Prior Authorization Review Panel
MCO Policy Submission

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Plan: Keystone First Community HealthChoices	**Submission Date**: October 26, 2021
Policy Number: CCP.1193	**Effective Date:** 1/2016 **Revision Date:** October 5, 2021
Policy Name: Brachytherapy of coronary arteries	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☑ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

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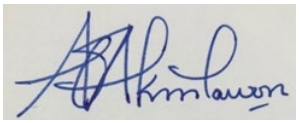
Name of Authorized Individual (Please type or print): Akintayo Akinlawon, MD	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Brachytherapy of coronary arteries

Clinical Policy ID: CCP.1193

Recent review date: 10/2021

Next review date: 2/2023

Policy contains: Brachytherapy of coronary arteries, drug-eluting stents, percutaneous coronary intervention, restenosis.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' 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 Keystone First Community HealthChoices 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. Keystone First Community HealthChoices' 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. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Brachytherapy for coronary arteries intervention is 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 (Smith, 2006).
- When drug-eluting stents or drug-eluting balloons have repeatedly failed (Williams, 2016).

Limitations

No limitations were identified during the writing of this policy.

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. Re-stenosis, defined as a decrease in the luminal diameter by more than 50% in the stented area of the vessel (Hamid, 2007), occurs in 10% 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; Ohri, 2015), but has become more popular in recent years due to persistently high rates of re-stenosis (Khattab, 2021).

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 applicable for patients with stent procedures performed years ago, stents that 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).

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, 2011; Levine, 2016) do not include recommendations for brachytherapy. The guidelines reference studies demonstrating the superiority of drug-eluting stents over brachytherapy. The 2016 American Heart Association/American College of Cardiology 2016 guideline on lower extremity peripheral artery disease also does not mention brachytherapy (Gerhard-Herman, 2017).

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 pattern of brachytherapy associated with improved or effective outcomes in the short term (12 months follow-up or less), but not after 12 months, is apparent in the professional literature.

SHORT-TERM (12 MONTHS OR LESS) OUTCOMES – BRACHYTHERAPY INSIGINFICENTLY DIFFERENT

- An article of 186 patients concluded that intravascular brachytherapy is a safe treatment for recurrent drug-eluting stents in-stent restenosis, based on a 1% 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%, *P* = .19). Post procedural event rates were less than 5% in both groups. Readmission rate at 30 days was insignificantly lower in the brachytherapy group and 3.7% versus 5.4% in the control group (*P* .65) (Ohri, 2015).

LONG-TERM (OVER 12 MONTHS) OUTCOMES – SIGNIFICANTLY BETTER FOR BRACHYTHERAPY

- 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), lower binary restenosis (0.51 versus 0.57), and late loss (-0.73 mm) after intermediate (6 – 24 months) follow-up, and major cardiac events (0.72) at long-term (over three years) follow-up (Oliver, 2008).
- A Cochrane review of eight trials (n = 1,090) 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 (Andras, 2014).
- A randomized trial of patients who underwent percutaneous coronary intervention for recurrent drug-eluting stents in-stent restenosis compared 197 patients who also underwent brachytherapy and 131 who did not. A composite rate of target lesion revascularization, myocardial infarction, and all-cause mortality after 12 months was significantly lower in patients undergoing brachytherapy (13.2% versus 28.2%, *P* = .01) (Varghese, 2018).
- A systematic review/meta-analysis of five studies (n = 917) of patients with recurrent (at least two episodes) in-stent restenosis tracked patients for an average of months. Target vessel revascularization occurred in 29.2% of patients, while myocardial infarction and all-cause deaths occurred in 4.3% and 7.3%, respectively. Authors conclude that Intravascular brachytherapy can be used to treat recurrent in-stent restenosis (Megaly, 2021).

LONG-TERM (OVER 12 MONTHS) OUTCOMES – SIMILAR FOR BRACHYTHERAPY

- A meta-analysis of 12 studies (n = 1,942) 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).
- A meta-analysis of 31 studies covering 8,157 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 randomized controlled trial compared safety and efficacy of sirolimus-eluting stent (n = 259) and vascular brachytherapy (n = 125) for bare metal stent in-stent restenosis five years after treatment. No significant differences were observed for target lesion revascularization (*P* = .179), target vessel failure (*P* = .568), major adverse cardiac event (*P* = .648), survival free from target lesion revascularization (*P* = .08), target vessel failure (*P* = .349), or definite/probable stent thrombosis (*P* = .182) (Alli, 2012).
- A 17-year follow-up study of 133 patients who received radioactive stents and 301 patients treated with intracoronary radiation brachytherapy adjunctive to percutaneous coronary intervention, matched with 266 and 602 controls (routine percutaneous coronary intervention). No between-group differences were observed for major adverse cardiac events were (hazard ratios of 1.55 and 1.41), or all-cause mortality (0.92 and 0.95) (Radhoe, 2020).

LONG TERM (OVER 12 MONTHS) OUTCOMES – WORSE FOR BRACHYTHERAPY

- 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 study of 680 patients treated with intracoronary brachytherapy for coronary in-stent restenosis from 1998-2005 reviewed outcomes 10 years after the procedure. The patient population was a high-risk one, as 70% were smokers, 94% had hyperlipidemia, and 77% had multivessel disease. After 10 years, elevated rates were observed for all deaths (25%), myocardial infarction (22.4%), and target vessel revascularization (48%), indicating steady declines in outcomes starting five years after the procedure (Nakahama, 2018).
- 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 meta-analysis of 28 trials (n = 6,662), 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* < 0.0001), 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 comparing drug-eluting stents with vascular brachytherapy covered a 2 – 5 year follow-up of five studies (three randomized controlled) with 1,375 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 with 8,157 patient-years of follow-up 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 = 4,880) 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 = 5,923) 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%), sirolimus-eluting stents (-9.4%), paclitaxel-eluting stents (-10.2%), vascular brachytherapy (-19.2%), bare metal stents (-23.4%), balloon angioplasty (-24.2%), and rotablation (-31.8%) (Siontis, 2015).

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On July 1, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “vascular brachytherapy,” “intravascular brachytherapy,” “intracoronary brachytherapy,” “brachytherapy coronary arteries,” “drug-eluting stents,” “percutaneous transluminal coronary angioplasty,” and “in-stent restenosis.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

9/2015: initial review date and clinical policy effective date: 1/2016

9/2016: Policy references updated.

9/2017: Policy references updated.

9/2018: Policy references updated.

10/2019: Policy references updated. Policy ID changed to CCP.1193.

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