Subject: Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension	Original Effective Date:
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Contents

DISCLAIMER

This Molina clinical policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina clinical policy document and provide the directive for all Medicare members.

RECOMMENDATION

This policy addresses radiofrequency ablation (RFA) procedures specifically to ablate (or denervate) the sympathetic renal nerves for the treatment of resistant hypertension (RH).

RFA of the renal sympathetic nerves is considered experimental, investigational and/or unproven for the treatment of resistant hypertension. RFA is an alternative treatment option for, or an improvement on existing therapies, for resistant hypertension; however, significant benefit in blood pressure measurements following RFA has not been proven. The evidence is insufficient to determine the effects of the technology on health outcomes.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Resistant hypertension (RH) is above-goal elevated blood pressure (BP) despite the concurrent use of 3 antihypertensive drug classes, usually a regimen of a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. RH also includes individuals whose BP achieves target values on 4 or more antihypertensive medications (Carey RM, et al. 2018). The antihypertensive drugs should be administered at maximum or maximally tolerated doses and at the appropriate dosing frequency. Multiple comorbidities and a higher risk for adverse outcomes are associated with RH (i.e. myocardial infarction, stroke, heart failure, and kidney failure). Different approaches, including a more intensified antihypertensive therapy, lifestyle modifications, or both, have largely failed to improve patients' outcomes and to reduce cardiovascular and renal risk (Coppolino G, et al. 2017). Non-pharmacologic interventions for RH include modulation of the baroreflex receptor and/or radiofrequency (RF) denervation of the renal nerves. According to Carey et al. in 'A Scientific Statement from the American Heart Association' (2018): 'The role of device-based sympatholytic treatments, as with renal denervation and baroreceptor stimulation, remains to be clarified. Although previously approved and utilized in different countries worldwide, validation of clinical benefit has not been confirmed in rigorous, double-blind comparisons with sham intervention. Incorporation of device-based therapies into current treatment algorithms based on lifestyle and pharmacological therapies would be appropriate with validation of clinical benefit.'

RF Denervation of the Renal Sympathetic Nerves

RFA of the renal sympathetic nerves may act as a nonpharmacologic treatment for hypertension and has been proposed as a treatment option for patients with resistant hypertension. Renal denervation is the procedure where bilateral renal nerves (traveling along renal artery) are destroyed by radiofrequency or ultrasound ablation catheters percutaneously inserted through femoral artery or via perivascular injection of neurotoxic drugs such as alcohol (2018 ESC/ESH Guidelines).

RFA for the treatment of HTN is assumed to decrease both the afferent sympathetic signals from the kidneys to the brain and the efferent signals from the brain to the kidneys. This decreases sympathetic activation, decreases vasoconstriction, and decreases activation of the renin-angiotensin system, which potentially lowers the BP (Zile, 2012). RFA is a minimally invasive procedure performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery and a controlled low-power energy is delivered to the arterial walls to ablate the renal sympathetic nerves. RFA is administered in a tertiary care center.

U.S. Food and Drug Administration (FDA)

No RFA devices have been approved by the FDA for ablation of the renal sympathetic nerves as a treatment for hypertension. Several devices have been developed for this purpose and are in various stages of application for FDA approval (FDA product code: DQY) including (list may not be all-inclusive):

- Symplicity™ Renal Denervation System (Medtronic, Minneapolis, MN)
- The EnligHTN™ Multi-Electrode Renal Denervation System (St. Jude Medical, Plymouth, MN): RFA catheter using a 4-point multiablation basket design. The EnligHTN™ Renal Guiding Catheter was cleared for marketing by the FDA through the 510(k) process on January 2014

- The OneShot™ Renal Denervation System (Covidien, Dublin): An irrigated RFA balloon catheter, consisting of a spiral-shaped electrode surrounding a balloon. NOTE: Covidien abandoned development of its OneShot™ Renal Denervation program in 2014
- The Vessix™ Renal Denervation System (Boston Scientific, Marlborough, MA; formerly the V2 renal denervation system, Vessix Vascular): A a combination of an RF balloon catheter and bipolar RF generator technologies, intended to permit a lower voltage intervention.

Other RFA catheters (e.g., Thermocouple Catheter™ [Biosense Webster, Diamond Bar, CA]) used for other types of ablation procedures (e.g., cardiac electrophysiology procedures) have been used off-label for RFA of the renal arteries.

SUMMARY OF MEDICAL EVIDENCE

Clinical trials have shown some promising outcomes for renal denervation (RDN) in the treatment of drug-resistant hypertension; however, additional studies with larger numbers of participants and longer-term follow-up is required to confirm both long-term safety and efficacy. Potential complications such as vascular access, renal artery perforation, and renal artery stenosis are outcomes that require further assessment from clinical trials.

Renal denervation (RDN) in the treatment of drug-resistant hypertension have been assessed by randomized controlled trials (RCTs), systematic reviews, and nonrandomized comparative studies and case series have reported inconsistent results. **The Symplicity HTN-3 trial, a large single-blinded trial of sham-controlled design, showed no significant improvements in blood pressure at six months with renal denervation and concluded no significant benefits with renal denervation. While other trials showed significant benefit using renal denervation for the treatment of resistant hypertension. It should be noted that studies showing favorable benefits of renal denervation were either non-randomized single-arm trials or randomized unblinded trials without a sham control group*.**

> **Rapid Renal Sympathetic Denervation for Resistant Hypertension (RAPID); Renal Denervation for Hypertension (DENERHTN) trial; Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter (REDUCE-HTN); EnligHTN (Observational Study of the EnligHTN Renal Denervation System), Renal Denervation in Hypertension (DENER-HTN); (Renal Denervation in Patients with Refractory Hypertension (Symplicity HTN-1); Renal Denervation in Patients with Uncontrolled Hypertension (Symplicity HTN-2)*

The DENERHTN and Symplicity HTN-2 trials reported a reduction of blood pressure over a six-month period compared with a control group, a significant benefit in patients treated with renal denervation. Possible explanations for the differences in the treatment effect between the Symplicity HTN-3 trial and the unblinded trials may be a placebo effect or other nonspecific effects of participating in a trial. Alternatively, blood pressure control in the control arm might have been better in Symplicity HTN-3 trial than in earlier studies. Meta-analyses of the systematic reviews have also reported no significant benefit in blood pressure measurements following RFA and inconsistent findings between analyses leading to the conclusion that **the evidence is insufficient to determine the effects of the technology on health outcomes.** Multiple interventional trials and RCTs of new RDN catheters are in progress for the treatment of resistant HTN (Azizi, 2018; Mauri, 2018; de Jager, 2017; Kandzari, 2016).

Randomized Controlled Trials

The Symplicity HTN-3 trial presents the most rigorous evidence about the efficacy of renal denervation with unfavorable results while other studies, DENERHTN and Symplicity HTN-2, showed benefit of renal denervation in the treatment of resistant hypertension. Of note, the studies showing favorable benefits of RDN were either non-randomized single-arm trials or randomized unblinded trials without a sham control group.

Symplicity HTN-3

SYMPLICITY HTN-3 (Bakris GL et al.) prospective, single-blind, randomized, controlled study of the safety and effectiveness of renal denervation in subjects with uncontrolled hypertension. Bilateral renal denervation was performed using the Symplicity Catheter, a percutaneous system that delivers radiofrequency (RF) energy through the luminal surface of the renal artery. 535 total participants with severe, resistant hypertension and a systolic blood pressure (SBP) of 160 mm Hg or higher were randomized to renal denervation with the Symplicity renal denervation catheter or to renal angiography only (sham control). A regimen of at least 3 antihypertensive medications of maximally tolerated doses, including one diuretic at the recommended dose was required, and changes in antihypertensive medication were not allowed during the six-month follow-up unless considered clinically necessary.

- The primary efficacy endpoint was the mean change in office SBP from baseline to 6 months in the denervation group compared with the sham control group. The secondary efficacy endpoint was the change in mean 24-hour ambulatory SBP at 6 months. The primary safety endpoint was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal artery or other vascular complications, or hypertensive crisis within 30 days or new renal artery stenosis of more than 70% within 6 months.
- There was a change in SBP of -14.13 mm Hg in the denervation group vs -11.74 mm Hg in the sham control group, for an absolute difference of -2.39 mm Hg. At 6-month follow-up, the change in 24-hour ambulatory SBP was -6.75 ± 15.11 mm Hg in the RDN group and -4.79 ± 17.25 mm Hg in the sham-procedure group, for a difference of -1.96 mm Hg. Major adverse event rates were similar between the denervation (1.4%) and control (0.6%) groups. There were no significant differences in safety between the two groups.

In comparison to a sham control, the trial did not show a significant reduction in SBP in patients with resistant HTN 6 months after RDN (Bhatt, 2014). Furthermore, articles with up to 12-month results of the SYMPLICITY HTN-3 trial have also concluded that a reduction in ambulatory SBP in either the 24-hour or day and-night periods, as compared with sham was not demonstrated (Bakris, 2014; Bakris, 2015).

The key strengths of the trial were its large size and blinded, sham-controlled design and the limitation is the short duration of the follow-up period which may have resulted in the under-identification of the treatment benefit differences between the groups over time.

The manufacturer, Medtronic, Inc., announced in January 2014 that its pivotal trial SYMPLICITY HTN-3 did not meet the primary and secondary efficacy endpoints (noted above), and the decision to end the SYMPLICITY HTN-4 trial as part of the application process for regulatory approval. Since the SYMPLICITY HTN-3 failed to meet its endpoints, Medtronic, Inc. modified and redesigned the catheter with added branch vessels and more electrodes to deliver up to four simultaneous RFAs in a helical pattern. The modified catheter, the SYMPLICITY

SPYRAL™ System, has obtained an FDA investigational device exemption (IDE) approval for two initial trials to evaluate the device and is as part of the SPYRAL HTN Global Clinical Trial Program. The trials are designed as randomized, sham-controlled studies to include 433 subjects at 50 sites in the U.S., Europe, Australia, and Japan. Medtronics also announced a SPYRAL HTN Global Clinical Program comprised of a panel of independent physicians and researchers to advise on its global hypertension clinical trial program and continued access to the SYMPLICITY technology in countries with regulatory approval for the device. Enrollment in the Global SYMPLICITY Registry will also continue.

DENERHTN Trial (Renal Denervation for Hypertension)

Azizi et al. conducted a prospective, open-label randomized controlled trial to evaluate treatment with renal denervation (RDN) plus standardized antihypertensive treatment (SSAHT) (n=53) versus standardized antihypertensive treatment alone (control group, n=53). Treatment resistance was confirmed by administration of indapamide 1.5 mg, ramipril 10 mg, and amlodipine 10 mg daily for 4 weeks. SSAHT treatment includes spironolactone 25 mg, bisoprolol 10 mg, prazosin 5 mg, and rilmenidine 1 mg daily from months 2-5 if blood pressure was more than or equal to135/85 mm Hg. The primary endpoint was the mean change in daytime systolic blood pressure (SBP) from baseline to 6 months as assessed by ambulatory blood pressure (BP) monitoring. The safety outcomes were the incidence of acute adverse events of the RDN procedure and the change in estimated glomerular filtration rate from baseline to 6 months. At 6 months, the mean change in daytime ambulatory SBP was -15.8 mmHg in the RDN group and -9.9 mmHg (-13.6 to -6.2) in the group receiving SSAHT alone, a baseline-adjusted difference of -5.9 mmHg. The numbers of antihypertensive drugs and drug adherence at 6 months were similar between the two groups. Three minor RDN-related adverse events were noted (lumbar pain in two patients and mild groin hematoma in one patient). The authors concluded that among patients with resistant hypertension, renal denervation plus standardized antihypertensive treatment was more effective at reducing ambulatory blood pressure compared with standardized antihypertensive treatment alone. **Limitations of the trial include small sample size and lack of a sham control group. Further study of renal artery denervation is necessary before the procedure is used clinically. (Azizi M, et al. 2016)**

Renal Denervation in Patients with Uncontrolled Hypertension (Symplicity HTN-2)

Esler et al. (2010) assessed the effectiveness and safety of catheter-based renal denervation (RDN) for BP reduction in patients with treatment-resistant hypertension in Symplicity HTN-2 trial. A total of 106 patients with resistant hypertension were randomly assigned to either RDN with medical treatment (treatment arm, n=52) or medical treatment alone (control arm, n=54). The primary endpoint of the study was change in office-based measurement of SBP at six months. At six months, there was a significant reduction in office-based BP measurements in the treatment arm (change of 32/12 mmHg, standard deviation [SD] 23/11, baseline of 178/96 mmHg), compared to the control arm (change of 1/0 mmHg, SD 21/10, baseline of 178/97 mmHg). Between-group differences in BP at six months were 33/11 mmHg ($p<0.0001$). Additionally, at six months, 41 (84%) out of 49 patients in the treatment arm had a reduction in SBP of 10 mmHg or more, compared with 18 (35%) of 51 controls. No serious procedural complications were noted. The authors concluded that catheter-based RDN can safely be used to substantially reduce BP in treatment-resistant hypertensive patients. **However, additional studies with larger sample size and longer-term outcomes data is needed confirm the safety and efficacy of RDN for BP reduction in patients with treatment-resistant hypertension. Due to the potential for post-**

treatment re-innervation of the treated renal nerves to diminish therapeutic effect over time following the RFA procedure, durability of treatment effect also requires further assessment (Esler et al. 2010).

Follow-up was available at 36 months in 40 of 52 subjects in the initial renal denervation group and at 30 months in 30 of 37 subjects who crossed over and received renal denervation at 6 months. At 30-month post-RDN, the original RDN group and the crossover group had a similar reduction in SBP and similar response rates regardless of a different baseline measurement at time of treatment. It was noted that at 3 years RDN maintained the lowering of BP in a selected population of subjects with severe, treatment resistant HTN with no adverse effects. **However, the limitation of the longer-term findings of the trial was due to the crossover design and the lack of comparison to a control group (since the crossover subjects represent a subset of the control group) which may have caused a selection bias of subjects who continued to have a SBP ≥160 mmHg and who chose to crossover (Esler, 2014).**

Nonrandomized Comparative Studies and Case series

Several nonrandomized studies with a control group and case series have been published; however, are not discussed in this policy since there are randomized control trials establishing the overall body of evidence (Brandt MC, et al. 2012; Mahfoud F, et al. 2012; Ukena C, et al. 2011; 2014)

Systematic Review and Meta-Analysis

Sardar P, et al. (2019) conducted a meta-analysis which included 977 adults with hypertension in 6 randomized trials with ≥ 50 patients comparing catheter-based renal sympathetic denervation vs. sham. The renal denervation procedure performed by radiofrequency ablation in 5 trials and endovascular ultrasound in 1 trial. This meta-analysis of these 6 sham-controlled randomized controlled trials demonstrated statistically significant reductions in blood pressure with RSD in patients with hypertension. **It was concluded that these results should inform the design and powering of larger, pivotal trials to evaluate the long-term efficacy and safety of RSD in patients with uncontrolled and resistant hypertension.**

Coppolino et al. (2017), in a systematic review of 12 randomized trials, compared renal denervation versus usual care or sham procedure in 1,149 adults with resistant hypertension. Overall, there was no evidence of benefits of renal denervation over standard treatment on cardiovascular morbidity and mortality. Similarly, renal denervation had no tangible effects on blood pressure control and renal function. However, it was associated with an increased risk of episodes of bradycardia (very slow heart rate). The authors concluded that the evidence accrued so far is insufficient to support the use of renal denervation as a clinically useful procedure for improving cardiovascular risk and blood pressure control in patients with resistant hypertension. **The Cochrane review reported that none of the trials was designed to evaluate clinical endpoints as primary outcomes.** The evidence for clinical endpoints (e.g., all-cause mortality, hospitalization, cardiovascular events) was of low-quality. **Comparisons of clinical outcomes in sham versus renal denervation groups showed no significant differences between groups in myocardial infarction, ischemic stroke, or unstable angina.** Focused trials, powered for patient-centered instead of surrogate outcomes, with longer follow-up periods, larger sample sizes, more standardized procedural methods, and possibly examining particular subgroups of patients with resistant hypertension (e.g. subjects with different cardiovascular or renal risk profile) are needed to clarify the optimal target population for

this procedure. Study design providing a sham control procedure and blinded outcome assessors are indispensable for minimizing bias and improving reliability of findings.

Professional Society Guidelines and Other Publications

Agency for Healthcare Research and Quality (AHRQ)

A technical brief 'Renal Denervation in the Medicare Population' was conducted by Johns Hopkins University Evidence-based Practice Center and published in 2016 (AHRQ 2016). The brief evaluated the effectiveness of renal denervation for resistant hypertension to determine its applicability to the Medicare population through a systematic review which included abstraction from 83 studies, including 9 RCTs, 8 comparative cohorts, and 66 non-comparative cohorts. The report noted the following:

- Limitations: 'The study populations from the included studies were only partially comparable to the Medicare-eligible population. Data were scant on clinical endpoints (i.e. stroke, myocardial infarction, kidney events, hospitalization, or death) and none of the studies were designed or powered to detect a long-term difference between groups in these clinical endpoints and few studies reported these outcomes.'
- Adverse effects were uncommon but potentially serious, and included hematomas, pseudoaneurysms, and renal artery interventions.
- The brief concluded: 'Limited evidence suggests that renal denervation in patients with treatment resistant hypertension lowers systolic blood pressure, but the results were highly variable, and the studies reviewed were not designed to determine improvement in clinical endpoints. The most rigorously conducted RCTs showed much smaller blood pressure reduction as compared with observational non-comparative studies. Further research is needed to identify optimal candidates for renal denervation, refine next generation renal denervation technology, develop methods for assessing completeness of renal denervation procedure, and demonstrate efficacy of renal denervation in reducing blood pressure and improving clinical endpoints including the risk of stroke, myocardial infarction, heart failure, and death in patients with hypertension.' **(Shafi, AHRQ, 2016).**

American Heart Association (AHA), American College of Cardiology (ACC), and American Society of Hypertension (ASH)

The AHA, ACC, and ASH published joint guidelines (2015) on the treatment of hypertension in patients with coronary artery disease noting that **'additional randomized controlled trials are required since Symplicity HTN-3 trial did not find a significant benefit from renal denervation.'**

'Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults' published in 2018 by the AHA, ACC, and 9 specialty societies addressed resistant hypertension and noted: **"Several studies have investigated devices that interrupt sympathetic nerve activity (carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves); however, these studies have not provided sufficient evidence to recommend the use of these device in managing resistant hypertension."** (ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, 2018)

European Society of Cardiology/European Society of Hypertension (ESC/ESH)
Recommendations for patients with resistant hypertension: Do not use device-based therapies for routine hypertension treatment until additional evidence for efficacy and safety becomes available unless setting for use is randomized controlled trial or clinical study (ESC/ESH Class III, Level B)

DEFINITIONS

Radiofrequency ablation (RFA): Minimally invasive surgical procedure utilizing low power radiofrequency energy to ablate (or destroy) various tissues of the body.

Renal denervation: Catheter-based radiofrequency ablation of renal sympathetic nerves, which may reduce blood pressure in patients with resistant hypertension, but data on its effectiveness are conflicting.

Resistant hypertension (HTN): Blood pressure (BP) above goal despite treatment with three antihypertensive agents, of different classes ideally including a diuretic, all prescribed at optimal dose amounts.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural road mapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural road mapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral

HCPCS	Description

ICD-10	Description: [For dates of service on or after 10/01/2015]

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Review/Revision History:

Q4 2020: New Policy. Advanced Medical Review (AMR): Policy reviewed by practicing MD Board-Certified in Internal Medicine, Cardiovascular Disease. 11/6/2020