy failure than did the rest of the population. The overall incidence of recurrent DES failure at 1-year follow-up was 12.2%, which was similar among the 3 groups ($P=0.41$). The rate of the composite end point (death, Q-wave-MI and target lesion revascularization) at 1-year follow-up was 14.1% for re-DES, 17.5% for vascular brachytherapy, and 18.0% for conventional balloon angioplasty ($P=0.57$). After univariable analysis tested the traditional known covariates related to ISR, none of them were associated with repeat target lesion revascularization.

Conclusions—Recurrence of ISR after DES treatment failure is neither infrequent nor benign, and optimal therapy remains unclear and challenging. Given the absence of traditional risk factors for ISR in this population, further research is required to elucidate both the correlates involved in DES ISR and the optimal treatment for this condition. (Circ Cardiovasc Interv. 2012;5:12-19.)

Key Words: drug-eluting stent • restenosis • correlates

Drug-eluting stent (DES) implantation arose as a safe and effective approach to prevent restenosis for de novo lesions and to treat in-stent restenosis (ISR) after bare metal stent (BMS) failure. The long-term follow-up of the pivotal randomized clinical trials for sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) showed yearly rates of angiographic restenosis of 6.8 to 7.9%. Those trials, however, have not tested DES in complex lesions, such as long lesions, smaller-diameter vessels, saphenous vein grafts, in bifurcation and ostial locations, or in high-risk populations, such as patients with diabetes or chronic renal failure, where the expected occurrence of ISR is certainly higher. Indeed, data derived from small trials that tested the efficacy of DES in such higher complex lesions and from large clinical series reported significantly higher rates of DES ISR. As a result, presentation with DES restenosis is not an infrequent clinical problem that represents a major challenge for the interventional cardiologist. There are several percutaneous options to treat this condition, including repeat DES (re-DES), vascular brachytherapy (VBT), and conventional balloon angioplasty (c-PCI), but the optimal treatment has not yet been defined. Limited information, however, is available on the clinical outcomes after a DES failure and the correlates for recurrent DES ISR. We therefore aimed to report the clinical outcomes after DES failure treated with...
the available percutaneous strategies and to identify the covariates associated with recurrence of DES ISR.

WHAT IS KNOWN

● DES restenosis is not an infrequent clinical problem, particularly when treating complex lesions/patients.
● The optimal treatment for this condition remains unknown.

WHAT THE STUDY ADDS

● Recurrence of ISR after DES treatment failure is not infrequent; there is a 12.2% rate of clinically driven revascularization at 1-year follow-up.
● None of the traditional risk factors for ISR predicts the occurrence of recurrent DES-ISR in this series. Re-DES, VBT, and c-PCI appear to be similarly efficient.
● Despite the fact that patients treated with VBT were sicker and had more complex disease, they had comparable results to re-DES or balloon angioplasty strategy.

Methods

Study Sample

An ongoing registry of catheter-based coronary procedures is maintained in our center. From May 2003 to September 2008, all patients presenting with recurrent symptoms and/or ischemia after DES implantation performed in our center and angiographic evidence of ISR were included. Patients presenting with ST-elevation myocardial infarction (MI), cardiogenic shock, or angiographic evidence of stent thrombosis were excluded from this analysis. During the study period, 563 patients who met the inclusion/exclusion criteria presented with DES failure. Of these, 327 were treated with re-DES (58.1%), 132 underwent VBT (23.4%), and 104 were treated using c-PCI (18.5%). (Figure 1) All patients gave written consent for the PCI procedure, and the study was conducted under local Institutional Review Board approval.

PCI Procedures and Adjunctive Medical Therapy

All patients underwent their procedure in our center, a tertiary referral hospital with 11 catheterization laboratories serviced by 31 independent interventional cardiologists. At the initial procedure, patients received either SES (Cypher, Cordis, Johnson & Johnson Services Inc, Miami Lakes, FL; diameters 2.5 to 3.5 mm, lengths 8 to 33 mm) or PES (Taxus, Boston Scientific Corporation, Natick, MA; diameters 2.5 to 3.5 mm, lengths 8 to 32 mm). When DES ISR was diagnosed, patients were treated with re-DES implantation (using any of the DES available at the time of the procedure), VBT, or c-PCI at operator discretion. For re-DES, depending of the time period, SES, PES, zotarolimus-eluting stents (Endeavor, Medtronic, Inc, Minneapolis, MN; diameters 2.25 to 4.0 mm, lengths 8 to 30 mm) or everolimus-eluting stents (EES, Xience V, Abbott Vascular, Santa Clara, CA; diameters 2.5 to 4.0 mm, lengths 8 to 28 mm) were used as physician preference.

PCI was performed using standard technique via the femoral approach. All patients were treated with 325 mg of aspirin prior to PCI and loaded with 300 to 600 mg of clopidogrel. Dual antiplatelet therapy was recommended to all study patients for a minimum of 12 months. During PCI, patients were anticoagulated with either bivalirudin (a bolus of 0.75 mg/kg, followed by an intravenous infusion of 1.75 mg/kg/h) or unfractionated heparin (a bolus of 40 U/kg and additional heparin) to achieve an activated clotting time of 250 to 300 seconds. Use of adjunctive devices (including debulking systems, cutting balloon, intravascular ultrasound, and platelet glycoprotein IIb/IIIa inhibitors) were at the discretion of the operator.

Vascular Brachytherapy Details

Selection of the radiation system was at the operator’s discretion. The following radiation systems and radiation doses were used: the Beta Rail system (Novoste [now Best Vascular, Inc], Norcross, GA), with a strontium-90/yttrium-90 source at a prescription dose of 18 to 23 Gy, 2 mm from the center of the source, based on vessel diameter; the Galileo system (Guidant [now part of Boston Scientific Corporation], Santa Clara, CA), with a phosphorus-32 β source at a prescription dose of 20 Gy, 1 mm from the balloon surface into the vessel wall; and the Checkmate system (Cordis Corporation, Miami, FL), with an iridium-192 β source at a dose of 15 Gy, 2 mm from center of the source. Radiation therapy was performed after balloon angioplasty, with coverage of the treated segment and ≥5 mm from the injured segment.

Clinical End Points and Definitions

The primary end point of the study was defined as the rate of clinically driven target lesion revascularization (TLR) at 1-year follow-up. Major adverse cardiac event (MACE) was defined as the composite of death, Q-wave MI, and TLR at 1-year follow-up. Death was all-cause mortality. Cardiac death included all deaths where a noncardiac cause could not be demonstrated. Q-wave myocardial infarction (MI) was defined as an elevation in creatinine kinase-MB ≥2 times the upper normal value (2.6 ng/mL) in the presence of new Q waves on the ECG in ≥2 contiguous leads. Non Q-wave MI was defined as an elevation in creatine kinase-MB ≥2 times the upper normal value (2.6 ng/mL) in absence of new Q waves. Time to failure was defined as time from DES implantation to subsequent clinical failure treated within our center.
ISR was defined as >50% luminal stenosis within the stent or 5 mm proximal or distal to the stent. **Focal ISR** was defined as a restenotic lesion length <10 mm. **Intermediate ISR** was defined as a restenotic lesion length between 10 and 20 mm. **Diffuse ISR** was defined as a restenotic lesion >20 mm and **proliferative ISR** as lesion >20 mm extending outside of the stent. **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** was defined as either percutaneous or surgical revascularization of the stented epicardial vessel. **Stent thrombosis** was classified by the Academic Research Consortium definitions of definite or probable.1 The definition of definite stent thrombosis required the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion. Probable stent thrombosis included unexplained deaths 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation. **Angiographic success** was defined as a residual stenosis <30% with Thrombolysis In Myocardial Infarction grade 3 flow. **Chronic renal failure** was defined as known history of renal failure or when serum creatinine on admission was >2 mg/dL.

**Data Collection and Follow-Up**

Demographic, clinical, and procedural data, along with in-hospital outcomes, were collected and entered into a prospective database. Data were obtained from hospital chart reviews by independent research personnel blinded to the study objectives. All data management and analyses were performed by a dedicated data coordinating center (Data Center, Cardiovascular Research Institute, Washington, DC). Clinical follow-up was performed at 12 months by trained quality assurance nurses who worked exclusively with the database to determine post-PCI clinical events. Clinical follow-up was performed by telephone contact or office visit. A committee independently adjudicated all subsequent clinical events. Clinical follow-up was available on all patients in the study sample.

**Statistics**

Continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as absolute numbers and percentages. The different groups were compared using the χ² test or the Fisher exact test for categorical variables and the Student unpaired t test or ANOVA test for continuous variables as appropriate. Cumulative survival-free rates from TLR and MACE were estimated using the Kaplan–Meier method. Probability values were determined by the use of the log-rank statistic. Univariable and multivariable Cox proportional hazard modeling was used to determine the association with the primary end point—TLR at 1-year follow-up. The following variables were entered into the multivariable model: age, history of diabetes, chronic renal failure, American College of Cardiology/American Heart Association type C lesion, ostial location, history of prior stent failure, prior VBT failure, modality of ISR treatment, diffuse/proliferative restenosis pattern (>20 mm), mean stent diameter (average of DES diameters used per lesion), mean of total stent lengths (average of sum of DES lengths used per lesion), time to failure (time from initial DES implantation to date of failure), and time to recurrent failure (time from initial DES implantation to the last failure event). The probability values were two-sided and taken as significant at <0.05 with a step-down Bonferroni adjustment applied to all data array. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

**Results**

**Baseline Clinical Characteristics**

Baseline clinical characteristics are displayed in Table 1. This cohort had a high prevalence of comorbidities, including hyperlipidemia (95.0%), hypertension (93.4%), diabetes (43.7%), previous MI (45.8%), prior coronary bypass graft surgery (39.2%), chronic renal failure (18.8%), and heart

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics and Clinical Presentation</th>
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<tr>
<td><strong>Baseline Characteristics, n (%)</strong></td>
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<tr>
<td>Overall Population (n=563)</td>
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<tr>
<td>Re-DES (n=327)</td>
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<td>VBT (n=132)</td>
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<td>c-PCI (n=104)</td>
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<td><strong>P Value</strong></td>
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<td>Age, y (±SD)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Diabetes</td>
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<td>Hypertension</td>
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<td>Hypercholesterolemia</td>
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<td>Family history of CAD</td>
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<td>Chronic renal failure</td>
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<td>History of heart failure</td>
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<td>LV ejection fraction, % (±SD)</td>
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<td><strong>Clinical presentation</strong></td>
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<tr>
<td>Time to failure, days (±SD)</td>
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<tr>
<td>Stable angina</td>
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<td>Unstable angina</td>
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<td>Non-Q wave MI</td>
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**DES** indicates drug-eluting stent; **VBT**, vascular brachytherapy; **c-PCI**, conventional balloon percutaneous coronary intervention; **SD**, standard deviation; **BMI**, body mass index; **CAD**, coronary artery disease; **MI**, myocardial infarction; **CABG**, coronary bypass graft surgery; **LV**, left ventricle.
failure (17.3%). The 3 groups were balanced in terms of the baseline profile, except for the rate of hypertension, which was higher in the re-DES group and the frequency prior coronary bypass graft surgery, which was significantly higher in the VBT group. Clinical presentation for DES ISR was most commonly unstable angina (63.3%), followed by stable angina (32.9%), not significantly different among the 3 groups; however, patients undergoing VBT developed DES failure significantly faster than the rest of the population.

Characteristics of the Failed DES Procedure
Indications and implantation details of the failed DES are described in Table 2. Overall, this cohort included 582 lesions treated by PCI. Indication for the failed DES implantation was significantly different among the 3 groups. De novo lesions were more common in patients treated with re-DES, whereas BMS ISR was more frequent in patients treated with c-PCI, and DES ISR and VBT failure were more common in patients treated with VBT. The mean stent diameter (2.98±0.53 mm) and the mean total stent length (26.8±13.33 mm) were similar among the 3 groups. Overall, SES was the most common used DES (81.8%), without significant difference among the 3 groups.

Angiographic and Procedural Details
Lesion-based angiographic and procedural characteristics are detailed in Table 3. Of the 582 DES restenotic lesions, 337 were treated with re-DES, 139 with VBT, and 106 with c-PCI. Patients treated with VBT presented more frequently with more complex lesions than the rest of the population, including saphenous vein grafts location, type C American College of Cardiology/American Heart Association lesions, and diffuse/proliferative patterns of ISR. Cutting balloon was more commonly used in patients undergoing VBT, as intravascular ultrasound guidance was, overall, performed in 57% of the cases, less frequently used in the c-PCI group. Of the 139 lesions treated with VBT, 121 were treated with the Novoste system (87.8%), 13 with the Galileo device (9.4%), and 3 with the Checkmate system (2.2%).

Clinical Outcomes
Angiographic success was achieved in 562 patients (99.8%) of the treated restenotic lesions. No Q-wave MI occurred during the admission, and all patients were discharged alive after PCI of the failed DES procedure. One-year outcomes are shown in Table 4. One-year clinical follow-up was completed in 418 patients from the initial cohort. Figure 2 and 3 show the Kaplan–Meier survival curves free from TLR and MACE, respectively, at 12 months. The overall 1-year rate of the primary end point (clinically driven TLR) was 12.2%, not significantly different among the 3 therapeutic groups (P=0.41). The rate of the composite MACE was 14.1% for re-DES, 17.5% for VBT, and 18.0% for c-PCI (P=0.57). No significant difference was observed among the 3 groups in terms of definite/probable stent thrombosis rate. After univariable and multivariable Cox proportional analysis, including the known covariates related with ISR, none of the tested variables were associated with the occurrence of TLR at 1-year follow-up.

Subgroup Analysis
Patients presenting with diffuse/proliferative (n=113, 20.3%) and nondiffuse/proliferative (n=442, 79.7%) ISR pattern had similar baseline clinical and angiographic characteristics. Patients with diffuse/proliferative ISR compared with those without diffuse/proliferative ISR received more stents (1.3±0.6 versus 1.2±0.4, P=0.005) and longer stents (30.6±16.8 mm versus 25.9±12.2 mm, P=0.005) and were more frequently treated with VBT (34.5% versus 20.3%, respectively, P<0.001), whereas stent diameters were similar between the 2 groups (3.0±0.3 mm versus 3.0±0.6 mm, P=0.34); however, the rate of the composite MACE at 1-year follow-up remained similar among patients with diffuse/proliferative ISR (16.1%) and those without it (16.9%) (P=0.77), including similar rates of repeat TLR (11.4% versus 12.6%, respectively, P=0.65).

From 327 patients approached with re-DES, 160 patients were treated with the same stent: SES (n=143, 43.7%) and PES (n=17, 5.2%), and 167 patients were treated with a
different stent: PES on SES (n=108, 33.0%), SES on PES (n=49, 15.0%), EES on SES (n=4, 1.2%), zotarolimus-eluting stents on SES (n=3, 0.9%). Patients treated with the same DES and different DES were similar in terms of baseline clinical and angiographic characteristics. The number of implanted stents, the mean diameter, and the total length of the DES were similar among patients treated with the same or different DES (1.2±0.4 mm versus 1.1±0.4 mm, P=0.32; 3.0±0.8 mm versus 3.0±0.3 mm, P=0.5; 26±14.0 mm versus 25±10.9 mm, P=0.35; respectively). Patients initially treated with SES were more frequently retreated with the same DES (n=141, 87.6%), whereas patients initially treated with PES were more commonly re-treated with a different DES (n=115, 65.3%). The rate of 1-year composite MACE tended to be lower in patients treated with a different DES (11.9%) than those treated with same DES (18.6%); however, this difference did not reach statistical significance (P=0.18), including the rate of repeat TLR (8.4% for a different DES group versus 12.2% for the same DES group, P=0.38).

Discussion
The major findings of this study are that recurrence of ISR after DES treatment failure is not benign and re-restenosis rate remains relatively high, independent of the treatment modality used. Interestingly, traditional predictors for BMS ISR did not correlate with DES ISR in the studied population. In addition, this study demonstrated that the implantation of a second DES to treat DES ISR is feasible and suggests that repeat or switch re-DES strategies are associated with comparable efficacy, which is consistent with recently published data.12 Although more complex lesions were treated with VBT, this study suggests VBT to be a safe strategy to treat DES ISR and is associated with comparable efficacy to c-PCI and re-DES.

The overall study population represents a high-risk population for recurrent cardiovascular events, with a high prevalence of comorbidities, including diabetes, history of prior MI, prior coronary bypass graft surgery, chronic renal failure, and complex coronary lesions, such as previous history of stent failures. This population’s characteristics are likely responsible for the high rates of observed repeat TLR and MACE. As previously reported, regardless of the treatment modality used, the rate of cardiovascular events and TLR in such a complex population is expected to be high.13–15

Different mechanisms have been enunciated as possible etiologies for recurrent DES failure. On one hand, mechanical factors, such as stent underexpansion or strut fracture, have
been linked to stent failure.\textsuperscript{16–19} Given the relatively high frequency of intravascular ultrasound performed in this study at the initial procedure and at the time of DES failure treatment, it seems unlikely that mechanical factors play a significant role. On the other hand, biological-related factors, such as antiproliferative drug resistance, insufficient drug dose, or hypersensitive reactions related to the polymer have been also implicated.\textsuperscript{20,21} Biological effects of any locally delivered drug are influenced by local transport forces, which are related to the properties of the target tissue.\textsuperscript{22} In the setting of multiple treatment failures, it is reasonable to set forth that a large amount of neointimal hyperplastic tissue and/or multiple stent layers might alter the drug diffusion rate toward the tunica media, minimizing the drug effect. In our data, regardless of the treatment choice or the lesion characteristic, a high rate of ISR recurrence was observed, and none of the traditional known risk factors for ISR were associated with its occurrence.

The appropriate treatment of restenotic lesions after DES failure remains under debate. Although the pivotal trials SISR\textsuperscript{23} and TAXUS-IV\textsuperscript{24} have proven superiority of DES over VBT to treat BMS ISR in terms of TLR-target vessel recalcification, safety remained similar between both treatment modalities. Currently, no trial has randomly compared repeat DES with VBT to treat DES ISR. No significant outcome differences were noted in our series among the therapeutic options, the described groups are different, and, therefore, comparisons must be carefully interpreted. In particular, patients treated with VBT in this series represented a more intricate subgroup of patients presenting more commonly with more complex lesions, more SAPHENOUS VEIN GRAFTS lesions, more diffuse/proliferative ISR patterns, and higher prevalence of prior stent and VBT failure. Interestingly, this subgroup of patients failed faster than the rest of the population after the initial procedure, suggesting that patients selected for VBT had a more aggressive neointimal proliferative response to the initially placed DES. In addition, the rate of the observed definite/probable stent thrombosis in patients treated with VBT was no different than the rest of the population. Our results and prior reported data suggest coronary brachytherapy as a reasonable, safe, and effective method to treat DES ISR, but it does not seem to be superior to other alternatives.\textsuperscript{25,26} We speculate that VBT may play a particular role in treating complex recurrent lesions when previous treatments have failed, and a different therapeutic option to prevent neointimal proliferation is theoretically desired.

Balloon angioplasty is a simple approach to treat focal ISR and is particularly useful when mechanical factors are involved (ie, stent underexpansion); however, it has been associated with a higher recurrence rate for diffuse ISR.\textsuperscript{27} Nevertheless, the 1-year results of the presented data from the CRISTAL study, which randomly compared SES with balloon angioplasty to treat DES ISR, did not demonstrate clinical superiority of SES over c-PCI, with marginal angiographic benefit in favor of the re-DES strategy.\textsuperscript{28} Similarly,
our series suggests that either repeat or switch re-DES strategies are associated with comparable efficacy but are not superior to c-PCI. Restenting with either the same or a different DES type has reported high rates of recurrent failure at 1-year follow-up, irrespective of the strategy used.\(^{13,15}\) The published results from the randomized ISAR-DESIRE 2 study demonstrated that the implantation of a second DES is feasible and safe to treat SES restenosis.\(^{12}\) Finally, the promising initial results reported with the use of drug-eluting balloons to treat BMS ISR\(^{29}\) has not been tested yet in failed DES. Therefore, further research is required to evaluate the role of drug-eluting balloons in DES ISR.

**Limitations**

The present study carries with it several limitations. This is a retrospective, uncontrolled study, which may lead to potential confounder bias, particularly a selection bias imposed by patient complexity and by therapy modality chosen by the operator. It lacks systemic angiographic follow-up and had incomplete clinical follow-up limited to 1 year, which could potentially underestimate the true event rates. Furthermore, it was difficult to track the prior attempts to recanalize the ISR, and it seems that patients who were referred for VBT had higher prior recurrences and more diffuse patterns of ISR. We recognize that our study might be underpowered to detect risk factors associated with repeat TLR and outcome difference among the compared therapeutic strategies used to treat DES ISR; nevertheless, this study represents the largest published clinical series of DES ISR. In addition, intravascular ultrasound variables were not retrospectively available to be included in this analysis.

**Conclusion**

Recurrence of ISR after DES treatment failure is neither infrequent nor benign, and optimal therapy remains unclear and challenging. Given the absence of conventional risk factors for ISR in this population, further research is required to elucidate both the correlates involved in DES ISR and the optimal treatment for this condition.

**Disclosures**

None.

**References**


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