Renal Denervation
Ultima Ratio or Standard in Treatment-Resistant Hypertension
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Online Data Supplement

The term “ultima ratio” has multiple, though related, meanings. The motto “ultima ratio regum,” cast on the cannons of the French army of King Louis XIV, meant that war is the last argument of kings, that is, the one to be used after all diplomatic arguments have failed. Along similar lines, we propose that, given the current evidence, renal denervation should be used as a last resort, after state-of-the-art drug treatment optimized at expert centers failed to control blood pressure.

Hypertension affects an estimated 20% to 30% of the world’s adult population.1 Despite the availability of numerous safe and effective pharmacological therapies, including single-pill combinations of 2 to 3 drugs, the percentage of patients achieving adequate blood pressure control meeting guideline targets remains low.1,2 Resistant hypertension is a blood pressure that remains above goal in spite of the concomitant use of antihypertensive medications from ≥3 drug classes.3 Patients who require >4 drug classes to have their blood pressure controlled are also considered to have resistant hypertension. Preferably, the regimen should include a diuretic, and all of the doses should be optimal.3,4

Treatment-Resistant Hypertension

The online-only Data Supplement provides an overview of the epidemiology of treatment-resistant hypertension and the role of the sympathetic nervous system in maintaining uncontrolled hypertension.

Results of the SYMPLICITY Studies

SYMPLICITY Hypertension-1

In 2009, Krum et al5 reported a nonrandomized proof-of-concept study (NCT 00483808 and NCT 00664638) showing that percutaneous radiofrequency catheter-based renal sympathectomy was feasible, effective, and safe. Among 45 analyzed patients enrolled in this first-in-human open study, on treatment with 4.5 antihypertensive drugs, blood pressure at entry was 177/101 mmHg and decreased by 27/17 mmHg 12 months after renal denervation.5

SYMPLICITY Hypertension-2

After the proof-of-concept study,5 the SYMPLICITY Hypertension-2 (SIMPLICITY HTN-2) investigators published a randomized clinical trial.6 Patients were eligible if they had a baseline systolic blood pressure of ≥160 mmHg (150 mmHg for patients with type 2 diabetes mellitus) while taking ≥3 antihypertensive drugs. Of 190 patients screened at 24 centers, 106 (55.8%) were randomly allocated to undergo renal denervation plus previous treatment (n = 52) or to maintain previous treatment alone (control group; n = 54); 49 (94.2%) who underwent renal denervation and 51 (94.4%) of controls had their systolic blood pressure measured at the office at 6 months, the primary end point. In the renal denervation group, office blood pressure decreased by 32/12 mmHg (P < 0.0001) from the baseline value of 178/96 mmHg, whereas the corresponding 1/0-mmHg change from 178/97 to 179/97 mmHg in the control group was not significant (P = 0.77). At 6 months, the between-group difference in the office blood pressure averaged 33/11 mmHg (P < 0.0001).6 Of the patients who completed the trial, 41 (83.7%) who underwent renal denervation had a reduction in systolic blood pressure of ≥10 mmHg compared with 18 controls (35.3%; P < 0.0001).6

Among the patients with a 6-month follow-up, more had drug reductions in the renal denervation group than in the control group (20.4% versus 5.9%; P = 0.04), with no between-group differences in the proportion of patients who...
had their drug treatment intensified (8.2% versus 11.8%; \( P=0.74 \)).\(^6\) There were no serious procedure-related or device-related complications, and occurrence of adverse events did not differ between groups. In particular, renal function and the albumin:creatinine ratio at 6 months were not significantly different from baseline.\(^6\)

SYMPPLICITY HTN-1 Registry

Between June 6, 2007, and May 1, 2010, the SYMPPLICITY HTN-1 investigators applied renal sympathetic denervation in 153 patients,\(^7\) including the 45 patients from the SYMPPLICITY HTN-1 Study.\(^5\) They published follow-up information in May 2011.\(^7\) Mean age was 57 years, 39% were women, 31% were diabetic, and 22% had coronary artery disease. Before renal denervation, office blood pressure measured on a mean of 5 antihypertensive medications averaged 176/98 mmHg. At 1, 3, 6, 12, and 18 months, the percentage of patients followed up for blood pressure amounted to 90.2%, 88.2%, 56.2%, 41.8%, 23.5%, and 11.8%, respectively.\(^7\) At these time points, the blood pressure reductions averaged 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mmHg (Figure, A). These findings were consistent after censoring for increases in antihypertensive medication and in a cohort of 18 patients (11.8%) with a 2-year follow-up.

At baseline, the estimated glomerular filtration rate (eGFR) was 83 mL/min per 1.73 m\(^2\). During the first year of follow-up, eGFR remained stable, with changes at 1, 3, 6, and 12 months of +0.1, −1.6, −0.1, and −2.9 mL/min per 1.73 m\(^2\), when the percentage of patients remaining in follow-up for renal function was 73.2%, 66.7%, 56.9%, and 41.8%, respectively.\(^7\) Only 10 patients (6.5%), had eGFR measured at 2 years. eGFR fell by 16.0 mL/min per 1.73 m\(^2\) in all of the patients (Figure B) and by 7.8 and 24.2 mL/min per 1.73 m\(^2\) in patients who did not have (\( n=5 \)) or did have (\( n=5 \)) a diuretic added to their treatment. No patient experienced a doubling of serum creatinine, developed class IV chronic kidney disease (15–29 mL/min per 1.73 m\(^2\)), or progressed to dialysis.\(^7\) In 149 patients (97.4%), renal denervation was without complication. Acute procedural complications included 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae.\(^7\)

Limitations of the Evidence Supporting Renal Denervation

Duration and Completeness of Follow-Up

The SYMPPLICITY HTN-1\(^5\) and SYMPPLICITY HTN-2\(^6\) studies covered only 6 months. The proportion of patients in the SYMPPLICITY HTN-1 registry,\(^5\) with a follow-up of 1 and 2 years, was 41.8% and 11.8% for blood pressure and 41.8% and 6.5% for eGFR (Figure). To what extent incomplete follow-up beyond 6 months reflects dropout of patients is not documented in the report on the SYMPPLICITY Registry.\(^7\)

Definition and Management of Resistant Hypertension

The definition of treatment-resistant hypertension in the SYMPPLICITY reports, although in line with the contemporary guidelines,\(^7,10\) was not stringent. In SYMPPLICITY HTN-1,\(^5\) treatment resistance included intolerance to blood-pressure-lowering drugs, which often occurs in nonadherent patients. At screening for SYMPPLICITY HTN-2,\(^6\) patients recorded the intake of medications during 2 weeks, but the number of patients excluded because of nonadherence was not reported. No attempt was made to ascertain in a verifiable manner adherence to or persistence of antihypertensive drug treatment.

Furthermore, the management of hypertension was not optimal in all of the patients. The SYMPPLICITY researchers did not report how lifestyle measures were reinforced before enrollment and followed up by serial measurements of body mass index or 24-hour urinary sodium.\(^11\) At inclusion, 11% and 5% of the patients enrolled in SYMPPLICITY HTN-2\(^6\) and the SYMPPLICITY HTN-1 registries\(^7\) were not taking diuretics, and only 17% and 22% were taking aldosterone antagonists, a drug class strongly recommended in treatment-resistant patients,\(^12\) particularly if plasma renin activity is low.\(^13\) Risk of hyperkalemia or degradation of renal function cannot explain the underuse of aldosterone antagonists, be-
cause patients with an eGFR <45 mL/min per 1.73 m² were ineligible. Finally, drug treatment was not standardized or described in detail in the SYMPLICITY studies. 5–7 In view of the highly prevalent nonadherence among treatment-resistant patients, ideally, long-acting, so-called forgiving, drugs, 14 that is, with a slow loss of blood pressure–lowering effect during drug holidays, and single-pill combinations of various antihypertensive agents 15 should have been prescribed.

**Diagnosis of Secondary Hypertension**

A systematic search for secondary hypertension is key in the management of treatment-resistant hypertension, because this condition is more common in patients with resistant than controlled hypertension. 3,16 Treating the underlying cause in secondary hypertension allows to improve blood pressure control. Unfortunately, in both SYMPLICITY HTN studies, 5,6 screening for secondary hypertension was not mandatory, and the procedures for a diagnostic workup were not standardized. In SYMPLICITY HTN-1, 5 known secondary hypertension was an exclusion criterion, whereas secondary hypertension was not mentioned among the SYMPLICITY HTN-2 eligibility criteria. 6

**Blood Pressure Measurement**

Compared with office measurement, ambulatory blood pressure monitoring removes observer bias and measurement error, minimizes the white coat effect and has greater reproducibility, and, therefore, provides a better estimate of a patient’s usual blood pressure and cardiovascular prognosis. 17,18 Self-measurement of blood pressure at home offers several of the well-recognized advantages of the more complex approach of ambulatory monitoring. 19,20 Current guidelines 9,10,20 recommend one of these out-of-the-office modalities of automated blood pressure measurement as state-of-the-art in the management of hypertensive patients. In particular, in patients with resistant hypertension, monitoring blood pressure outside of the medical environment is essential to distinguish true resistant hypertension from white coat–resistant hypertension. 21 In the Spanish Ambulatory Blood Pressure Monitoring registry, 21 white coat hypertension had a prevalence of 37.5% among 8295 patients with apparently resistant hypertension. Patients with white coat–resistant hypertension have a better cardiovascular prognosis than those with truly resistant hypertension. 22,23 Furthermore, in a cohort of 109 treatment-resistant hypertensive patients followed up for 4.8 years, higher ambulatory blood pressures predicted cardiovascular morbidity and mortality, whereas office blood pressure had no prognostic value. 24

Notwithstanding the overwhelming evidence in favor of the superiority of out-of-office blood pressure measurement, 17–20 in particular, in treatment-resistant patients, 24 in both SYMPLICITY trials 5,6 and even in the ongoing SYMPLICITY HTN-3 Study (NCT01418261), 25 the primary end point rested on office blood pressure. In SYMPLICITY HTN-1, 5 only 12 (27%) of 45 patients had adequate ambulatory blood pressure monitoring at baseline and >30 days after denervation. The 24-hour systolic blood pressure decreased by 11 mmHg in 9 responders according to office systolic blood pressure and by 10 mmHg in 3 nonresponders. In SYMPLICITY HTN-2, 6 all of the eligible patients received an Omron HEM-705 monitor to record seated blood pressure daily during 2 weeks, 3 times in the morning and 3 times in the evening. At 6 months, the home blood pressure fell by 20/12 mmHg in 32 patients in the renal denervation group compared with a rise of 2/0 mmHg (13/7) in 40 controls, resulting in a between-group difference of 22/12 mmHg (P < 0.0001); the 24-hour blood pressure decreased by 11/7 mmHg in 20 patients randomized to renal denervation and did not change (−3/−1 mmHg) in 25 controls, resulting in a between-group difference of 14/8 mmHg (P = 0.02). 6 The SYMPLICITY HTN-2 investigators did not report the baseline values of the ambulatory or self-measured blood pressures, so that the prevalence of white coat hypertension at entry among the SYMPLICITY patients cannot be assessed.

**Assessment of Adherence**

Adherence evaluated by electronic monitoring falls from 79% in patients taking medications once daily to 51% with 4 times daily dosing. 26 Approximately half of hypertensive patients do not take their medications as prescribed. 27 Nonadherent patients have an increased probability of receiving add-on drug therapy while staying uncontrolled and remaining at higher cardiovascular risk than their adherent counterparts. 28 Poor medication-taking behavior is a major problem among patients with hypertension and is one of the main causes of failure to achieve blood pressure control. 8 More information on nonadherence is available in the online-only Data Supplement.

The prevalence of diabetes mellitus and hypercholesterolemia in SYMPLICITY HTN-2 was 34.0% and 51.9%, respectively. 6 The SYMPLICITY patients were at high risk of nonadherence, because, in addition to taking 4 to 5 antihypertensive drugs, many were also on lipid-lowering, antplatelet, and/or antidiabetic drugs. Assessment of adherence in the SYMPLICITY studies 5–7 was suboptimal. SYMPLICITY HTN-1 did not report on adherence. 5 In SYMPLICITY HTN-2, 6 eligible patients had to comply with ≥3 drugs, including a diuretic. After the 2-week run-in period, 36 of the SYMPLICITY HTN-2 patients (19%) were excluded, because their blood pressure fell below the inclusion threshold, perhaps because of improved adherence. However, this does not mean that all of the randomized patients were adherent and even less so that they remained adherent during the entire follow-up.

**Safety**

Animal studies on the safety of the SYMPLICITY Catheter System are scarce. Only in 2011, after publication of SYMPLICITY HTN-2 6 and after the catheter had obtained a CE label in Europe, 29 Rippy et al 29 published results obtained 4 years earlier in 7 swine. In animals euthanized 6 months after the procedure, the renal arteries showed fibrosis from 10% to 25% of the total media and the underlying adventitia, with mild disruption of the external elastic lamina.

*CE stands for Conformité Européenne, meaning European Conformity (http://icqc.eu/userfiles/File/DECISION-768-2008-EC.pdf). The CE label ascertainment that a product conforms with all applicable EC directives. Medical devices must not only be safe, but also function in a medical-technical way as described in the manufacturer’s intended purpose (http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf).
Short-term (14–30 days) follow-up angiograms in 18 SYMPLECTITY HTN-1 patients showed no evidence of renal artery stenosis or other abnormalities. Magnetic resonance angiograms in 14 patients, 6 months after the procedure, did not reveal any irregularities in any treatment locations. Of 49 patients who underwent renal denervation in SYMPLECTITY HTN-2, 43 had renal imaging at 6 months, including 37 renal duplex imaging, 5 MRI, and 5 computerized tomographic angiography. In the registry, 81 of 153 patients underwent imaging of the renal arteries 6 months after renal denervation by magnetic resonance angiography, computed tomographic angiography, or renal duplex. In the SYMPLECTITY studies, imaging of the renal arteries was neither standardized in terms of the technique used at baseline and follow-up nor in terms of the operators, an issue that might be most relevant for duplex imaging. Only a minority of patients were examined by magnetic resonance angiography and even less by computerized tomographic renal angiography, which is the gold standard. In view of the nonstandardized and suboptimal imaging approach in the SYMPLECTITY studies, the risk of intervention-related renal artery abnormalities, stenosis or aneurysms remains a legitimate concern, in particular beyond 6 months of follow-up. The registry also does not provide any substantial information on renal function beyond 6 months and even suggests that, at 2 years, renal function substantially declined at least in the small subset of patients with follow-up to that time point (Figure, B).

Issues to Be Addressed

Blinded and Randomized Study Design

In the SYMPLECTITY studies, the decrease in systolic blood pressure at 6 months was in the range of 25 to 30 mmHg for the office blood pressure and ≈20 mmHg for the home blood pressure, whereas, on 24-hour ambulatory monitoring, it was only ≈10 mmHg. The difference between these estimates remains to be clarified.

Blood pressure–lowering effects estimated by out-of-the-office techniques amount usually to ≈60% to 70% of the effects seen on office measurement. There is no proof for the suggestion that renal denervation would blunt the white coat effect. Selection of patients for ambulatory blood pressure monitoring or the use of short-acting antihypertensive drugs might partially explain the discrepancy. However, the most likely explanation is that ambulatory blood pressure monitors operate in a blinded fashion. In contrast, all of the estimates of the changes in the office and home blood pressures in the SYMPLECTITY studies were collected in an unblinded fashion and are vulnerable to bias introduced by physicians and patients. The SYMPLECTITY protocol (version April 4, 2009) instructed investigators as follows: (1) to measure blood pressure ≥3 times; (2) to take additional measurements until they were consistent within 5 mmHg; and (3) to record 3 consistent readings on the case report forms. The number of readings required to reach consistency and those selected to be recorded on the patient forms (consecutive or not) are not in the public domain. The number of repetitions might have been different between randomized groups, particularly at the time of the assessment of the primary end point. Moreover, patients randomized to the control group in SYMPLECTITY HTN-2 were offered access to renal denervation after 6 months of follow-up. In unblinded patients not accountable for adherence, this offer is unlikely to have stimulated controls to relentlessly take their multiple drugs for 6 months in a row.

The nonrandomized design of SYMPLECTITY HTN-1 and the registry also makes it likely that part of the blood pressure–lowering effect is attributed to regression to the mean. Placebo, or nocebo effects; attenuation of the white coat reaction; and modification of the patients’ behavior in response to the study context (Hawthorne effect). Future studies on the effects of renal denervation should not only be blinded but should have a randomized design with a control group. Unfortunately, this is not the case (Tables 1 and 2). For end points measured on a continuous scale, such as blood pressure or eGFR, reports might include a graphical representation of the distribution of the responses in the randomized groups. The Hypertension Optimal Treatment investigators published an example for the blood pressure changes in their trial (Figure S, available in the online-only Data Supplement). A similar approach in future studies of renal denervation might clearly illustrate the heterogeneity and overlap of the responses within and particularly between the randomized groups.

Definition of Treatment-Resistant Hypertension

In our opinion, the current definition of resistant hypertension, applied in the SYMPLECTITY studies, needs revision for various reasons. First, single-pill combinations of ≥3 antihypertensive agents became available in varying dosages, so most hypertensive patients can be controlled with fewer pills per day in a cost-effective fashion. The number of tablets taken per day is, therefore, no longer a valid criterion to assess treatment resistance. Second, the current definition of treatment resistance does not include assessment of out-of-the-office blood pressure or adherence. Third, some patients might interpret the current definition that, once they are taking 3 antihypertensive drugs, they qualify as candidates for renal denervation. Fourth, the diagnosis of treatment-resistant hypertension implies that all lifestyle and pharmacological approaches to control blood pressure have been implemented or at least tried. Pimenta et al studied 12 treatment-resistant patients (≥3 medications including a diuretic) in a randomized crossover fashion on low- (50 mmol) and high- (250 mmol) sodium diets, each period lasting 7 days separated by a 2-week washout period. At baseline, office blood pressure averaged 145.8/83.9 mmHg. Mean urinary sodium excretion was 46.1 versus 252.2 mmol/24 hours during low- versus high-salt intake periods. Compared with a high-salt diet, low-salt intake entailed a fall in the office blood pressure by 22.7/9.1 mmHg. In a retrospective cohort study of 140126 treatment-resistant US patients (≥4 medications), the most frequently prescribed antihypertensive drug classes were angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (96.2%), diuretics (93.2%), calcium channel blockers (83.6%), and β-blockers (80.0%). Long-acting chlorthalidone (3.0%) and aldosterone antagonists (5.9%)—recommended drugs in treatment-resistant hypertension—
were underused, whereas dual renin system inhibition, a potential deleterious combination,\(^{51,52}\) was used in 15.6% of patients.

Redefinition of treatment-resistant hypertension should involve substantially more than just the number of drugs taken.\(^{26,53}\) The following might be accounted for: (1) a standardized diagnostic work-up to exclude secondary hypertension; (2) out-of-the-office blood pressure measurement to exclude white coat hypertension; (3) verified implementation of lifestyle recommendations; and (4) an elaborate assessment of adherence, for instance by administering a questionnaire\(^ {54}\) but preferably by measuring biomarkers,\(^ {55,56}\) drugs or their metabolites in biological fluids, or by the use of electronic pill boxes.\(^ {57,58}\)

### Selection of Treatment-Resistant Patients for Renal Denervation

In multivariable analyses of the SYMPLICITY registry, 7 significant independent predictors of greater systolic blood

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**Table 1. Randomized Controlled Clinical Trials**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SYMPLICITY HTN-3</th>
<th>DEPART</th>
<th>ReSET</th>
<th>MRT</th>
<th>DENER-HTN</th>
<th>PRAGUE-15</th>
<th>INSPIRED</th>
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<td>01459900 (A)</td>
<td>01117025 (A)</td>
<td>01570777 (A)</td>
<td>01560312 (A)</td>
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<td>Yes</td>
<td>Yes</td>
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<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
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<td>Primary end point (mo)</td>
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<td>24-h ABP (6) eGFR (6)</td>
<td>24-h ABP (3)</td>
<td>DBP (24)</td>
<td>Daytime ABP (6)</td>
<td>Office SBP (6)</td>
<td>Daytime ABP (36)</td>
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<td>RDN</td>
<td>RDN</td>
<td>RDN</td>
<td>RDN</td>
<td>RDN</td>
<td>RDN</td>
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<tr>
<td>Control</td>
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<td>RA catheterization without RDN</td>
<td>RA catheterization without RDN</td>
<td>PV plus RDN</td>
<td>Optimized AH drug treatment</td>
<td>Optimized AH drug treatment</td>
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<td>Age, y</td>
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<td>20–75</td>
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<td>. . .</td>
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<td>ABP, mm Hg</td>
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<td>Daytime SBP; ≥135 and/or 24-h DBP; ≥85; patients taking ≥3 AH drugs are eligible irrespective of BP</td>
<td>Daytime SBP; ≥145</td>
<td>. . .</td>
<td>Daytime ABP; ≥135/85 on optimized treatment</td>
<td>24-h SBP; ≥130</td>
<td>24-h SBP; ≥130 and/or DBP; ≥80</td>
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<td>≥3 drugs including thiazide or loop diuretic; spironolactone attempted, unless contraindicated</td>
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<td>≥3 drugs</td>
<td>≥3 drugs</td>
<td>≥3 drugs</td>
<td>≥3 drugs</td>
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<tr>
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<td>≥30</td>
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<td>No stenosis or abnormalities; no previous intervention</td>
<td>Kidneys ≥90 mm and suitable anatomy of renal arteries</td>
<td>Diameter ≤4 mm; length ≤20 mm;</td>
<td>Diameter ≤4 mm; length ≤20 mm; no stenosis; no previous intervention</td>
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<td>Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
<td>Excluded</td>
<td>Excluded except adrenal hyperplasia</td>
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<td>Safety follow-up</td>
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<td>mgGFR, cystatin C</td>
<td>. . .</td>
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<td>. . .</td>
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<td>Arteriography (6) Angio CT (12, 24, 36)</td>
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**Trial acronyms:** SYMPLICITY HTN-3, Renal Denervation in Patients with Uncontrolled Hypertension; DEPART, Catheter Based Renal Denervation Therapy in Hypertension; ReSET, Renal Sympathectomy in Treatment Resistant Essential Hypertension, a Sham Controlled Randomized Trial; MRT, Meshalkin Research Institute Trial; DENER-HTN, Renal Denervation in Hypertension; PRAGUE-15, Renal Denervation–Hope for Patients with Refractory Hypertension; INSPIRED, Investigator Steered Project of Intravascular Renal Denervation. NCT No. is the identification No. in the trial registry (http://www.clinicaltrials.gov) of the National Institutes of Health. A (academic) and I (industry) refer to the sponsor. Numbers between parentheses indicate the timing in months after randomization when end point or measurement will be assessed. HT indicates treatment-resistant hypertension; AF, atrial fibrillation; PV, pulmonary vein isolation; eGFR/mGFR, estimated/measured glomerular filtration rate; SCrt, serum creatinine concentration; AE, adverse events; RA, renal artery; OBP/ABP, office/ambulatory blood pressure; BP, blood pressure; RDN, renal denervation; . . ., unspecified information.
pressure response were higher baseline systolic blood pressure ($P<0.0001$) and the use of central sympatholytic agents ($P=0.018$). The former association is spurious, whereas the second is counterintuitive, because patients on sympatholytic agents were excluded from SYMPLICITY HTN-1, which forms the nucleus of the SYMPLICITY registry. None of the SYMPLICITY analyses identified conditions associated with higher sympathetic activity, such as obesity, obstructive sleep apnea, or renal dysfunction, as predictors of the blood pressure response to renal denervation. Age did not determine the blood pressure response, although renal sympathetic denervation might be less effective to remediate isolated systolic hypertension in the elderly, because this condition is attributed to structural changes in the large arteries. Identifying reliable predictors of blood pressure reduction in response to sympathetic ablation is a priority issue, should renal denervation make it to clinical practice.

### Nervous and Hemodynamic Mechanisms Underlying the Antihypertensive Effect

Inhibition of the sympathetic nervous system might not be the only mechanism underlying the antihypertensive effect of renal denervation. The only direct measurements available came from 10 SYMPLICITY HTN-1 patients, in whom renal norepinephrine spillover decreased by 47% (95% CI, 28% to 65%) from baseline to 15 to 30 days after the procedure. In a single patient, Krum et al observed a decrease in whole-body spillover of norepinephrine and muscle sympathetic nerve activity 1 month after the procedure. Future trials should encompass a comprehensive evaluation in a randomized and blinded fashion of the sympathetic nervous activity, for instance by measuring changes in circulating or urinary catecholamines, microneurography, assessing heart rate variability, which is easily feasible. In the SYMPLICITY patients, the decline in blood pressure was progressive. Future studies should clarify to what extent changes in the circulating volume and sodium and fluid homeostasis play a role and identify the hemodynamic mechanisms underlying the blood pressure reduction, such as changes in peripheral resistance attributed to peripheral arteriolar vasodilatation (functional) or remodeling (structural). As highlighted by the SYMPLICITY HTN-1 investigators, an outstanding question with regard to renal denervation in general and the radiofrequency approach taken in particular regards the durability of the blood pressure--lowering effect. Effenter nerves anatomically regrow over a period of months to years, however, without consistent demonstration of functional reinnervation.
A Holistic and Comprehensive Assessment of Long-Term Outcomes

Renal denervation as a treatment option for resistant hypertension still awaits a balanced evaluation of its potential benefits and harms over a time period of 3 to 5 years. Such assessment should include blood pressure control in adherent and nonadherent patients, residual need of antihypertensive medications, quality of life, the incidence of cardiovascular morbidity and mortality, and a cost-effectiveness analysis based on state-of-the-art methodology. In the SYMPLECTICITY registry (Figure, B), eGFR declined faster than in recent trials of hypertensive and/or high-risk patients, such as those enrolled in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), in the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND), or in the Avoiding Cardiovascular Events Through Combination Therapy In Patients Living With Systolic Hypertension trial (ACCOMPLISH). If patients with more severe renal dysfunction than in the SYMPLECTICITY studies would become eligible for enrollment in future trials, the long-term assessment of renal function and alterations in the structure of the renal arteries subjected to radiofrequency energy should move to the forefront of research.

Novel Renal Denervation Systems

The evidence available from the SYMPLECTICITY studies was obtained with the first-generation 8F-compatible Ardian catheter, which had a design different from the currently marketed 6F devices. Newer ablation systems are being tested and will soon be released into the market, among them the St Jude Medical Renal Artery Ablation System, the Maya Medical One Shot Ablation System, the THERMOCOOL Irrigated Tip Catheter, the Integrated Ablation System, the ReCor Paradise System, and the VESSIX V2 renal denervation system (Table 2). Differences in design characteristics among catheters encompass the need for using a guiding sheet versus balloon-steered catheters; the application of radiofrequency versus ultrasound energy; single versus multiple radiofrequency electrodes; single-shot versus repeat energy delivery systems with or without adjustable energy delivery; the possibility to stabilize and center the catheter in the renal artery by balloon inflation or expanding the electrodes; and the possibility of controlling temperature by cooling. The St Jude catheter has an expandable basket of electrodes allowing fixation in the renal artery. The Maya approach allows radiofrequency energy application with a single device placement, reproducible electrode apposition using a balloon-guided technique, and includes a helical ablation pattern for more complete denervation. The THERMOCOOL catheter is already approved for ablation in atrial ablation. It is an open-loop irrigated catheter designed to maintain lower tip-to-tissue temperatures and to deliver a constant preset radiofrequency energy regardless of local blood flow cooling. The Paradise catheter is balloon guided, emits ultrasound energy circumferentially, and allows for cooling of the endothelium. The VESSIX V2 system is a balloon catheter with electrodes mounted on the exterior of the balloon to facilitate delivery of radiofrequency energy. Trials comparing these different approaches should focus on safety and the measurement of the activity of the sympathetic nervous system.

Position Statement on Renal Denervation

The message promulgated by manufacturers of renal denervation systems in the indication of treatment-resistant hypertension is as follows:

“This technology could potentially help alleviate some of the $500 billion impact that hypertension has on our health care systems by reducing or eliminating costly and lifelong medication use. Patients could potentially benefit through an overall reduction in risks for cardiovascular complications of hypertension, including death.”

There are no data to support such contentions. Moreover, marketers within these companies, with the help of invasive radiologists and cardiologists, are searching for new indications for renal sympathetic nervous denervation in patients with heart failure (Table 2), the metabolic syndrome or impaired glucose tolerance (Table 2), hypertension combined with atrial fibrillation (Table 1), obstructive sleep apnea (Table 2), left ventricular hypertrophy and diastolic dysfunction, or polycystic ovary syndrome. Despite the rationale underlying some of these indications, it is unsure whether the expectations raised mainly from uncontrolled observational studies, that one size might fit all, will materialize in properly powered randomized controlled trials.

Renal denervation is not a panacea, even in resistant hypertensive patients. Nowadays, it should not be considered as an alternative to well-conducted drug treatment, which includes documentation of adherence to and persistence of antihypertensive drugs and the use of recommended combinations of antihypertensive agents at the highest tolerated daily doses. The US Food and Drug Administration found the evidence summarized in this review too light to allow commercialization of the SYMPLECTICITY Catheter System. Medtronic Inc is, therefore, sponsoring the SYMPLECTICITY HTN-3 Trial, in which, at 27 locations, 530 patients will be randomized to renal denervation or a sham procedure (Table 1). Hypertension management before study enrollment will be more intensive as compared with the previous SYMPLECTICITY studies and involve the use of spironolactone. In both treatment groups, antihypertensive drugs will be continued throughout follow-up, which is limited to 6 months. Although a 24-hour blood pressure <135 mm Hg is an exclusion criterion, the primary end point is still the baseline-adjusted, between-group difference in the office systolic blood pressure, like in the SYMPLECTICITY HTN-2 Trial. The investigators are not blinded. Masking patients to randomization, as stated in the protocol, will be difficult, if not impossible. Table 1 summarizes the design characteristics of 4 other randomized controlled trials of renal denervation in the indication of treatment-resistant hypertension. At the time of writing of this review, ≥2 other randomized controlled trials were being set up or starting enrollment in Denmark (M.H. Olsen, Odense) and Norway (S.E. Kjeldsen, Oslo).

Unfortunately, manufacturers overtook European regulators in speed. CE-label certification of electric safety currently permits producers to sell catheter systems for renal
Renal Denervation for routine clinical use to any interventional facility, whereas the procedure should only be executed by experienced interventionalists in tertiary referral centers after careful selection of truly refractory hypertensive patients. Another major issue is that renal denervation is costly. If, as in the SYMPLICITY studies5–7 and several ongoing or planned studies (Tables 1 and 2), antihypertensive drug treatment must be continued, the procedure only inflates the costs of treatment-resistant hypertension without any proof of long-term benefit. In most countries, health care insurers do not reimburse the procedure. Inequality between patients in the possibility of accessing this new treatment modality is an additional argument to ban the procedure from regular hospital care until new evidence consolidates the initial claims of benefit.5–7

At this point in time, one can only hope that solid evidence from randomized clinical trials (Table 1) will not challenge the credibility of the large number of observational studies on renal denervation (Table 2). Such evidence should prevent that a promising technique will undergo the demise, as happened recently with devices for closure of the foramen ovale.78,79 Closing devices, not approved by the US Food and Drug Administration, were available for prevention of recurrent stroke,80 but the evidence rested only on small and poorly controlled observational studies.79 CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through Patent Foramen Ovale; NCT00201461)78 was a large randomized clinical trial involving 909 patients. It showed no benefit of closure with a device compared with medical therapy alone in terms of recurrent stroke or transient ischemic attack but instead increased risks of major vascular events and atrial fibrillation.78 The suggestion of the editorial, “Closing the Door Except for Trials,” might also be applicable for the legions of renal denervation systems (Table 2).80

Conclusions and Perspectives
Renal denervation for the management of treatment-resistant hypertension represents a more targeted approach for interfering with the sympathetic nervous system81 than the unselective sympatholytic surgery as practiced from the 1960s until the 1980s.82 Assuming that renal denervation would be efficacious in a large number of patients with a variety of conditions may be overly optimistic. Hypertension is not a single disease entity, as postulated by Platt.83 The evidence collected over the past 50 years demonstrated that Page et al84 and Pickering et al85 were right, respectively, in stating that hypertension is a mosaic of conditions and that arterial pressure is a continuous trait without dividing the line between normal and abnormal. Models of essential hypertension share the characteristic that renal sodium excretion is impaired at any degree of blood pressure.86–88 In rats, transplantation of a kidney from a hypertensive to a normotensive animal produces hypertension,89 although by definition the transplanted kidney is not innervated. Moreover, essential hypertension is characterized by generalized membrane abnormalities, which could affect the function of the vasculature and many organs in various ways.90,91 Isolated systolic hypertension in the elderly is caused by stiffening of the large arteries and not by an increased sympathetic tone.62

Future research on renal denervation as a way to treat hypertension should address unresolved issues, such as the size and durability of the antihypertensive, renal, and sympatholytic effects; long-term safety; quality of life; possibility to relax antihypertensive drug treatment after the procedure; cost-effectiveness; and, above all, the long-term benefit in terms of hard cardiovascular-renal outcomes. For now, renal denervation should remain the ultima ratio in adherent and truly resistant patients with severe hypertension, in whom all other efforts to reduce blood pressure have failed. The intervention should only be offered to patients within a context of clinical research in highly skilled tertiary referral centers that participate in international registries constructed independent of the manufacturers (Table 3). Consensus along these lines is rapidly growing, at least in Europe.92–94

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Disclosures
A.P. and J.R. were investigators in the SYMPLICITY HTN-2 Trial. A.P. organized a symposium on renal denervation (March 17, 2012, Diegem, Brussels) with nonbinding financial support from Medtronic Inc.

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<th>Table 3. Center Requirements for the Application of Renal Denervation in Treatment-Resistant Hypertension</th>
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<td><strong>Characteristic</strong></td>
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Modified according to the Joint United Kingdom Societies Consensus on Renal Denervation for Treatment-Resistant Hypertension (http://www.bhsoc.org/docs/The-Joint-UK-Societies'-Consensus-on-Renal-Denervation-for-resistant-hypertension.pdf).
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Renal Denervation: Ultima Ratio or Standard in Treatment-Resistant Hypertension
Alexandre Persu, Jean Renkin, Lutgarde Thijs and Jan A. Staessen

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Renal Denervation: *Ultima Ratio* or Standard in Treatment-Resistant Hypertension

Short title: Renal Denervation in Resistant Hypertension

Alexandre Persu, Jean Renkin, Lutgarde Thijs, Jan A. Staessen

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Summary and Keywords

Depending on studied populations and applied definitions, the prevalence of treatment-resistant hypertension (rHT) varies from 10% to 15%, but is higher in conditions associated with increased sympathetic drive, such as obesity, obstructive sleep apnea, diabetes or renal dysfunction. The SYMPLICITY studies recently demonstrated that reducing sympathetic tone by intravascular renal denervation (IRD) is feasible in rHT, but did not provide conclusive evidence on the size and durability of the antihypertensive, renal and sympatholytic effects, long-term safety, quality of life, the possibility to relax antihypertensive drug treatment, cost-effectiveness, and benefit in terms of long-term hard cardiovascular-renal outcomes. At the time of writing of this report, 28 IRD trials in various indications were registered at http://www.clinicaltrials.gov, but only seven had a randomized controlled design. In the US, IRD remains an investigational procedure that cannot be used in clinical practice, but in Europe, CE-label certification of electrical safety is permitting to market catheter systems to any interventional facility for regular clinical use. IRD should not be routinely applied as a substitute for the skilful management of resistant patients, which includes documentation of adherence to antihypertensive drugs, implementation of lifestyle measures and the use of recommended combinations of antihypertensive agents at the highest tolerated daily dose. For now, IRD should therefore remain the ultima ratio in adherent patients with severe rHT, in whom all other efforts to reduce blood pressure have failed. IRD should only be offered within a clinical research context at highly skilled tertiary referral centers that participate in international registries constructed independent of the manufacturers.

Keywords: ■ sympathetic nervous system ■ renal denervation ■ treatment-resistant hypertension
Hypertension affects an estimated 20% to 30% of the world’s adult population.\(^1\) Despite the availability of numerous safe and effective pharmacologic therapies, including single-pill combinations of 2–3 drugs, the percentage of patients achieving adequate blood pressure control meeting guideline targets remains low.\(^1,2\) Resistant hypertension is a blood pressure that remains above goal in spite of the concomitant use of antihypertensive medications from 3 or more drug classes.\(^3\) Patients who require more than 4 drug classes to have their blood pressure controlled are also considered to have resistant hypertension. Preferably, the regimen should include a diuretic and all doses should be optimal.\(^3\)

**Treatment-Resistant Hypertension**

**Epidemiology**

In clinical trials from 20% to 40% of randomized patients did not reach blood pressure targets.\(^4\) In the National Health and Nutrition Examination Survey (2003-2008), nonpregnant adults with hypertension were classified as resistant if their blood pressure was 140/90 mm Hg or higher and if they reported using antihypertensive medications from 3 different drug classes or drugs from 4 classes irrespective of blood pressure. Among the drug-treated population, the prevalence was 12.8%.\(^5\) Among 205,750 US patients with incident hypertension, 1.9% developed resistant hypertension within a median of 1.5 years of follow-up from starting up antihypertensive treatment (0.7 cases per 100 person-years of follow-up.).\(^6\) Risk factors for resistance include male sex,\(^6\) older age,\(^5,6\) obesity,\(^5\) and diabetes mellitus.\(^6\) In the Spanish Ambulatory Blood Pressure Monitoring Registry,\(^7\) 8295 of 68,045 treated patients (12.2%) had resistant hypertension, defined as an office blood pressure equal to or exceeding 140 mm Hg systolic and/or 90 mm Hg diastolic.\(^7\) Ambulatory monitoring showed that 62.5% of the resistant patients were truly resistant, whereas the remaining 37.5% had white-coat resistant hypertension.\(^7\) Treatment-resistant patients are more likely to have albuminuria, reduced renal function, and a history of diabetes mellitus, coronary heart disease, stroke or heart failure, and are therefore at high risk of cardiovascular complications.\(^3,5,6\)

**Role of the Sympathetic Nervous System**

Renal sympathetic nerves contribute to development and perpetuation of hypertension.\(^8\) In 99 young healthy men, norepinephrine and epinephrine concentrations during mental stress explained 12.7% of the variation in future systolic blood pressure after adjusting for initial resting blood pressure, family history, body mass index, and systolic blood pressure during a stress test.\(^9\) Increased renal norepinephrine spillover suggests that the sympathetic nervous drive to the kidneys is enhanced in untreated patients with essential hypertension. This particularly applies to hypertensive patients with renal insufficiency,\(^10\) obesity\(^11\) or diabetes mellitus.\(^12\) Sympathetic nerves to the kidney terminate in the juxtaglomerular apparatus, the renal tubules and blood vessels.\(^8\) The efferent sympathetic nervous outflow to the kidney stimulates renin release, enhances tubular reabsorption of sodium and water, and reduces renal blood flow.\(^8\) Afferent signals from the kidney modulate central sympathetic outflow and thereby contribute to the neurogenic elevation of blood pressure. Afferent reflexes enable total renal function to be self-regulated and balanced between the two kidneys.\(^8\)

Excessive activation of the sympathetic nervous system probably contributes to excessive fluid retention and the high blood pressure in treatment-resistant hypertension.\(^13\) Treatment-resistance is often associated with disorders characterized by enhanced sympathetic drive, such as obesity,\(^11,12\) obstructive sleep apnea,\(^14,15\) or chronic kidney disease.\(^14\) Surgical thoraco-abdominal sympathectomy and splanchnicectomy, as practiced from the 1940s to 1960s, resulted in substantial reduction of blood pressure and improved survival, but at a high cost of perioperative morbidity and long-term complications, such as bowel, bladder and sexual dysfunction and orthostatic hypotension.\(^16\) Because of these complications and the increasing availability of potent blood pressure lowering drugs with little side effects, surgical denervation was abandoned. Currently, techniques that modulate sympathetic nervous activity either directly via renal denervation\(^17,18\) or indirectly via baroreceptor stimulation,\(^19\) possibly offer new avenues for the management of treatment-resistant hypertension. This Brief review focuses on intravascular renal sympathetic denervation.
Assessment of Adherence

Medication-taking behavior encompasses both medication adherence and persistence, terms for which distinct definitions have been developed. Medication adherence can be defined as the extent to which a patient’s behavior, with respect to taking medication, corresponds with agreed recommendations from a healthcare provider. Medication persistence represents the accumulation of time from initiation to discontinuation of therapy. An important point to consider is that medication adherence varies over time. This is eloquently demonstrated by partial adherence, for example, in patients with highly variable medication adherence, whose medication-taking behavior often improves around the time of a scheduled clinic visit, but declines thereafter. Adherence can be readily evaluated using different methods, such as by validated questionnaires or pill counts, or more professionally by electronic pill boxes or measurement of biomarkers, drugs or their metabolites in body fluids.
References


Figure S1. Distribution of diastolic blood pressure according to different blood pressure targets in the Hypertension Optimal Treatment trial (reproduced with permission from reference 24). The results of the trial were considered as evidence in favor of lower blood pressure targets in diabetics. The Figure emphasizes the large overlap between the blood pressure distributions in randomized groups. A similar representation would allow assessing the separation versus overlap in the blood pressure outcomes in trials of renal denervation.