**EDITORIAL COMMENT**

# Coronary Brachytherapy 2016*

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Restenosis is a significant limitation of catheter-based treatment of coronary artery disease. Early in the development of balloon angioplasty, restenosis was quite common, occurring in 30% to 40% of patients (1). Following successful angioplasty, patients who had become symptom-free developed the same symptoms they had experienced prior to the intervention. Repeat angiography demonstrated a recurrence of narrowing at the site of the treated stenosis, sometimes more severe than the original lesion. Initially, treatment options were advancement of medical therapy alone, coronary bypass graft surgery, and repeated angioplasty. Most often at least 1 repeat angioplasty was attempted, although the likelihood of subsequent lesion recurrence was substantially higher than for those having a first angioplasty. Accordingly, restenosis was eventually termed the Achilles' heel of angioplasty and was a significant shortcoming of this approach to coronary revascularization.

Many efforts were explored to avoid restenosis. A host of pharmacological agents were studied in experimental and clinical settings. None were successful. Mechanical devices were also considered. Ablative devices, both mechanical and laser based, were investigated, with the thought that if better angioplasty were performed (i.e., less plaque remained following treatment), there would be more lumen to accommodate the healing that followed angioplasty. Clinical trials, however, failed to demonstrated success of these approaches.

In 1987, a stainless steel stent was developed that could be placed into a coronary artery (2). The initial use of these stents was primarily for treating abrupt coronary occlusion, which occasionally followed balloon angioplasty. Stents provided a mechanical scaffold for maintaining patency and restoration of coronary flow. Unfortunately, stents carried the risk for thrombosis, particularly if not maximally expanded. Over time, proper techniques for stent deployment and refinement of stent characteristics were identified that enhanced their safety and ease of use.

Eventually stents were considered an option for reducing restenosis. Effectiveness was demonstrated in the STRESS (Stent Restenosis Study) trial (3). In that randomized study of only 410 patients, rates of restenosis at 6 months were 31.6% in stented patients and 42.1% among those treated by balloon angioplasty (4). These findings were confirmed a European study (4).

Further reduction in restenosis followed the introduction of the drug-eluting stent (DES). In RAVEL (Randomized Study With the sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions), 238 patients undergoing angioplasty were randomly assigned to a bare-metal stent (BMS) or similar stent but coated with the antiproliferative agent sirolimus (5). At 6 months, there was less late luminal loss and no lesion >50% within the sirolimus group. In contrast, angiographic restenosis was evident in 26.6% of BMS patients, and 22.9% underwent repeat intervention. These findings were confirmed in a larger trial in the United States (6).

DES have been further refined with the addition of newer antiproliferative agents, thinner struts, less polymer, and improved designs. Rates of clinical restenosis, manifested as target lesion revascularization, appear to be in the range of 5% to 10% (7).

Despite all of the advances in DES technology, in-stent restenosis (ISR) still exists and for individual patients can be extremely incapacitating. Although initial episodes may be attributable to an under-deployed stent, data now suggest that treatment

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should consist of stent reexpansion and the implantation of an additional DES. Intravascular imaging can be helpful in determining deployed stent size.

Several types of DES have been used for DES ISR. One study suggested that everolimus-eluting stents are superior to others (8). Furthermore, catheters with balloons that are coated with the drug paclitaxel have also demonstrated effectiveness for DES restenosis. A comparison of these treatments approaches suggests superiority of drug-coated balloons, cutting or noncutting, and DES over balloon angioplasty alone (9).

Few data are available, however, regarding the optimal treatment of recurrent ISR (i.e., restenosis that follows second DES or drug-eluting balloon), and it is in this setting in which brachytherapy may be especially useful. The basis for brachytherapy is the understanding that one component of restenosis is neointimal hyperplasia, a natural response to the tissue injury caused by balloon expansion within an arterial segment. Cellular proliferation fills in voids in the media and can extend into the arterial lumen. The concept of intracoronary brachytherapy is that locally applied radiation can attenuate or eliminate neo-proliferation. Several trials, using either beta or gamma radiation sources, have demonstrated the effectiveness of brachytherapy in reducing the incidence of ISR. Brachytherapy was developed in the era of BMS; because of ease of use and in 1 trial more effectiveness, DES have supplanted the routine use of brachytherapy (10,11).

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In situations in which repeat DES or drug-eluting balloon implantation has failed, brachytherapy may be an option. In this issue of *JACC: Cardiovascular Interventions*, Negi et al. (12) present their experience with the use of brachytherapy for patients with recurrent ISR. They report their experience in 186 patients, nearly all of whom had 3 more prior episodes of ISR, the exact group of patients for whom optimal treatment is unknown. These patients had multiple risk factors for and presence of advanced coronary disease. Of interest, the majority of patients had balloon angioplasty only as the remedy for DES ISR. Repeat DES use was rare, and no patient was treated with a drug-eluting balloon, not approved for coronary use in the United States.

Brachytherapy in this report was limited to a strontium-90/yttrium source (beta radiation) and was performed following standard balloon angioplasty or a cutting balloon. An additional stent was "rarely used," which is helpful for us to understand the impact of brachytherapy alone. Follow-up extended

to 3 years for each patient. Subsequent target lesion revascularization by percutaneous coronary intervention or surgery was 22.2%, whereas target vessel revascularization was 33.3%, suggesting that some revascularization was performed for lesions other than those treated by brachytherapy. Early death was quite rare, supporting the short-term safety of the treatment, while death at 3 years was in the range of what might be expected for the types of patients included in the study. The investigators conclude that acceptable patency rates were seen at 1 year and that brachytherapy should be considered for DES ISR.

Several features of this report are noteworthy.

Brachytherapy is an uncommon practice, as this treatment is only rarely offered at hospitals in the United States. Nevertheless, for the types of patients treated in this study, the treatment offers substantial value.

The findings of this report must be considered in the context of the standard treatment options available for patients at the time they received brachytherapy. For example, this patient cohort dates back to 2004. Although each patient had DES restenosis, DES use then was limited to stents that are now considered inferior. The implantation of a second DES, recommended therapy now, was rarely performed in this trial. These findings are relevant in determining the likelihood of needing a treatment such as brachytherapy at the present time when rates of DES restenosis are considerably lower.

Patients in this study did not receive stents at the time of brachytherapy. From a scientific perspective, this strategy allows us to determine the safety and effectiveness of brachytherapy alone. The results of brachytherapy were not perfect, however, in that by 1 year, 1 of 6 patients required target lesion revascularization. Whether implanting a DES at the time of brachytherapy might further reduce the chance of lesion recurrence or is even a safe strategy is unknown.

How does the strategy of ISR therapy for patients included in this study compare with guideline recommendations? Current U.S. guidelines have relatively little to say in this regard. They state that patients with restenosis, initially treated with balloon angioplasty alone, should receive a stent, BMS or DES. Those with BMS restenosis should receive DES. For patients with DES restenosis, several options are listed, including balloon angioplasty alone, a BMS, or a DES. Interestingly, there is no mention of brachytherapy.

Although most patients in the study who received brachytherapy did not have recurrent treatment for

restenosis, we do not know if restenosis developed. There was no protocol-driven follow-up angiography. Thus, we do not know the real restenosis rate following brachytherapy. In some patients, brachytherapy failed. One wonders if the type of brachytherapy administered (beta vs. gamma) or the doses used were optimal. Finally, little is known about the potential for repeated brachytherapy.

One limitation of brachytherapy is the need for multiple, specialized personnel to perform the procedure and their availability, especially on short notice. Brachytherapy requires the presence of a radiation oncologist and at times a radiation physicist in addition to an interventional cardiologist. Assembling this team in one place and at one time may be difficult. Patients with ISR frequently present with unstable, acute coronary syndromes that may require prompt revascularization. Accordingly, percutaneous coronary intervention may be performed when brachytherapy is not readily available. One option for this scenario is a staged approach. Percutaneous coronary intervention is completed first, and then in a short time, in a separate setting, brachytherapy can be performed.

Brachytherapy is a treatment that should not disappear. Although there are fewer patients who may need brachytherapy for DES ISR, they will always exist. Given the findings from this study, this treatment can be highly effective. Physicians should be aware of the value of brachytherapy and be prepared to offer it to patients in need.

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