Clinical Policy Title: Renal denervation

Clinical Policy Number: CCP.1283

Effective Date: February 1, 2017
Initial Review Date: November 16, 2016
Most Recent Review Date: January 8, 2019
Next Review Date: January 2020

Related policies:

CCP.1108 Ambulatory blood pressure monitoring

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

Coverage policy

AmeriHealth Caritas considers the use of renal denervation to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of renal denervation are not medically necessary.

Alternative covered services:

- Antihypertensive medications.
- Diuretic therapy.

Background
The sympathetic nervous system is responsible for preparing the body for stressful or emergency situations, i.e., “fight or flight.” Its effects target kidney function and systemic hemodynamics. Renal injury or hypoxia further enhances systemic and renal sympathetic activity. Sympathetic hyperactivity has been implicated in the initiation and progression of multiple conditions including arterial hypertension, sleep apnea, metabolic syndrome, myocardial hypertrophy and heart failure, and cardiac arrhythmias (Bohm, 2014).

Renal denervation, also referred to as 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. The procedure usually takes from 45 minutes to 60 minutes with a single catheter or less time with a multi-electrode or balloon catheter, and analgesia and sedation are required (Bohm, 2014).

Renal denervation has been proposed as a nonpharmacologic treatment for treatment-resistant hypertension, which is common in patients with pre-existing comorbid atherothrombotic disease and obesity, and for other sympathetically driven conditions (Bohm, 2014). Renal denervation devices are available under investigational device exemption use only; none has received U.S. Food and Drug Administration (2017a and b) approval for commercial use.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.

We conducted searches on October 16, 2018. Search terms were: “renal denervation,” “ablation,” and “treatment resistant hypertension.”

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**
We included four systematic review/meta-analyses, three professional guidelines, and one cost-effectiveness analysis for this policy. Two systematic reviews/meta-analyses (Sharfi, 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 patients (Krum, 2014).
- SYMPLICITY HTN-2 was a multi-site, randomized controlled trial of 106 patients (Esler, 2014).
- SYMPLICITY HTN-3 was a multi-site randomized controlled trial with sham controls of 535 patients (Bakris, 2014; Bhatt, 2014).

The evidence 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. To note, while the most rigorously designed SYMPLICITY HTN-3 trial met its primary safety endpoint with a major adverse event rate of only 1.4 percent, it failed to meet its primary and secondary efficacy endpoints with no statistically significant difference in either blood pressure measurement between the renal denervation treatment and sham control arms.

Results of the SYMPLICITY studies cannot be extrapolated to less severe forms 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 nonrandomized smaller studies suggests a potentially important role for renal denervation in the management of other disease states characterized by sympathetic nerve overactivation. 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).

Policy updates:
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 long-term outcomes were lacking (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.

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. Policy ID changed from CP# 09.03.04 to CCP.1283.

Summary of clinical evidence:

<table>
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<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Coppolino (2017) | **Key points:**  
  - Systematic review and meta-analysis of 12 randomized controlled trials (1,149 total participants): renal denervation vs. sham (four randomized controlled trials); proximal ablation vs. complete renal artery denervation (one randomized controlled trial); renal denervation vs. standard or intensified antihypertensive therapy (seven randomized controlled trials).  
  - None of the included trials was designed to look at hard clinical endpoints as primary outcomes.  
  - Data were sparse or absent for all-cause mortality, hospitalization, fatal cardiovascular events, quality of life, atrial fibrillation episodes, left ventricular hypertrophy, sleep apnea severity, need for renal replacement therapy, and metabolic profile.  
  - Renal denervation:  
    - Does not change major cardiovascular events, and renal function (low-quality evidence).  
    - Does not change blood pressure (moderate-quality evidence).  
    - Caused an increase of bradycardia episodes (low-quality evidence).  
  - Future trials measuring patient-centered instead of surrogate outcomes, with longer follow-up periods, larger sample size, and more standardized procedural methods are necessary to clarify the utility of this procedure in this population. |
| Sharfi (2016) for the Agency for Healthcare Research and Quality | **Key points:**  
  - Systematic review and meta-analysis of nine randomized controlled trials, eight comparative cohorts, and 66 noncomparative cohorts (7,660 total patients).  
  - Overall quality: variable.  
  - Results depend in part on type of blood pressure measurement and study design:  
    - Randomized controlled trials using 24-hour systolic ambulatory blood pressure measurement found small mean between-group differences (range: -8.0 mm Hg to +2.1 mm Hg).  
    - Studies using office blood pressure measurement found higher within-group differences for randomized controlled trials and comparative cohorts (range: -42.0 mm Hg to -8 mm Hg) and noncomparative cohorts (range: -58.2 mm Hg to 12 mm Hg). Likely overestimated due to white coat effect, observation bias, and placebo effect. |
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<td><strong>Fadl Elmula (2015)</strong>&lt;br&gt;Renal denervation for resistant hypertension</td>
<td><strong>Key points:</strong>&lt;br&gt;Meta-analysis of seven randomized controlled trials using renal denervation with SYMPLICITY catheters (985 total patients).&lt;br&gt;Overall quality: moderate. Six months follow-up.&lt;br&gt;Age averaged 58.1 years; average office blood pressure measurement 168.5/93.3 mmHg; 24 h ambulatory blood pressure measurement 151.8/86.1 mmHg; estimated glomerular filtration rate 79.3 ml/min/1.73 m².&lt;br&gt;Pooled effects (control minus renal denervation): office blood pressure measurement -4.9/-3.5 mmHg (95% confidence interval [CI] -20.9 to 11.1/-8.9 to 1.9); 24 h ambulatory blood pressure measurement -2.8/-1.5 mmHg (-6.5 to 0.8/-3.3 to 0.4); estimated glomerular filtration rate 0.81 ml/min/1.73 m² (-1.69 to 3.30).&lt;br&gt;Adverse events: 7.4% in controls and 9.9% in renal denervation group ($P = .24$).&lt;br&gt;In selected patients with resistant hypertension on antihypertensive drugs, renal denervation with the SYMPLICITY system does not significantly decrease blood pressure but is safe.&lt;br&gt;Future trials with next-generation catheters should aim at identifying responders in patients with evidence of sympathetic nervous overactivity.</td>
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<td><strong>Pan (2015)</strong>&lt;br&gt;Renal denervation and type 2 diabetes mellitus</td>
<td><strong>Key points:</strong>&lt;br&gt;Narrative review of one nonrandomized controlled study and four observational studies (53 total patients).&lt;br&gt;Overall quality: low with high risk of bias, small study sizes, no control groups, varied patient selection.&lt;br&gt;Conflicting results regarding improvement in hypertension and glycemic control.&lt;br&gt;Inconclusive. Large-scale randomized controlled trials needed to confirm results.</td>
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<td><strong>Shantha (2015)</strong>&lt;br&gt;Renal denervation and apnea-hypopnea index (AHI) in patients with obstructive sleep apnea</td>
<td><strong>Key points:</strong>&lt;br&gt;Systematic review and meta-analysis of four before and after studies and one compared continuous positive airway pressure with renal denervation (49 total patients).&lt;br&gt;Six months post-renal denervation:&lt;br&gt;Significant reduction in mean apnea-hypopnea index (weighted mean difference -9.61, 95% CI -15.43 to -3.79, $P = .001$).&lt;br&gt;One study reported improvement in oxygen desaturation index and Epworth sleepiness scale.&lt;br&gt;Promising results require validation in randomized controlled trials.</td>
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<td><strong>Schlaich (2013)</strong>&lt;br&gt;International Expert Consensus Statement</td>
<td><strong>Key points:</strong>&lt;br&gt;Consensus primarily based on data from SYMPLICITY HTN-1 and SYMPLICITY HTN-2 trials.&lt;br&gt;Renal denervation improves blood pressure control in patients with resistant hypertension.</td>
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| hypertension, with acceptable safety up to three years for the degree and reliability of blood pressure improvement. The effects may extend beyond blood pressure control. Long-term safety data are lacking.  
  - Resistant hypertension = systolic office blood pressure measurement ≥ 160 mm Hg or ≥ 150 mm Hg in patients with type 2 diabetes, despite treatment with ≥ three antihypertensive drugs of different types, including one diuretic agent.  
  - Contraindications to renal denervation: Hemodynamically or anatomically significant renal artery abnormalities (e.g., stenosis or fibromuscular dysplasia), previous renal artery interventions including renal stent procedures, unstable clinical conditions (e.g., acute cardiovascular events), or in children or patients with preeclampsia (insufficient evidence).  
  - Renal denervation not recommended outside of research settings for less severe forms of HTN or in other conditions characterized by heightened renal sympathetic nerve activity, such as heart failure, metabolic syndrome, heart arrhythmias (e.g., atrial fibrillation), chronic and end-stage renal disease, and others (insufficient evidence). | |
| Geisler (2012) | Key points:  
  - Assumptions based on SYMPPLICITY HTN-2 study findings.  
  - Renal denervation substantially reduced event probabilities (10-year/lifetime relative risks: stroke 0.70/0.83; myocardial infarction 0.68/0.85; all coronary heart disease 0.78/0.90; heart failure 0.79/0.92; end-stage renal disease 0.72/0.81).  
  - Median survival: renal denervation 18.4 years versus standard of care 17.1 years.  
  - Discounted incremental cost-effectiveness ratio (ICER) was $3,071 per quality-adjusted life-year (QALY); 95% credible interval for ICER was cost-saving to $31,460 per QALY.  
  - Stable over various input parameters except for systolic blood pressure reduction, baseline systolic blood pressure, and effect duration. Office blood pressure measurement used in calculations.  
  - Results are not generalizable to other renal denervation systems. | |
| National Institute for Health and Care Excellence (2012) | Key points:  
  - Insufficient evidence of long-term efficacy, which is important for treating resistant hypertension.  
  - Renal denervation should only be used with special arrangements for clinical governance, consent, and audit or research. | |

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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