Resistant Hypertension
Medical Management and Alternative Therapies

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KEYWORDS

• Hypertension • Joint National Committee • Resistant hypertension • Secondary hypertension • Device

KEY POINTS

- Resistant hypertension (HTN) is failure to achieve goal blood pressure (BP) in spite of using a minimum of 3 antihypertensive drugs of different classes, at maximal tolerated doses, one of which must be a diuretic.
- In patients with resistant HTN, causes of pseudoresistance (both patient- and provider-related factors), and secondary HTN should be ruled out.
- Treatment of resistant HTN focuses on lifestyle modification and pharmacologic management. The basic principle for intervention is to ensure that all possible mechanisms for BP elevation are blocked.
- In general, most patients with resistant HTN should be on a renin angiotensin system blocker along with a calcium antagonist and a diuretic. Further medications can be added on an individual basis.
- Device-based therapies for resistant HTN should be reserved for those in whom available pharmacologic agents failed to control BP.

INTRODUCTION

Hypertension (HTN) is a major public health problem that affects approximately 1 billion people worldwide.[1] In the United States, 1 in 3 adults (≈73 million) has high blood pressure (BP).[2] Several studies, including meta-analyses, have demonstrated a linear relationship between BP level and the risk for cardiovascular events, such as stroke, myocardial infarction, congestive heart failure, and chronic kidney disease (CKD), with the risk of cardiovascular mortality doubles with every 20/10 mm Hg increase in systolic and diastolic BP.[3] In the United States, the total cost of treating HTN in 2010 was estimated to be $76 billion.[2] Persistent, suboptimal BP control is consequently the most common attributable risk for death worldwide, being responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease as well as the progression of CKD, and an estimated 7 million deaths and 64 million disability-adjusted life years annually.[4,5] Analyses of the National Health and Nutrition Examination Survey (NHANES) have demonstrated that not

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Cardiol Clin 33 (2015) 75–87
http://dx.doi.org/10.1016/j.ccl.2014.09.003
0733-8651/15/$ – see front matter

only is HTN awareness poor, but approximately 50% of hypertensive patients are not adequately treated to their goal BP of less than 140/90 mm Hg, with worse control rates in participants greater than 60 years of age, CKD and diabetes mellitus (DM).[6] Several, large HTN outcome trials also demonstrate a failure to achieve BP goals despite protocol-defined treatment regimens; 20% to 35% of participants were unable to achieve BP control despite receiving 3 antihypertensive medications or more.[7–9] These patients, by definition, are referred to as having refractory or resistant HTN.

Evaluation and treatment of patients with resistant HTN should be focused on identifying and removal of contributing factors, correct diagnosis and management of secondary causes, and use of effective multidrug regimens. Management of these patients often necessitates consultation with an HTN specialist.

DEFINITION OF RESISTANT HYPERTENSION

The Seventh Joint National Committee Report on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined resistant HTN as failure to achieve goal BP less than 140/90 mm Hg or less than 130/80 mm Hg in patients with DM or CKD in patients with HTN who are on maximum doses of an appropriate antihypertensive drug regimen consisting of 3 or more agents of different classes, including a diuretic.[10] The American Heart Association, however, defined resistant HTN as uncontrolled HTN despite at least 3 antihypertensive drugs or controlled HTN with at least 4 medications.[11] Although resistant HTN was not specifically addressed in the JNC-8 2014 Hypertension Guidelines, recommended goal BP was raised to less than 150/90 mm Hg in adults aged 60 years or older, and less than 140/90 mm Hg in patients less than 60 years old, including those with CKD, DM, or both.[12] Resistant HTN is not synonymous with uncontrolled HTN (**Box 1**). The latter includes all hypertensive patients who lack BP control under treatment, namely those receiving an inadequate treatment regimen, those with poor compliance, those who have elevated BP in the office but normal at home (white coat HTN) and those with undetected secondary HTN, as well as those with true treatment resistance.

Box 1
Definitions of various forms of hypertension

Resistant hypertension

Failure to achieve goal BP using a minimum of 3 antihypertensive drugs at maximal tolerated doses, 1 of which must be a diuretic.

Controlled resistant hypertension[11]

Patients who meet the definition of resistant hypertension but whose BP is controlled on maximal tolerated doses of 4 or more antihypertensive medications.

Refractory hypertension

Patients who meet the definition of resistant hypertension but whose BP is not controlled on maximal tolerated doses of 4 or more antihypertensive medications.

Pseudoresistance

Lack of BP control with appropriate treatment in a patient who does not have resistant hypertension.

White-Coat hypertension

Patients who have clinic/office BP readings above goal on at least 3 separate visits with 2 measurements taken at each visit, and at least 2 BP readings at or below goal taken outside the clinic/office, and show no evidence of end-organ damage.

Masked hypertension

Patients who have normal clinic but high ambulatory BPs (opposite of white-coat hypertension).

Abbreviation: BP, blood pressure.

PREVALENCE OF RESISTANT HYPERTENSION

Several clinical trials and epidemiologic data have estimated the prevalence of resistant HTN to be 20% to 30%,[7–9,13–15] although the exact prevalence has been difficult to determine owing to the lack of large, prospective cohort studies of patients with true resistant HTN. Individuals with resistant HTN are more likely to be older than age 55, male, non-Hispanic black, have a high body mass index, with a history of DM, renal dysfunction, and cardiovascular disease, including coronary heart disease, heart failure, and stroke.[6] A 2012 estimation by the American Heart Association based on NHANES 2005–2008 data showed that only 54% of hypertensive participants had a well-controlled BP on medications and that the prevalence of uncontrolled HTN despite being on 3 medications has almost doubled from 16% in 1998 through 2004 to 28% in 2005 through 2008.[16] In patients with controlled as well as uncontrolled HTN, the number of medications taken has increased with time.[6] NHANES data from 2005 through 2008 has shown that

28% of uncontrolled hypertensive patients are on at least 3 medications and 7.3% of controlled patients are on at least 4 BP medications. Based on the JNC-7 recommended BP goals for patients with CKD and DM, only 37% of patients with CKD[17] and 25% of those with diabetes were controlled to the recommended level.[18–20] One should keep in mind that many of these studies had limitations owing to the lack of control over medication adherence, use of suboptimal dosages and inappropriate drug combinations, lack of workup for patients with possible white coat HTN or secondary causes of HTN and therefore may have overestimated the prevalence of resistant HTN. Regardless, given the trend of a more obese and older population with increased numbers of comorbidities, such as DM and CKD, the prevalence of resistant HTN will most likely increase over the next decade.

PROGNOSIS

Evidence suggests that the prognosis of individuals with long-standing, poorly controlled, resistant HTN is unfavorable. Major cohort studies have shown that the extent of BP elevation directly increases the relative risk of stroke, myocardial infarction, kidney failure, and congestive heart failure in patients with HTN.[21–25] Ambulatory BP monitoring has played a special role in the diagnosis of resistant HTN, in differentiation with pseudoresistance, and in the assessment of cardiovascular risk and prognosis. Large cohort, cross-sectional studies have confirmed that individuals whose resistant HTN was diagnosed on the basis of ambulatory BP monitoring had a higher number of comorbidities, more target-organ damage (including left ventricular hypertrophy, impaired renal function, and microalbuminuria), and higher rates of cardiovascular morbidity and mortality, even after adjustment for different cardiovascular risk factors.[26–30] A nondipping, nocturnal BP pattern and the ambulatory arterial stiffness index are other variables that have been independently associated with increased cardiovascular events in patients with resistant HTN.[28,29] However, the extent to which the excess cardiovascular morbidity and mortality related to resistant HTN is reduced by adequate BP control remains unknown.

DIAGNOSIS, EVALUATION, AND MONITORING

Evaluation of patients with resistant HTN should focus on identifying patients who meet the definition criteria for resistant HTN, confirming true treatment resistance, identification of causes contributing to treatment resistance (including secondary causes of HTN), and documentation of target-organ damage. In most cases, treatment resistance is multifactorial in etiology, and factors such as lifestyle, medications, associated conditions, and identifiable causes contribute to the difficulty in achieving BP control in patients with resistant HTN (**Box 2**).

Pseudoresistant Hypertension

Pseudoresistance refers to lack of BP control with appropriate treatment in a patient who does not actually have resistant HTN. Various factors, such as suboptimal BP measurement, white coat effect, poor compliance with prescribed therapy, heavily calcified, sclerotic, and noncompressible

Box 2
Patient characteristics associated with treatment-resistant hypertension

- Older age
- High baseline blood pressure
- Obesity
- Smoking
- Excessive dietary salt intake
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy
- Black race
- Female sex
- Heavy alcohol intake (>3 drinks/d)
- Medications
  - Nonnarcotic analgesics
    - Nonsteroidal antiinflammatory agents, including aspirin
    - Selective cyclooxygenase-2 inhibitors
  - Sympathomimetic agents (decongestants, diet pills, cocaine)
  - Stimulants (amphetamine, methamphetamine)
  - Corticosteroids
  - Oral contraceptives
  - Cyclosporine and tacrolimus
  - Erythropoietin
  - Natural licorice
  - Herbal compounds (ginseng, ephedra, yohimbine, or ma huang)

arteries, and inappropriate medication combination or dosing can result in elevated BP readings and produce the misconception of resistant HTN (**Box 3**). Careful evaluation to exclude these factors should be performed on all patients who present with resistant HTN.

White coat HTN is a cause of pseudoresistance and refers to patients with elevated BP in the clinical setting while having significantly lower or normal blood pressures at home. The white coat effect is not uncommon and as many as 25% of patients referred for resistant HTN have been shown to be at goal BP control when ambulatory measurements are performed.[31,32] These patients have less target-organ damage compared with truly resistant hypertensive patients; however, their prognosis is worse than that of the general normotensive population.[25,33,34] In patients with white coat HTN, continued home BP or repeated ambulatory BP monitoring within 3 to 6 months is recommended because 20% to 25% of these patients may go on to develop true resistant HTN.[35]

Poor compliance is another common cause of apparent resistant HTN. Studies have shown that up to 50% of newly diagnosed hypertensive patients stop taking their medications during the first year, and only 40% of the remaining patients continue to take their medications over the next 5 to 10 years.[36–39] Single-point measurement of drug concentration in urine samples or therapeutic drug monitoring in serum samples in patients with resistant HTN have shown that 50% to 60% of patients had medication noncompliance.[40] This problem might be less common (about 16%) among patients followed by HTN specialists.[41] Once medication nonadherence is established, efforts should be made to identify the barriers to adherence. Factors that improve medication compliance include use of agents with a low side effect profile, avoidance of complicated dosing schedules, use of pill boxes, patient education regarding importance of BP management, and use of medications with lower out-of-pocket costs.[42,43] Electronic monitoring systems to assess drug adherence have demonstrated that one third of hypertensive patients who are poorly controlled on an adequately dosed triple therapy actually normalized their BP when drug adherence was monitored.[21,39,44]

Physician-related factors contributing to resistant HTN include inappropriate selection and dosing of medication, as well as "clinical inertia," defined as the conscious decision by a clinician to not adequately treat a condition despite knowing that it is present.[45] Clinical inertia, which is not uncommon among physicians, may be owing to lack of training and experience in the proper use of antihypertensive agents.[46] An open survey among primary care physicians in 1596 centers from 16 countries in four different continents showed that the main reasons for not intensifying antihypertensive treatment when BP remained above goal were the assumption that the time after starting the new drug was too short to attain its full effect, the satisfaction with a clear improvement of BP or with a BP nearing the goal, and the acceptance of good self-measurements.[47]

Box 3
Causes of pseudoresistant hypertension

- Improper technique
  - Wrong cuff size
  - One reading only
  - Patient not sitting quietly for 3–5 minutes before measurement
- White coat hypertension
- Recent smoking or caffeine intake before measurement
- Noncompressable calcified or atherosclerotic arteries in elderly
- Poor patient compliance
  - Medication side effects
  - Medication cost
  - Complicated drug dosing
  - Lack of patient education
- Physician-related factors
  - Inadequate/incorrect regimen
  - Physician inertia to add or modify drug regimen

Secondary Causes of Hypertension

Secondary causes of HTN are thought to occur in fewer than 10% of hypertensive individuals (**Box 4**). Correct diagnosis and treatment can help with achieving goal BP and in some cases, can lead to potential cure. Patients with known or suspected secondary HTN should be referred to an HTN specialist for workup and management.

Primary aldosteronism is the most common cause of resistant HTN, with a prevalence of 10% to 30%.[48–50] Hypokalemia may not be present early in the stage of the disease and is thought to be a late manifestation of this disorder.[50] A plasma aldosterone level/plasma renin

Box 4
Causes of secondary hypertension

Primary aldosteronism

Renovascular disease

- Atherosclerotic renal artery stenosis
- Fibromuscular dysplasia

Obstructive sleep apnea

Chronic kidney disease

Hypothyroidism/hyperthyroidism

Cushing syndrome

Pheochromocytoma

Coarctation of the aorta

Hyperparathyroidism

ratio of greater than 20 in the setting of a plasma aldosterone concentration greater than 15 ng/dL is highly suggestive of primary hyperaldosteronism. However, confirmatory assessment with an intravenous or oral salt suppression test is required to confirm the diagnosis. Adrenal vein sampling is the gold standard for localizing aldosterone-producing adenomas in patients with primary hyperaldosteronism. Medical management with a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone, has been shown to control BP in patients with primary aldosteronism, especially those with bilateral adrenal hyperplasia. Patients with unilateral adenoma should undergo surgical removal, which has been shown to cure HTN in 50% to 60% of patients.[51]

Renovascular disease is a common finding in hypertensive patients occurring in approximately 20% of patients undergoing cardiac catheterization.[52] More than 90% of cases are atherosclerotic in origin, with a higher likelihood occurring in older patients with a history of smoking, known atherosclerotic disease, especially peripheral artery disease, DM, and sudden loss of renal function after the initiation of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ARB). Even though several, prospective, randomized trials over the past decade have failed to demonstrate clinical advantages to revascularization compared with medical therapy (**Table 1**), management of patients with renovascular disease remains controversial.[34,53–58] Many criticized that these trials were subject to selection bias by excluding patients with severe cases of stenosis or HTN and progressive renal disease, and including patients with minor renovascular disease; therefore, the outcomes of these studies cannot be generalized to all patients. In addition, observational studies support the concept that BP control, improvement in kidney function, and reversal of progressive kidney injury can be improved in some patients after revascularization. Medical therapy should be the first line of treatment in patients with presumed renovascular HTN. For patients who fail medical therapy or

Table 1
Summary of trials of renal artery stenting versus medical therapy in the management of atherosclerotic renal artery stenosis

Study	Year	Country	Patient Population	Follow-up (mo)	Outcomes
ASTRAL[55]	2009	UK, Australia, New Zealand	806 patients with refractory HTN or CKD, 54% with bilateral RAS	34	No difference in BP, renal function or mortality between the groups
STAR[54]	2009	The Netherlands, France	138 patients with CKD; 48% with bilateral RAS	24	No difference in renal function; significant complication with the procedures
CORAL[53]	2013	US	947 patients with HTN or CKD, 20% with bilateral RAS	43	No difference in incidence of renal or cardiovascular events, or all-cause mortality; modest difference in systolic BP (−2 mm Hg) in stent group

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; HTN, hypertension; RAS, renal artery stenosis.

develop progressive loss of renal function, renal revascularization offers therapeutic benefit. In patients less than 50 years of age, especially women, fibromuscular dysplasia should be considered.

CKD is both a common cause and a complication of long-standing, poorly controlled HTN. In the antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, CKD, as indicated by a serum creatinine of greater than 1.5 mg/dL, was a strong predictor of failure to achieve goal BP.[7] Increased sodium and fluid retention, and consequently an expansion of intravascular volume, is the main factor leading to treatment resistance in patients with CKD.[59]

Obstructive sleep apnea (OSA) is very common in patients with resistant HTN, with prevalence rates of up to 83% based on an apnea–hypopnea index greater than 10 events per hour in patients with unsuspected sleep apnea.[60–65] OSA is both more common and more severe in men. A history of snoring and daytime sleepiness, especially in the presence of obesity, should prompt one to suspect OSA. Both nocturnal and daytime BP are increased with a lack of nocturnal dipping. The more severe the sleep apnea, the less likely BP is controlled despite the use of an increasing number of medications.[62,65] However, results of several clinical trials have shown only modest BP reductions (3–5 mm Hg) after treatment of OSA with continuous positive airway pressure.[63,64,66]

Pheochromocytoma is very rare, with a prevalence in a general hypertensive population of only 0.1% to 0.6%.[67] The diagnosis should be considered in a hypertensive patient with a combination of headaches, palpitations, and sweating, typically occurring in an episodic fashion. The best screening test for pheochromocytoma is plasma free metanephrines (normetanephrine and metanephrine), which carries a 99% sensitivity and an 89% specificity. Surgical resection of the tumor is the treatment of choice for this group of patients.

TREATMENT

Lifestyle Modification

All patients with HTN should be counseled about lifestyle modification. Although not specifically evaluated in patients with resistant HTN, lifestyle modifications, such as weight loss, dietary salt reduction, diet rich in fruit and vegetables and low in saturated fats (ie, the Dietary Approaches to Stop Hypertension [DASH] diet), increased physical activity, limiting daily alcohol consumption to no more than 2 drinks for men and 1 drink for women, and ingestion of a high-fiber, low-fat diet, have clear benefit in terms of reducing BP.[68–71] In the United States, the average sodium consumption is approximately 8.5 g/d. High sodium intake is among the major contributing factors to resistant HTN and a sodium restriction to 1.7 g/d is associated with a reduction in BP with a more pronounced effects in patients with resistant HTN.[23]

Pharmacologic Treatment

Inappropriate antihypertensive drug combinations or suboptimal dosing are the most common causes of resistant HTN. In a retrospective cohort study in a large population with resistant HTN, only 3% and 5.9% of patients were on chlorthalidone or a mineralocorticoid receptor antagonist, respectively, both of which are evidence-based recommended antihypertensive agents.[72]

The basic principle for intervention in resistant HTN is to ensure that all possible mechanisms for BP elevation, including volume expansion, renin–angiotensin–aldosterone system activation, and peripheral vascular resistance, are blocked. Moreover, there are few fixed-dose combination antihypertensive agents that have been approved by the Food and Drug Administration for use as first-line therapy. These have been especially useful for patients with resistant HTN who have compliance problems.[73] In general, most patients with resistant HTN should be on a renin–angiotensin–aldosterone system blocker along with a calcium antagonist and a diuretic, all of which are preferred to be prescribed in full dosages and for appropriate time intervals.

An appropriate diuretic to decrease volume overload remains a cornerstone of therapy and can help about 60% of patients achieve BP goals.[13,14,41,74] Chlorthalidone, a thiazidelike diuretic, has been shown to provide greater BP reduction, longer duration of action, and better cardiovascular risk profile compared with hydrochlorothiazide 50 mg/d,[75,76] and was the only diuretic recommended by the American Heart Association position statement in 2008.[11] In patients with CKD stage 4 or 5 (glomerular filtration rate of <30 mL/min), loop diuretics should be used for effective volume and BP control.[11] Furosemide or bumetanide must be given twice or even thrice daily, because the once-daily use is associated with intermittent natriuresis and consequent reactive sodium retention caused by increases in renin–angiotensin–aldosterone system activity. Torsemide has a longer duration of action; therefore, once or twice daily dosing may be sufficient.

Aldosterone blockade by adding spironolactone or eplerenone to a 3-medication regimen may be beneficial in reducing BP in patients with or without

primary hyperaldosteronism, especially in certain settings, such as obesity or sleep apnea.[77–83] However, results of several randomized and nonrandomized studies on the BP-lowering effect of aldosterone antagonists has been inconclusive.[84–86] A meta-analysis of 13 studies (3 randomized and 10 observational) in 2640 patients, that evaluated the antihypertensive benefit of aldosterone antagonists as an add-on therapy in patients with resistant HTN, showed an average systolic BP reduction between 16 and 20 mm Hg in patients treated with aldosterone antagonists.[83] Reduction in BP was more pronounced in patients with a baseline systolic BP greater than 150 mm Hg; however, a mild but significant increase in serum potassium and creatinine was also present in treated patients. Amiloride is an inhibitor of the aldosterone-regulated epithelial sodium channel in the distal nephron, and in a prospective, randomized, placebo-controlled, double-blind study of African-American patients, it was shown to provide a reduction in BP comparable to spironolactone.[87]

β-Blockers should be used as fifth-line drug therapy unless there are compelling indications, such as congestive heart failure or prior myocardial infarction, to initiate them earlier. Large clinical trials have shown inferior cardiovascular protection with the combination of β-blockers and thiazide diuretics in comparison with combinations of calcium channel blockers plus an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker plus thiazide diuretic.[8]

Device Therapies for Resistant Hypertension

Despite lifestyle modification and the various pharmacologic agents available, there remains a subset of patients who are unable to reach goal BP. Over the last decade, 2 new approaches to treat resistant HTN have been developed that mainly target the sympathetic nervous system: catheter-based renal denervation (RDN) ablation therapy and carotid sinus baroreflex activation therapy (BAT; **Table 2**). Increased sympathetic tone increases peripheral vascular resistance, which leads to increased renin secretion, reduced renal blood flow, and increased sodium retention. Stimulation of carotid baroreceptors via BAT or ablation of the renal nerve via RDN, leads to sustained reduction in arterial pressure and heart rate by suppressing sympathetic activity.

Carotid Baroreflex Activation Therapy

BAT uses a carotid sinus baroreceptor stimulator that is surgically implanted by means of open carotid exposure and activates the receptors with variable and programmable amounts of energy. Similar to a pacemaker, the generator is implanted in a pocket in the infraclavicular space. Electrical stimulation of the carotid baroreceptors has been shown to cause a depressor response through sympathetic inhibition. Both the Rheos system (CVRx, Minneapolis, MN, USA) and the newer generation BAT, Barostim neo (CVRx), have been shown to reduce BP in patients with resistant HTN.[88–93] The efficacy and safety of Rheos system was investigated in the phase II, multicenter, nonrandomized Device Based Therapy of Hypertension Trial (DEBuT-HT) in 45 patients with drug-resistant HTN. After 1 year of therapy, patients demonstrated a mean decrease of 30 ± 6 mm Hg for systolic BP, which was maintained for 2 years.[93] Shortly thereafter, a double-blind, randomized, prospective, multicenter, placebo-controlled trial in the United States of 265 subjects with resistant HTN, demonstrated a reduction of systolic BP by greater than 30 mm Hg with 55% of patients achieved goal BP with BAT,[90] which persisted for up to 53 months.[91] However, this trial did not meet the acute efficacy endpoint for the proportion of patients with at least a 10 mm Hg-drop in systolic BP with a superiority margin of 20% between the 2 groups at 6 months. In addition, the implant procedure safety did not meet the pre-specified 82% event-free objective performance criterion; however, the adverse event profile compared favorably with results from endarterectomy trials, which were more like the dissection for the Rheos procedure in the carotid region.

Owing to the higher than expected device-related complications with the Rheos system in the pivotal trial, a second-generation system for delivering BAT, the Barostim neo system, was developed which involves unilateral lead placement (instead of bilateral with the Rheos system), a much smaller implantable device, and a safety profile comparable with that of a pacemaker. In a single-arm, open-label study of 30 patients with resistant HTN (including patients with prior RDN), a systolic BP reduction of 26 mm Hg after 6 months was demonstrated in patients with baseline systolic BP of 172 mm Hg, which is comparable to the results seen with the Rheos system, with minor procedure-related complications.[92] Currently, a randomized BP efficacy trial has started in the United States with the Barostim neo system. The Barostim neo is approved for sale in Europe; however, the indication is restricted to patients with therapy-resistant HTN or heart failure. However, it is registered as an investigational device and limited to investigational use by the US law.

In addition to BP control, BAT may provide additional cardiovascular benefit. In early stage

Table 2
Trials on device-based approaches to management of resistant hypertension

Study	Year	Study Type	No. of Patients	Mean SBP	No. of Antihypertensive Medications	Outcome Summary
Carotid baroreceptor activation therapy						
DEBuT-HT[93]	2010	Single arm, Open label	45	179	5.0	Reduction in systolic BP of 30 mm Hg at 1, 2 and 3 y; 67% of patients with systolic BP <140 mm Hg at 3 y
Rheos Pivotal[90]	2011	2:1 randomized (active: control)	265	168 ± 26	5.2 ± 1.6	Reduction in systolic BP by 26 mm Hg at 6 mo and 35 mm Hg at 12 mo; 63% of patients achieved SBP <140 mm Hg at 1 y
Barostim neo[92]	2012	Single arm, open label	30	172 ± 20	6.1 ± 2.7	Reduction in systolic BP by 26 mm Hg at 6 mo; reduction in systolic BP by 22 mm Hg in subset of patients with prior RDN therapy
Renal denervation						
Symplicity HTN-1[95]	2009	Single arm, Open label	45	177 ± 19	4.7 ± 1.4	Reduction in systolic BP by 22 mm Hg at 6 and 27 mm Hg at 12 mo
Symplicity HTN-2[96]	2010	1:1 Randomized	106	178 ± 18	5.2 ± 1.5	Reductions in systolic BP by 32 mm Hg at 6 mo in patients treated with RDN; no difference in 24-h ambulatory BP
Symplicity HTN-3[97]	2014	2:1 Randomized (active: control)	535	180 ± 16	5.1 ± 1.4	No difference in systolic BP between the groups at 6 mo (14 mm Hg SBP reduction in RDN group, 12 mm Hg SBP reduction in control group)

Abbreviations: BP, blood pressure; RDN, renal denervation; SBP, systolic BP.

heart failure patients with resistant HTN, BAT lowered BP and effectively reversed cardiac remodeling with a significant reduction in left ventricular mass index and concentric hypertrophy.[94] In another analysis, 3 months of BAT reduced left ventricular mass index similarly to a 12-month course of ARB therapy, and a 12-month therapy with BAT provided twice the effect of reducing left ventricular mass index as did 12 months of ARB therapy.

Renal Denervation Therapy

RDN therapy using a radiofrequency ablation catheter that directly targets the sympathetic nerves adjacent to the renal artery is a recently

proposed, minimally invasive procedure to control BP.[95–97] The Symplicity Renal Denervation System involves an endovascular energy delivery catheter and an automated generator. Once in place within the renal artery, the tip of the catheter is placed against the arterial wall in several places where it delivers radiofrequency energy to the surrounding sympathetic nerves. Typical procedure comprises 4 to 6 treatments for each renal artery.[95]

The Symplicity -1 study was the first clinical trial that enrolled 50 patients with resistant HTN (on 4.7 $\pm$ 1.4 medications at the beginning of the study) and an estimated glomerular filtration rate of greater than 45 mL/min/1.73 m^2, at 5 Australian and European centers.[95] In this cohort study, RDN lowered office systolic BP by 14 mm Hg at 1 month and by 27 mm Hg at 12 months; 85% of the patients responded to therapy with a reduction of office systolic BP exceeding 10 mm Hg. RDN successfully restored nocturnal dipping in 50% of previously nondipping or reverse-dipping patients.[95] However, the study did not include a control group. In a subsequent multicenter, prospective, randomized study, Symplicity HTN-2, patients with resistant HTN were randomly assigned to undergo RDN with medical therapy (n = 52) or to medical therapy alone (control group; n = 54).[96] Similar to the Symplicity HTN-1 trial, patients with type 1 diabetes and a glomerular filtration rate of less than 45 mL/min/1.73 m^2 were excluded. Six-month office-based BP measurements were significantly lower in the RDN group (32/12 mm Hg reduction compared with 0/1 mm Hg change in control group, both from a baseline of 178/96 mm Hg). However, home BP and 24-hour ambulatory BP were similar in the two groups.[96] Symplicity HTN-3, a large, US, randomized, controlled trial included 535 patients with resistant HTN who were assigned in a 2:1 ratio to RDN or a sham procedure. However, this study showed no difference in the office BP or 24-hour ambulatory BP in the RDN group compared with the sham procedure group treated with medical therapy alone.[97,98]

Although reported procedure-related complications of RDN in all 3 Symplicity-HTN trials were low, recent reports suggest that diffuse renal artery constriction owing to vasospasm and local tissue damage at the ablation site with endothelial edema and thrombus formation may occur after RDN.[99,100]

SUMMARY

Treating resistant HTN, particularly in patients who are already prescribed 4 or more drugs, is a true challenge. Entertaining correct diagnosis, ruling out secondary causes of HTN, dealing with patients' noncompliance and proper medication dosing, and selecting appropriate additional BP-lowering agents are issues that commonly need attention. Choice of medication should be based not only on the antihypertensive efficacy but also on the incremental cost, the adverse effect profile, and its potential cardiovascular benefits. Ongoing investigation and research on development of new fixed-dose combination medications and innovative medical, minimally invasive or invasive methods of BP management are arenas never to be left abandoned.

REFERENCES

1. Wolf-Maier K, Cooper R, Banegas J, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003;289:2363–9.
2. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):e21–181.
3. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomized trials. BMJ 2008;336:1121–3.
4. Mancia G, DeBacker G, Dominiczak A, et al. ESH-ESC Practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens 2007;25(9):1751–62.
5. Perkovic V, Huxley R, Wu Y, et al. The burden of blood pressure-related disease: a neglected priority for global health. Hypertension 2007;50: 991–7.
6. Egan B, Zhao Y, Axon R, et al. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation 2011; 124:1046–58.
7. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288(23):2981–97.
8. Dahlof B, Devereux R, Kjeldsen S, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint Reduction in Hypertension

Study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995–1003.
9. Pepine C, Handberg E, Cooper-DeHoff R, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–16.
10. Chobanian A, Bakris G, Black H. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.
11. Calhoun D, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 2008;51:1403–19.
12. James P, Oparil S, Carter B. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507–20.
13. Black H, Elliott W, Grandits G, et al. Principal results of the controlled onset verapamil investigation of cardiovascular end points (CONVINCE) trial. JAMA 2003;289(16):2073–82.
14. Jamerson K, Weber M, Bakris G, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial. N Engl J Med 2008;359(23):2417–28.
15. Sarafidis P, Bakris G. State of hypertension management in the United States: confluence of risk factors and the prevalence of resistant hypertension. J Clin Hypertens (Greenwich) 2008;10:130–9.
16. Roger V, Go A, Lloyd-Jones D, et al. Heart disease and stroke statistics 2012 update: a report from the American Heart Association. Circulation 2012;125(1):e2–220.
17. Peralta C, Hicks L, Chertow G, et al. Control of hypertension in adults with chronic kidney disease in the United States. Hypertension 2005;45:1119–24.
18. Hajjar I, Kotchen T. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA 2003;290:199–206.
19. Ong K, Cheung B, Man Y, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. Hypertension 2007;49:69–75.
20. Sarafidis P, Li S, Chen S, et al. Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med 2008;121(4):332–40.
21. McAdam-Marx C, Ye X, Sung JC, et al. Results of a retrospective, observational pilot study using electronic medical records to assess the prevalence and characteristics of patients with resistant hypertension in an ambulatory care setting. Clin Ther 2009;31:1116–23.
22. Daugherty S, Powers J, Magid D, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012;125(13):1635–42.
23. Gupta A, Nasothimiou E, Chang C, et al. Baseline predictors of resistant hypertension in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT): a risk score to identify those at high-risk. J Hypertens 2011;29(10):2004–13.
24. Persell S. Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension 2011;57(6):1076–80.
25. Pierdomenico S, Lapenna D, Bucci A, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens 2005;18:1422–8.
26. de-la-Sierra A, Banegas J, Oliveras A, et al. Clinical differences between resistant hypertensives and patients treated and controlled with three or less drugs. J Hypertens 2012;30(6):1211–6.
27. de-la-Sierra A, Segura J, Banegas J, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 2011;57:898–902.
28. Muxfeldt E, Cardoso C, Dias V, et al. Prognostic impact of the ambulatory arterial stiffness index in resistant hypertension. J Hypertens 2010;28:1547–53.
29. Muxfeldt E, Cardoso C, Salles G. Prognostic value of nocturnal blood pressure reduction in resistant hypertension. Arch Intern Med 2009;169:874–80.
30. Salles G, Cardoso C, Muxfeldt E. Prognostic influence of office and ambulatory blood pressures in resistant hypertension. Arch Intern Med 2008;168:2340–6.
31. Brown M, Buddle M, Martin A. Is resistant hypertension really resistant? Am J Hypertens 2001;14:1263–9.
32. Hermida R, Ayala D, Calvo C, et al. Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension. Hypertension 2005;46:1053–9.
33. Muxfeldt E, Bloch K, Nogueira A, et al. Twenty-four hour ambulatory blood pressure monitoring pattern of resistant hypertension. Blood Press Monit 2003;8:181–5.
34. Textor SC, Lerman LO. Renal artery stenosis: medical versus interventional therapy. Curr Cardiol Rep 2013;15(10):409.
35. Muxfeldt E, Fiszman R, deSouza F, et al. Appropriate time interval to repeat ambulatory blood

pressure monitoring in patients with white-coat resistant hypertension. Hypertension 2012;59: 384–9.
36. Daugherty S, Powers J, Magid D, et al. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. Hypertension 2012;60: 303–9.
37. Mazzaglia G, Mantovani L, Sturkenboom M, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J Hypertens 2005;23:2093–100.
38. VanWijk B, Klungel O, Heerdink E, et al. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens 2005;23:2101–7.
39. Vrijens B, Vincze G, Kristanto P, et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ 2008;336:1114–7.
40. Jung O, Gechter JL, Wunder C, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. Journal of hypertension 2013;31(4):766–74.
41. Garg J, Elliot W, Folker A, et al. Resistant hypertension revisited: a comparison of two university-based cohorts (RUSH Hypertensive Service). Am J Hypertens 2005;18(5 Pt 1):619–26.
42. Haynes R, Yao X, Degani A, et al. Interventions to enhance medication adherence. Cochrane Database Syst Rev 2005;(4):CD000011.
43. Takiya L, Peterson A, Finley R. Meta-analysis of interventions for medication adherence to antihypertensives. Ann Pharmacother 2004;38:1617–24.
44. Burnier M, Schneider MP, Chiolero A, et al. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. Journal of Hypertension 2001;19(2):335–41.
45. Phillips L, Branch W, Cook C, et al. Clinical inertia. Ann Intern Med 2001;135:825–34.
46. Oliveria S, Lapuerta P, McCarthy B, et al. Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med 2002;162:413–20.
47. Ferrari P. Reasons for therapeutic inertia when managing hypertension in clinical practice in non-Western countries. J Hum Hypertens 2009; 23(3):151–9.
48. Aronova A, Fahey T, Zarnegar R. Management of hypertension in primary aldosteronism. World J Cardiol 2014;6(5):227–33.
49. Calhoun D, Nishizaka M, Zaman M, et al. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 2002;40: 892–6.
50. Fardella C, Mosso L, Gómez-Sánchez C, et al. Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. J Clin Endocrinol Metab 2008;85:1863–7.
51. Rossi GP, Cesari M, Cuspidi C, et al. Response to effectiveness of adrenalectomy and aldosterone antagonists for long-term treatment of primary aldosteronism. Hypertension 2013;62(4):e14.
52. Aqel RA, Zoghbi GJ, Baldwin SA, et al. Prevalence of renal artery stenosis in high-risk veterans referred to cardiac catheterization. J Hypertens 2003;21(6):1157–62.
53. Cooper C, Murphy T, Cutlip D, et al, For The CORAL Investigators. Stenting and medical therapy for atherosclerotic renal artery stenosis. N Engl J Med 2014;370(1):13–22.
54. Bax L, Woittiez A, Kouwenberg H, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med 2009;150:840–8.
55. Wheatley K, Ives N, et al, For The ASTRAL Investigators. Revascularization versus medical therapy for renal- artery stenosis. N Engl J Med 2009; 361(20):1953–62.
56. Watson P, Hadjipetrou P, Cox S, et al. Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. Circulation 2000;102:1671–7.
57. Chrysochou C, Kalra PA. Current management of atherosclerotic renovascular disease–what have we learned from ASTRAL? Nephron Clin Pract 2010;115(1):73–81.
58. Burket M, Cooper C, Kennedy D, et al. Renal artery angioplasty and stent placement: predictors of a favorable outcome. Am Heart J 2000;139:64–71.
59. Campese VM, Mitra N, Sandee D. Hypertension in renal parenchymal disease: why is it so resistant to treatment? Kidney Int 2006;69(6):967–73.
60. Logan A, Perlikowski S, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001;19:2271–7.
61. Nieto F, Young T, Lind B, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829–36.
62. Lavie P, Hoffstein V. Sleep apnea syndrome: a possible contributing factor to resistant. Sleep 2001;24(6):721–5.
63. Lozano L, Tovar JL, Sampol G, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. Journal of hypertension 2010; 28(10):2161–8.
64. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013;310(22):2407–15.

65. Grote L, Hedner J, Peter J. Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension. J Hypertens 2000;18:679–85.
66. Duchna H, Orth M, Schultze-Werninghaus G. Long-term effects of nasal continuous positive airway pressure on vasodilatory endothelial function in obstructive sleep apnea syndrome. Sleep Breath 2005;9:97–103.
67. Hodin R, Lubitz C, Phitayakorn R, et al. Diagnosis and management of pheochromocytoma. Curr Probl Surg 2014;51(4):151–87.
68. Aucott L, Poobalan A, Smith W, et al. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. Hypertension 2005;45:1035–41.
69. Vollmer W, Sacks F, Ard J, et al, DASH Sodium Trial Collaborative Research Group. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med 2001;135:1019–28.
70. Whelton S, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med 2002; 136:493–503.
71. Dimeo F, Pagonas N, Seibert F, et al. Aerobic exercise reduces blood pressure in resistant hypertension. Hypertension 2012;60:653–8.
72. Zhang X, Eirin A, Li ZL, et al. Angiotensin receptor blockade has protective effects on the post-stenotic porcine kidney. Kidney Int 2013;84(4): 767–75.
73. Khanna A, Lefkowitz L, White W. Evaluation of recent fixed-dose combination therapies in the management of hypertension. Curr Opin Nephrol Hypertens 2008;17:477–83.
74. White WB, Calhoun DA, Samuel R. Improving blood pressure control: increase the dose of diuretic or switch to a fixed-dose angiotensin receptor blocker/diuretic? the valsartan hydrochlorothiazide diuretic for initial control and titration to achieve optimal therapeutic effect (Val-DICTATE) trial. Journal of clinical hypertension 2008;10(6):450–8.
75. Ernst M, Carter B, Goerdt C, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006;47:352–8.
76. Khosla N, Chua D, Elliott W, et al. Are chlorthalidone and hydrochlorothiazide equivalent blood-pressure-lowering medications? J Clin Hypertens (Greenwich) 2005;7:354–6.
77. Nishizaka M, Zaman M, Calhoun D. Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens 2003;16:925–30.
78. Pratt-Ubunama M, Nishizaka M, Boedefeld R, et al. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. Chest 2007;131:453–9.
79. Cheung CM, Chrysochou C, Shurrab AE, et al. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. Nephrol Dial Transplant 2010;25(4):1133–40.
80. Alvarez-Alvarez B, Abad-Cardiel M, Fernandez-Cruz A, et al. Management of resistant arterial hypertension: role of spironolactone versus double blockade of the renin-angiotensin-aldosterone system. Journal of Hypertension 2010;28(11): 2329–35.
81. Calhoun D, Nishizaka M, Zaman M, et al. Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. Chest 2004;125:112–7.
82. Calhoun DA, White WB. Effectiveness of the selective aldosterone blocker, eplerenone, in patients with resistant hypertension. Journal of the American Society of Hypertension JASH 2008;2(6): 462–8.
83. Liu G, Zheng XX, Xu YL, et al. Effect of aldosterone antagonists on blood pressure in patients with resistant hypertension: a meta-analysis. Journal of Human Hypertension 2014.
84. Hanselin MR, Saseen JJ, Allen RR, et al. Description of antihypertensive use in patients with resistant hypertension prescribed four or more agents. Hypertension 2011;58(6):1008–13.
85. Saha C, Eckert GJ, Ambrosius WT, et al. Improvement in blood pressure with inhibition of the epithelial sodium channel in blacks with hypertension. Hypertension 2005;46(3):481–7.
86. Cefalu WT, Boulton AJ, Tamborlane WV, et al. Status of Diabetes Care: "It just doesn't get any better… or does it?". Diabetes Care 2014;37(7): 1782–5.
87. Lane DA, Beevers DG. Amiloride 10 mg is less effective than spironolactone 25 mg in patients with hypertension resistant to a multidrug regime including an angiotensin-blocking agent. Journal of Hypertension 2007;25(12):2515–6.
88. Bisognano J, Sloand J, Papademetriou V, et al. An implantable carotid sinus baroreflex activating system for drug-resistant hypertension: interim chronic efficacy results from the multicenter Rheos Feasibility Trial. Circulation 2006;114(Suppl 18):II575.
89. Illig K, Levy M, Sanchez L, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: surgical technique and short-term outcome from the multicenter phase II Rheos Feasibility Trial. J Vasc Surg 2006;44(6):1213–8.
90. Bisognano J, Bakris G, Nadim M, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. J Am Coll Cardiol 2011;58: 765–73.

91. Bakris G, Nadim M, Haller H, et al. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. J Am Soc Hypertens 2012;6:152–8.
92. Hoppe U, Brandt M, Wachter R, et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. J Am Soc Hypertens 2012;6:270–6.
93. Scheffers IJ, Kroon AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. Journal of the American College of Cardiology 2010;56(15):1254–8.
94. Bisognano J, Kaufman C, Bach D, et al, DEBuT-HT, Rheos Feasibility Trial Investigators. Improved cardiac structure and function with chronic treatment using an implantable device in resistant hypertension: results from European and United States trials of the Rheos system. J Am Coll Cardiol 2011;57:1787–8.
95. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373:1275–81.
96. SYMPLICITY-HTN-2-Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The SYMPLICITY HTN-2 Trial): a randomized controlled trial. Lancet 2010;376(9756):1903–9.
97. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. The New England Journal of Medicine 2014;370(15):1393–401.
98. Bakris GL, Townsend RR, Liu M, et al. Impact of Renal Denervation on 24-hour Ambulatory Blood Pressure: Results from SYMPLICITY HTN-3. Journal of the American College of Cardiology 2014. May 17.
99. Stabile E, Ambrosini V, Squarcia R, et al. Percutaneous sympathectomy of the renal arteries: the OneShot Renal Denervation System is not associated with significant vessel wall injury. EuroIntervention 2013;9(6):694–9.
100. Templin C, Jaguszewski M, Ghadri JR, et al. Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison with the Simplicity catheter system and the EnligHTN multi-electrode renal denervation catheter. Eur Heart J 2013;34(28):2141–8, 2148b.