AmeriHealth Caritas Ohio

Renal denervation

Clinical Policy ID: CCP.1283

Recent review date: 1/2023

Next review date: 5/2024

Policy contains: Renal sympathetic ablation; renal denervation; treatment-resistant hypertension.

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

Coverage policy

Renal denervation for treatment resistant hypertension is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Medically prescribed antihypertensive therapy.
- Standard medical treatment of underlying disorders.

Background

Hypertension is largely viewed as a major modifiable risk factor associated with multiple mortality. It effects the cardiovascular and renal systems as well as contributing to complications of other diseases (Sarathy, 2021)..

The sympathetic nervous system is activated in stressful or emergency situations and often referred to as the fight-or-flight response. The kidneys play a major role in the response by increasing secretion of renin, to activate a chemical chain reaction that changes the hemodynamic system of the body and provide the protective physiological response needed for a person to react. The systemic effects include arterial blood vessel constriction, increased heart rate, dilated pupils and elevation of blood pressure (Sarathy, 2021). Sympathetic hyperactivity mediated resistant hypertension has been associated with multiple conditions, including but not

limited to stroke, obstructive sleep apnea, metabolic syndrome, myocardial hypertrophy and heart failure, and cardiac dysrhythmias (Hou, 2018; Sarathy, 2021; Bohm, 2014). Renal injury or hypoxia can further result in systemic and renal sympathetic activity (Hou, 2018).

Renal denervation, also referred to as endovascular renal sympathetic ablation, is a minimally invasive percutaneous procedure that uses a radiofrequency catheter inserted through the femoral artery to selectively engage the sympathetic nerve fibers surrounding the renal artery. The desired result is to interrupt the influence of the sympathetic reflexes on the kidney and systemic hemodynamics and therefore provide a simple solution to the complex issue of hypertension (Persu, 2020). The procedure usually takes from 45 to 60 minutes when a single catheter is used, or less time with a multi-electrode or balloon catheter. Analgesia and sedation are required (Böhm, 2014).

Renal denervation has been proposed as a non-pharmacologic treatment for treatment-resistant hypertension, which is common in patients with pre-existing comorbid atherothrombotic disease and obesity, and for other sympathetically driven conditions (Böhm, 2014). Renal denervation devices are available under investigational device exemption use only; none has received U.S. Food and Drug Administration (2020a, 2020b) approval for commercial use.

Findings

We included four systematic review/meta-analyses, three professional guidelines, and one cost-effectiveness analysis for this policy. Two systematic reviews/meta-analyses (Shafi, 2016; Fadl Elmula, 2015), the cost-effectiveness analysis (Geisler, 2012), and all three guidance documents (Lobo, 2015; Schlaich, 2013; National Institute for Health and Care Excellence, 2012) evaluated renal denervation for treatment-resistant hypertension. Two systematic reviews examined the role of renal denervation for treatment of Type 2 diabetes mellitus and obstructive sleep apnea (Pan, 2015; Shantha, 2015).

There is insufficient evidence to support the clinical use of catheter-based renal denervation for any indication. The evidence comprises observational data from multiple small case series and limited comparative clinical trials using the SYMPLICITY™ Renal Denervation System (Medtronic, Inc, Santa Rosa, California). The SYMPLICITY trials enrolled patients with severe treatment-resistant hypertension who were receiving a stable antihypertensive regimen of at least three drugs including a diuretic, and had adequate renal function:

- SYMPLICITY HTN-1 was the first in-human, proof-of-concept and safety study of 45 participants (Krum, 2014).
- SYMPLICITY HTN-2 was a multi-site, randomized controlled trial of 106 participants (Esler, 2014).
- SYMPLICITY HTN-3 was a multi-site, randomized controlled trial of 535 participants with sham controls (Bakris, 2014; Bhatt, 2014).

The evidence from these trials suggests that renal denervation in patients with treatment-resistant hypertension is safe, may be cost-effective, and lowers systolic blood pressure in the short term and medium term, but the results are highly variable. Long-term safety data beyond three years follow-up are lacking. Reduction in systolic blood pressure after renal denervation was greater in observational studies than randomized studies, and in studies that used office blood pressure measurement rather than ambulatory blood pressure measurement as an efficacy endpoint. Of note, while SYMPLICITY HTN-3, the most rigorously designed trial, met its primary safety endpoint with a major adverse event rate of only 1.4%, it failed to meet its primary and secondary efficacy endpoints; no statistically significant difference was shown in blood pressure measurement between the renal denervation treatment and sham control arms.

Methodological and technical issues were reexamined. The failure was thought to be due in part to something going wrong with the development of the renal denervation device and/or the targeted fibers that were impacted.

It was thought that the upper proximal area where the nerve fibers were most concentrated would be the effective to target. Then the strategy was to decrease sympathetic outflow by reducing the amount of fibers associated in modulating blood pressure, with the remaining controversy surrounding the distal fibers being more effectively treated as the priority rather than the proximal ones. Finally, after a comparison of the denervation of the renal main arteries alone, a combination of treatment of additional branches resulted in more improved blood pressure. Technical improvements were made to the renal denervation catheter design to address the challenge of treating the smaller and accessory branches of the arteries but with only modest benefits at this point in time, and is equivalent to the effectiveness of one antihypertensive medication (Persu, 2020).

Results of the SYMPLICITY studies cannot be extrapolated to less severe or secondary forms of hypertension or to other catheter-based systems. Several factors may influence the findings, such as ethnicity, age, renal status, other comorbidities, and technical proficiency; efforts to address the design of future studies have been reported (Lobo, 2015; White, 2014). A growing body of evidence from non-randomized smaller studies suggests a potentially important role for renal denervation in the management of other disease states characterized by overactivation of sympathetic nerves. Further research using randomized, appropriately controlled, blinded designs, and large-scale registries is needed to identify optimal candidates for renal denervation, refine the technology, define procedural success and clinical efficacy of renal denervation in reducing blood pressure, and improve important clinical outcomes (e.g., risk of stroke, myocardial infarction, heart failure, and death).
In 2018, we added one new Cochrane review that found low- to moderate-quality evidence from randomized controlled trials did not support a clear benefit of renal denervation for treatment-resistant hypertension, and lacked long-term outcomes (Coppolino, 2017). The U.S. Food and Drug Administration has still not approved renal denervation for commercial use in the United States. No policy changes are warranted.

Mechanism responsible for hypertension needs to be explored further. It is a complex result of many systems that work in concert with one another to trigger catecholamine release. Current evidence doesn't support the importance of treating afferent fibers versus efferent fibers for control of blood pressure. Studies are demonstrating strong proof that renal denervation as a minimally invasive safe surgery is a promising non medication alternative to controlling resistant hypertension in patients, but evaluation of the long term effects are still lacking (Liang, 2021).

In 2019, we added one guideline from the American Heart Association (Carey, 2018). In the United States, renal denervation continues to be available under research protocols only. No policy changes are warranted. The policy ID was changed from CP# 09.03.04 to CCP.1283.

In 2020, we added four systematic reviews and meta-analyses confirming previous policy findings that renal denervation could safely reduce blood pressure compared with sham control, but incomplete medication adherence was common (Agasthi, 2019; Cheng, 2019; Liu, 2019; Lobo, 2019). Clinical studies to evaluate the safety and effectiveness of these devices are progressing (U.S. Food and Drug Administration, 2018). Such studies will employ randomization, sham controls, careful attention to medication adherence (on and off antihypertensive medications), careful ambulatory blood pressure measurement to evaluate efficacy, and careful attention to patient preferences to address the limitations that occurred in previous research. No policy changes are warranted.

In 2021, we added two registry studies (Lee, 2019; Rodriguez-Leor, 2020) and one longitudinal study (Naduvathumuriyil, 2020) that suggest renal denervation is safe and effective for patients with treatment-resistant hypertension with a clinically significant antihypertensive effect. In all instances, the authors called for randomized controlled trials to determine the specific context within which renal denervation should be considered a therapeutic option in antihypertensive care. To that end, Böhm (2020) published study design details of two ongoing randomized, sham-controlled clinical trials that enrolled subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED Pivotal; clinicaltrials.gov identifier NCT02439749) or

presence (SPYRAL HTN-ON MED Expansion; clinicaltrials.gov identifier NCT02439775) of antihypertensive medications. Both studies are sponsored by Medtronic, Inc. (Santa Rosa, California) with an estimated completion date of March 2023.

In 2023, the studies continue. Hypertension is a condition that is complicated by underlying medical issues which makes it a challenge. Sarathy, a member of the American society of Nephrology, International Society of Nephrology, and National Kidney Association has a special interest in this topic. Researchers have agreed that renal denervation is a safe and effective method to decrease blood pressure short term as is medication treatment: but long term studies have yet to be completed. Although the procedure has not been shown to affect kidney function, those with moderate to severe chronic kidney disease and end stage renal failure were excluded from the clinical trials. While awaiting long term effect studies, it would be important to identify specific subpopulations that would benefit form this procedure, such as those high risk for cardiovascular (Sarathy, 2021).

A new guideline by Hypertension Canada (Hiremath, 2020) does not recommend renal denervation for the routine treatment of hypertension, because the device has not been approved for use in Canada, but they recommend investigating the device in the context of controlled clinical studies. No policy changes are warranted.

References

On November 9, 2022, 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 “renal denervation,” “ablation,” “sympathectomy,” and “treatment resistant hypertension.” 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.

Agasthi P, Shipman J, Arsanjani R, et al. Renal denervation for resistant hypertension in the contemporary era: A systematic review and meta-analysis. *Sci Rep.* 2019;9(1):6200. Doi: 10.1038/s41598-019-42695-9.

Bakris GL, Townsend RR, Liu M, et al. Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. *J Am Coll Cardiol.* 2014;64(11):1071-1078. Doi: 10.1016/j.jacc.2014.05.012.

Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370(15):1393-1401. Doi: 10.1056/NEJMoa1402670.

Böhm M, Linz D, Ukena C, Esler M, Mahfoud F. Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? *Circ Res.* 2014;115(3):400-409. Doi: 10.1161/circresaha.115.302522.

Böhm M, Townsend RR, Kario K, et al. Rationale and design of two randomized sham-controlled trials of catheter-based renal denervation in subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED pivotal) and presence (SPYRAL HTN-ON MED expansion) of antihypertensive medications: A novel approach using Bayesian design. *Clin Res Cardiol.* 2020;109(3):289-302. Doi: 10.1007/s00392-020-01595-z.

Carey RM, Calhoun DA, Bakris GL, et al. (2018). "Resistant hypertension: Detection, evaluation, and management: A scientific statement from the American Heart Association." *Hypertension* 72(5):e53-e90. Doi: 10.1161/HYP.0000000000000084.

Cheng X, Zhang D, Luo S, Qin S. Effect of catheter-based renal denervation on uncontrolled hypertension: A systematic review and meta-analysis. *Mayo Clin Proc*. 2019;94(9):1695-1706. Doi: 10.1016/j.mayocp.2019.07.005.

Coppolino G, Pisano A, Rivoli L, Bolignano D. Renal denervation for resistant hypertension. *Cochrane Database Syst Rev*. 2017;2:Cd011499. Doi: 10.1002/14651858.CD011499.pub2.

Esler MD, Böhm M, Sievert H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. *Eur Heart J.* 2014;35(26):1752-1759. Doi: 10.1093/eurheartj/ehu209.

Fadl Elmula FE, Jin Y, Yang WY, et al. Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension. *Blood Press.* 2015;24(5):263-274. Doi: 10.3109/08037051.2015.1058595.

Geisler BP, Egan BM, Cohen JT, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. *J Am Coll Cardiol.* 2012;60(14):1271-1277. Doi: 10.1016/j.jacc.2012.07.029.

Hiremath S, Sapir-Pichhadze R, Nakhla M, et al. Hypertension Canada's 2020 evidence review and guidelines for the management of resistant hypertension. *Can J Cardiol.* 2020;36(5):625-634. Doi: 10.1016/j.cjca.2020.02.083.

Hou H, Zhao Y, Yu W, et al. Association of obstructive sleep apnea with hypertension: A systemic review and meta-analysis. *J Glob Health.* 2018; 8(1): 010405.Doi: 10.7189/jogh.08.010405.

Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: Final 3-year report of the Symplicity HTN-1 study. *Lancet.* 2014;383(9917):622-629. Doi: 10.1016/s0140-6736(13)62192-3.

Lee CK, Wang TD, Lee YH, et al. Efficacy and safety of renal denervation for patients with uncontrolled hypertension in Taiwan: 3-year results from the global SYMPLICITY registry-Taiwan (GSR-Taiwan). *Acta Cardiol Sin.* 2019;35(6):618-626. Doi: 10.6515/acs.201911_35(6).20190826a.

Liang B, Liang Y, Li R, Gu N. Effect of renal denervation on long-term outcomes in patients with resistant hypertension. Cardiovascular Diabetology volume 20, Article number: 117 (2021). Published June 5, 2021. Accessed October 20, 2021.

Liu LY, Lin PL, Liao FC, et al. Effect of radiofrequency-based renal denervation: The impact of unplanned medication change from a systematic review and meta-analysis. *Acta Cardiol Sin*. 2019;35(2):144-152. Doi: 10.6515/acs.201903_35(2).20181231a.

Lobo MD, Sharp ASP, Kapil V, et al. Joint U.K. societies' 2019 consensus statement on renal denervation. Heart. 2019;105(19):1456-1463. Doi: 10.1136/heartjnl-2019-315098.

Lobo MD, de Belder MA, Cleveland T, et al. Joint UK societies' 2014 consensus statement on renal denervation for resistant hypertension. *Heart.* 2015;101(1):10-16. Doi: 10.1136/heartjnl-2014-307029.

Naduvathumuriyil T, Held U, Steigmiller K, et al. Clinical benefits and safety of renal denervation in severe arterial hypertension: A long-term follow-up study. *J Clin Hypertens (Greenwich).* 2020. Doi: 10.1111/jch.14005.

National Institute for Health and Care Excellence. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. Interventional procedures guidance [IPG418], https://www.nice.org.uk/guidance/ipg418/chapter/1-guidance. Published January 2012. Accessed November 10, 2022.

Pan T, Guo JH, Teng GJ. Renal denervation: A potential novel treatment for type 2 diabetes mellitus? *Medicine (Baltimore).* 2015;94(44):e1932. Doi: 10.1097/md.0000000000001932.

Persu A, Maes F, Renkin J, Pathak A. Renal denervation in hypertensive patients: Back to anatomy? Hypertension. 2020;76:1084–1086. Originally published 9 Sep 2020. https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.120.15834. Accessed November 10, 2022.

Rodriguez-Leor O, Segura J, García Donaire JA, et al. Renal denervation for the treatment of resistant hypertension in Spain. The Flex-Spyral Registry. *Rev Esp Cardiol (Engl Ed).* 2020;73(8):615-622. Doi: 10.1016/j.rec.2019.08.001.

Sarathy H, Cohen JB. Renal denervation for the treatment of hypertension: Unnerving of underappreciated? *CJASN.* 2021;(16):1426–1428. https://doi.org/10.2215/CJN.03070221. Published September 2021. Accessed November 9, 2022.

Schlaich MP, Schmieder RE, Bakris G, et al. International expert consensus statement: Percutaneous transluminal renal denervation for the treatment of resistant hypertension. *J Am Coll Cardiol.* 2013;62(22):2031-2045. Doi: 10.1016/j.jacc.2013.08.1616.

Shafi T, Chacko M, Berger Z, et al. Renal denervation in the Medicare population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US). https://www.ncbi.nlm.nih.gov/books/NBK390551/. Published July 2016. Accessed October 19, 2021

Shantha GP, Pancholy SB. Effect of renal sympathetic denervation on apnea-hypopnea index in patients with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Breath.* 2015;19(1):29-34. Doi: 10.1007/s11325-014-0991-z.

U.S. Food and Drug Administration. FDA 510(k) premarket notification database. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed October 19, 2021. (a)

U.S. Food and Drug. FDA premarket approval (PMA) database. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. Accessed October 19, 2021. (b)

U.S. Food and Drug Administration. Center for Devices and Radiological Health. Medical Devices Advisory Committee. Circulatory System Devices Panel. Public meeting. [Transcript.]. https://www.fda.gov/media/123048/download. Published December 5, 2018. Accessed October 19, 2021.

White WB, Turner JR, Sica DA, et al. Detection, evaluation, and treatment of severe and resistant hypertension: Proceedings from an American Society of Hypertension Interactive forum held in Bethesda, MD, U.S.A., October 10, 2013. *J Am Soc Hypertens.* 2014;8(10):743-757. Doi: 10.1016/j.jash.2014.06.005.

Policy updates

11/2016: initial review date and clinical policy effective date: 2/2017

1/2018: Policy references updated.

1/2019: Policy references updated and policy ID changed.

1/2020: Policy references updated.

1/2021: Policy references updated.

1/2022: Policy references updated.

1/2023: Policy references updated.