Clinical Policy Title: Brachytherapy of coronary arteries

Clinical Policy Number: CCP.1193

Effective Date: January 1, 2016
Initial Review Date: September 16, 2015
Most Recent Review Date: October 2, 2018
Next Review Date: October 2019

Related policies:

CCP.1117 Brachytherapy for localized prostate cancer
CCP.1183 Brachytherapy for cancers other than prostate

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of brachytherapy for coronary arteries intervention to be clinically proven and, therefore, medically necessary when the following criteria are met:

- When used as an adjunct to percutaneous coronary intervention for treatment of in-stent restenosis in a native coronary artery bare-metal stent.
- To treat in-stent restenosis in grafted coronary vessels — that is, saphenous vein grafts (Kushner, 2009; King, 2008).

Limitations:

All other uses of brachytherapy for coronary arteries intervention, including the use of drug-eluting stents, are considered experimental/investigational.

Alternative covered services:

Repeat percutaneous coronary intervention without brachytherapy.
Background

Intracoronary brachytherapy involves inserting a special catheter to radiate a local area in an artery. The procedure can be used to reduce recurrence of arterial obstruction or narrowing after stent placement (restenosis) during most angioplasty procedures. Restenosis, defined as a decrease in the luminal diameter by more than 50 percent in the stented area of the vessel (Hamid, 2007), occurs in 10 percent of patients with the relatively new drug-eluting stents, a large historical decline from earlier experience, first with balloon angioplasty, and then with bare metal stents (Byrne, 2015; Dangas, 2010).

The radiation used in brachytherapy inhibits the growth of certain cells that cause restenosis. Various radioactive isotopes, such as iridium-192 and strontium-90, are used in brachytherapy. However, the procedure never achieved widespread use due to logistical issues (Kolh, 2014). After two randomized trials found brachytherapy reduced restenosis, but no more effectively than paclitaxel and sirolimus drug-eluting stents, brachytherapy use sharply decreased in the United States (Stone, 2006).

Even with the emergence of drug-eluting stents that have reduced restenosis, clinicians recognize a need to continue to improve prevention of by better treating restenosis, using brachytherapy and other methods. Numerous reports in the professional medical literature continue to provide information on brachytherapy's experience in preventing restenosis, compared to other methods. Brachytherapy may be an option in situations when repeat drug-eluting stents or drug-eluting balloon implants have failed in cases of restenosis. Although brachytherapy is not often used in the U.S., the treatment may be applicable for patients with stent procedures performed years ago, when stents used are now considered inferior, or prior to when stents were used. Other brachytherapy-related issues include understanding if the radiation type used in brachytherapy (beta or gamma) provided different results, or whether results varied by dose (Williams, 2016).

Searches

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on August 17, 2018. Search terms were: “vascular brachytherapy,” “brachytherapy coronary arteries,” “drug-eluting stents,” “percutaneous transluminal coronary angioplasty,” and “in-stent restenosis.”

We included:

- Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic
reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A guideline update published by the American College of Cardiology, American Heart Association, and the Society for Cardiovascular Angiography and Interventions, states that vascular brachytherapy is a successful treatment for restenosis occurring within stents, while other adjunctive therapies, such as the cutting balloon, rotary ablation, excimer laser, and re-stenting show mixed results (Smith, 2006).

The 2006 guideline states that brachytherapy is a safe and effective treatment for in-stent restenosis (Class IIa recommendation). A Class IIa recommendation indicates that there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment, but that the weight of evidence is in favor of usefulness/efficacy. No changes to this recommendation occurred in focused updates to the percutaneous coronary intervention guideline (Kushner, 2009; King, 2008).

The American College of Cardiology Foundation percutaneous coronary intervention guidelines (Levine, 2016; Levine, 2011) do not include recommendations for brachytherapy. The guidelines reference studies demonstrating the superiority of drug-eluting stents over brachytherapy.

Guidelines on Myocardial Revascularization developed by The Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, state that intracoronary brachytherapy is currently of very limited use (Kolh, 2014; Windecker, 2014): restenosis rates have declined and in-stent restenosis after bare metal stents are typically treated by drug-eluting stents or coronary artery bypass graft.

Prior to the widespread use of drug-eluting stents, in-stent restenosis following percutaneous coronary intervention was a significant clinical problem, frequently resulting in the need for repeat revascularization procedures. Intracoronary brachytherapy was shown to be an effective treatment for in-stent restenosis of native coronary arteries or saphenous vein grafts.

In recent years, brachytherapy procedures have decreased in frequency and drug-eluting stents emerged as the treatment of choice, in the majority of cases. However, brachytherapy may still play a role in the treatment of in-stent restenosis in selected members. A recent article citing 186 patients concluded that intravascular brachytherapy is a safe treatment for recurrent drug-eluting stents in-stent restenosis, based on a one percent adverse event rate and no cases of acute thrombosis, with a low recurrence rate at 12 months (Negi, 2016). A randomized controlled trial compared intracoronary
brachytherapy (n=134) with a control group (n=37), defined as persons with at least two episodes of in-stent restenosis. Procedural complication rates were low in the control and brachytherapy groups (0.0 versus 4.5 percent, $P = .19$). Post procedural event rates were less than five percent in both groups. Readmission rate at 30 days was insignificantly lower in the brachytherapy group and 3.7 versus 5.4 percent in the control group ($P = .649$). Results lead authors to conclude that brachytherapy is safe to use in a high-risk population (Ohri, 2015).

Early studies appeared to confirm the superior performance of brachytherapy over other mechanical approaches (Alfonso, 2015). A meta-analysis of 14 studies (n=3,103) compared outcomes for drug-eluting stents and vascular brachytherapy coronary artery in patients requiring in-stent restenosis. Neither treatment affected rates of mortality or myocardial infarction. Brachytherapy was associated with greater reductions than drug-eluting stents in revascularization (Risk Ratio = 0.59 versus 0.51), major adverse cardiac events (0.58 versus 0.55), binary restenosis (0.51 versus 0.57), and late loss (-0.73 mm) after intermediate follow-up, and major cardiac events (0.72) at long-term follow up (Oliver, 2008).

A meta-analysis of 12 studies (n=1942) compared outcomes of restenosis for drug-eluting stents and intracoronary brachytherapy. At midterm follow-up, use of drug-eluting stents was significantly more effective in reducing target-vessel revascularization ($P = .009$) and binary restenosis ($P < .00001$). No significant differences were observed between the two groups in cardiac death, myocardial infarction, and late stent thrombosis. After long-term follow-up, statistical significance has been found between the groups in target-vessel revascularization ($P = .005$), with no significant differences in cardiac death and myocardial infarction (Lu, 2011).

Over time, outcomes for restenosis using brachytherapy were identified in many studies as equally effective or less effective (especially drug-eluting stents) than other treatments. A systematic review/meta-analysis of six articles (n=687) analyzed outcomes for percutaneous femoropopliteal angioplasty with versus without brachytherapy. After 12 months, the brachytherapy group had a significantly lower restenosis rate ($P = .008$), but rate reductions were equal at 24 months. Significantly more new lesions elsewhere in the treated artery were observed in the brachytherapy group ($P = .002$). Authors were not able to recommend brachytherapy for routine use (Mitchell, 2012).

A meta-analysis of 40 randomized controlled trials, analyzed various techniques for infrainguinal peripheral arterial occlusive disease. After six months, self-expanding stents showed a significantly reduced restenosis rate (Risk Ratio = 0.49), as did drug-coated balloons (0.40), and at 12 months for brachytherapy (0.63). Stent-grafts significantly reduced restenosis compared with balloon angioplasty, as did drug-eluting stents versus bare-metal stents. Re-intervention rates were significantly less for drug-coated balloons (versus angioplasty) at six and 24 months (0.24, 0.27) of follow-up. Conclusions state self-expanding stents, drug-eluting stents and drug-coated balloons are superior (Simpson, 2013).

A Cochrane review of eight trials (n=1090) assessed efficacy and complications of intravascular brachytherapy. Studies compared two groups which included percutaneous transluminal angioplasty with or without stenting; one group had brachytherapy in addition, the other did not. Patients were
followed from six months to five years. The brachytherapy group had a significantly greater cumulative patency at 24 months ($P = .002$), and a significantly lower restenosis at six months ($P = .004$), 12 months ($P = .0002$) and 24 months ($P = .007$). Need for target lesion revascularization was significantly lower for brachytherapy ($P = .04$) six months after the interventions. Other measures found superior outcomes for the brachytherapy group, or no consistent difference between the two groups according to the length of follow-up. Authors conclude evidence for using brachytherapy as an adjunct to angioplasty, as reporting of main outcomes was inconsistent (Andras, 2014).

A meta-analysis of 28 trials (n=6662), 17 of which were randomized controlled trials, compared outcomes of drug-eluting stent and conventional treatments (including brachytherapy) for restenosis. Drug-eluting stents had superior outcomes in target lesion revascularization ($P < .00001$), major adverse cardiac events ($P = .001$), Late Lumen Loss ($P < .00001$), stenosis of lumen diameter ($P < .00001$), and restenosis ($P < .00001$). No significant outcomes were documented for cardiac death ($P = .25$), myocardial infarction ($P = 1.00$), and late thrombosis ($P = .18$) (Sun, 2014).

A meta-analysis of 31 studies covering 8157 patient-years follow up measured target vessel vascularization for balloon angioplasty, compared to other methods. It determined that balloon angioplasty is not significantly different from cutting balloon (Hazard Ratio 0.73), excimer laser (0.89), rotational atherectomy (0.96), and vascular brachytherapy (0.60). Balloon angioplasty was inferior to all drug-eluting treatments, leading authors to conclude drug-eluting stents, particularly everolimus-eluting stent, or paclitaxel-eluting cutting balloon and paclitaxel-eluting balloon are the treatment of choice for in-stent restenosis (Sethi, 2015).

A meta-analysis comparing drug-eluting stents with vascular brachytherapy covered a 2 – 5 year follow-up of five studies (three randomized controlled) with 1375 patients. There was no significant difference between the two groups for myocardial infarction ($P = .49$), stent thrombosis ($P = .86$), cardiovascular mortality ($P = .35$), and overall mortality ($P = .71$). However, target lesion and target vessel revascularization rates were elevated ($P < .001$) and $P = .05$) in the brachytherapy group (Benjo, 2016).

A meta-analysis of 31 studies found that brachytherapy had similar target vessel revascularization rates to balloon angioplasty, cutting balloon, excimer laser, and rotational atherectomy, but had higher rates than paclitaxel-eluting cutting balloon, everolimus-eluting stent, and paclitaxel-eluting balloon in patients with at least two restenosis treatments (Sethi, 2015).

A meta-analysis of 24 studies (n=4880) assessed performance of seven treatments for in-stent restenosis, including brachytherapy, which was included in three of the studies (n=909). Compared with plain balloons, the other six treatments (including brachytherapy) had a reduced risk of target lesion revascularization and major adverse cardiac events, and with reduced late lumen loss. Drug coated balloon and drug-eluting stents had the best outcomes (Giacoppo, 2015).

A meta-analysis of 27 studies (n=5923) of patients with drug-eluting stents were followed for 6 – 60 months after restenosis. Reduction in diameter stenosis with everolimus-eluting stents was greater
than drug-coated balloons (-9.0 percent), sirolimus-eluting stents (-9.4 percent), paclitaxel-eluting stents (-10.2 percent), vascular brachytherapy (-19.2 percent), bare metal stents (-23.4 percent), balloon angioplasty (24.2 percent), and rotablation (-31.8 percent) (Siontis, 2015).

A narrative review (Alfonso, 2015) reported that many randomized clinical trials have compared different therapeutic strategies in patients with coronary stent stenosis and restenosis. Among the interventions described for this condition are balloon angioplasty, ablative devices, brachytherapy, drug-eluting stents and drug-coated balloons. Contemporary guidelines suggest that both drug-eluting stents and drug coated balloons are effective therapy and safe for patients experiencing stent stenosis, but the treatment of choice for this condition is not conclusively established as of yet.

**Policy updates:**

A total of two guidelines/other and 11 peer-reviewed references were added to, and four peer-reviewed references removed from this policy in August 2018.

**Summary of clinical evidence:**

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<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Alfonso (2015)</td>
<td><strong>Key points:</strong></td>
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| Network meta-analyses on in-stent restenosis treatment: dealing with complexity to clarify efficacy and safety | • Many randomized clinical trials have compared different therapeutic strategies in patients with coronary stent stenosis and restenosis.  
• Among the interventions described for this condition are balloon angioplasty, ablative devices, brachytherapy, drug-eluting stents and drug-coated balloons.  
• Contemporary guidelines suggest that both are effective therapy and safe for patients experiencing in-stent restenosis, but the treatment of choice for this condition is not conclusively established as of yet. |
| Sethi (2015)      | **Key points:**                   |
| Comparison of re-stenosis interventions — target vessel revascularization rates | • Meta-analysis of 31 studies (8157 patient years), patients with at least two treatments for in-stent restenosis.  
• Brachytherapy has similar rate to balloon angioplasty, cutting balloon, excimer laser, and rotational atherectomy.  
• Brachytherapy has higher rates than paclitaxel-eluting balloon, paclitaxel-eluting stent, and sirolimus-eluting stent. |
| Siontis (2015)    | **Key points:**                   |
| Comparison of re-stenosis interventions – percent diameter stenosis at angiographic follow-up | • Meta-analysis of 27 studies, n=5923, follow-up 6 – 60 months.  
• Most effective treatment was everolimus-eluting stents; brachytherapy 19.2 percent (%) less.  
• Brachytherapy not as effective as drug coated balloons (-9.0%), sirolimus eluting stents (-9.4%), or paclitaxel-eluting stents (-10.2%).  
• Brachytherapy more effective than bare metal stents (-24.2%) and rotablation (-31.8%), |
| Andras (2014)     | **Key points:**                   |
| Cochrane review of eight trials (n=1090). |
Efficacy and complications for coronary brachytherapy

- Groups both included percutaneous transluminal angioplasty with or without stenting; one group had brachytherapy, one did not.
- Patients followed six months to five years.
- The brachytherapy group had a significantly greater cumulative patency at 24 months ($P = .002$), and a significantly lower restenosis at six months ($P = .004$), 12 months ($P = .0002$) and 24 months ($P = .007$).
- Need for target lesion revascularization was significantly lower for brachytherapy ($P = .04$) six months after the interventions.
- Evidence for using brachytherapy as an adjunct to angioplasty insufficient to support, mostly due to inconsistent reporting of main outcomes.

Oliver (2008)

Outcomes of brachytherapy and drug-eluting stents for in-stent restenosis

Key points:

- Meta-analysis of 14 studies/3103 patients.
- Neither treatment had any effect on mortality or rate of myocardial infarction.
- At intermediate follow-up, brachytherapy reduced the rate of revascularization, binary restenosis, and late loss vs. balloon angioplasty and selective bare metal stents alone.

References

Professional society guidelines/other:


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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