ANNUAL REVIEWS

Annual Review of Medicine

Management of Resistant Hypertension

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Annu. Rev. Med. 2024. 75:443–57

First published as a Review in Advance on September 22, 2023

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-050922-052605

Keywords

adherence, renal denervation, emerging drugs, device-based therapies

Abstract

Resistant hypertension (RH) is a severe form of hypertension associated with increased cardiovascular risk. Although true RH affects less than 10% of the patients receiving antihypertensive therapy, the absolute number is high and continues to increase. The workup of these patients requires screening for secondary hypertension and pseudoresistance, including poor adherence to prescribed medicines and the white-coat phenomenon. The treatment of RH consists of lifestyle modifications and pharmacological therapies. Lifestyle modifications include dietary adjustments, weight loss, physical activity, and limiting alcohol consumption; pharmacological therapies include diuretics, mineralocorticoid receptor antagonists, beta blockers, angiotensin receptor–neprilysin inhibitors, and others. Over the last 15 years, interventional approaches have emerged as adjunct treatment options; we highlight catheter-based renal denervation. This review summarizes the rationales and latest clinical evidence and, based thereon, proposes an updated algorithm for the management of RH.

INTRODUCTION

Arterial hypertension is an important risk factor for cardiovascular (CV) morbidity and mortality (1). Lowering blood pressure (BP) using antihypertensive medications reduces all-cause death and CV complications, including heart failure, coronary artery disease, renal failure, and stroke (2, 3). Despite the availability of safe and effective treatments, including lifestyle measures, pharmacological therapy, and, more recently, interventional approaches, disease awareness and rates of guideline-recommended BP control remain poor (4). BP control rates are particularly low in racial and ethnic minorities (5).

Definition of Resistant Hypertension

Resistant hypertension (RH) is defined as BP above target despite the use of at least three antihypertensive drugs of different substance classes, including a diuretic (**Table 1**) (6–10), in appropriate doses and combination. Pseudo-RH must be excluded before concluding that the patient is truly treatment resistant. Pseudo-RH can result from (*a*) poor adherence to prescribed medicines; (*b*) the white-coat phenomenon, in which office BP is elevated at normotensive ambulatory BP; (*c*) incorrect BP measurements; and (*d*) irrational therapy regimens and/or inadequate dosing. Therefore, ambulatory BP measurements and drug adherence testing may be helpful in the workup of apparent RH. Since adherence to medication is dynamic over time (11) and typically decreases with increasing treatment duration and intensity, periodic assessment of adherence should be considered. The 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) and 2023 ESH guidelines specifically recommend appropriate lifestyle measures in addition to pharmacological therapy (7, 10).

Epidemiology

In a meta-analysis including data from 91 cohort or cross-sectional studies comprising more than 3.2 million patients, the prevalence of apparent and true RH was 15% and 10% in treated patients

Table 1 Definition of resistant hypertension

	ACC/AHA (2017) (6)	ESC/ESH (2018) (7)	NICE (2019)	Japanese (2019) (8)	ISH (2020) (9)	ESH 2023 (10)
Definition	Office BP ≥130/80 mm Hg despite ≥3 antihypertensive medications at optimal doses, including a diuretic, if possible	Office BP ≥140/90 mm Hg (adults <80 years) despite the recommended treatment strategy, including appropriate lifestyle measures and treatment with optimal or best-tolerated doses of ≥3 drugs, which should include a diuretic	Clinic BP ≥140/90 mm Hg (adults <80 years) despite optimal tolerated doses of an ACEi/ARB + CCB + thiazide-like diuretic	Office BP ≥130/80 mm Hg (adults <75 years) despite use of ≥3 antihypertensive drugs or BP control with ≥4 antihypertensive drugs	Office BP >140/90 mm Hg despite optimal or maximally tolerated doses of ≥3 antihypertensive drugs	Office BP ≥140/90 mm Hg despite the maximum recommended and tolerated doses of an ACEi/ARB + CCB + thiazide/thiazide-like diuretic
Out-of-office BP measurement	ABPM, HBPM, or work BP readings required	ABPM or HBPM required	ABPM or HBPM (<135/85 mm Hg for adults <80 years) required	ABPM or HBPM (<125/75 mm Hg for adults <75 years) required	Out-of-office BP measurement required to exclude white-coat hypertension	ABPM (HBPM if ABPM is not feasible)

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HBPM, home blood pressure monitoring; ISH, International Society of Hypertension; NICE, National Institute for Health and Care Excellence.

with hypertension, respectively (12). The prevalence in the included studies ranged from 5% to 35%, highlighting three challenges in determining the true prevalence of RH. First, medical societies and studies have used various definitions of RH over time. Analyses of the Systolic BP Intervention (SPRINT) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, for example, showed that the prevalence of RH increased from 7.5% and 14%, respectively, to 22% and 36%, respectively, when applying the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (≥130/80 mm Hg) instead of their previous guidelines (≥140/90 mm Hg) (13). Second, the prevalence of RH depends on how rigorously causes of pseudo-RH, including nonadherence, inaccurate measurement methods, and white-coat hypertension, have been excluded. In some studies, more than two-thirds of the patients with apparent RH were pseudoresistant (12). Third, shifting from a sequential therapy with up-titration of each agent before adding further antihypertensives to the initial use of low-dose combination therapies targeting different BP-lowering mechanisms might affect the prevalence of RH (14).

Compared with the general population of patients with hypertension, the prevalence of RH is higher among patients with diabetes mellitus (15) and hypertension-mediated organ damage, including chronic kidney disease (12, 15) and left ventricular hypertrophy (16). Other risk factors for RH are the number of baseline antihypertensive drugs, baseline systolic BP, older age, male sex, obesity, and black race (15, 17). Moreover, somatization-related psychological factors strongly predict the severity of RH (18). In turn, RH is a risk factor for chronic kidney and CV disease, including myocardial infarction, stroke, and particularly heart failure (19).

Pathophysiology

RH is a state of increased sympathetic nerve activity and relative aldosterone excess causing salt retention and volume expansion (20–22). In patients with refractory hypertension, increased sympathetic nerve activity has been suggested to be the dominant factor (23).

GENERAL CONSIDERATIONS FOR THE MANAGEMENT OF RESISTANT HYPERTENSION

Management of RH should take place at specialized centers able to exclude causes of pseudoresistance and secondary hypertension (24). Other causes of RH should be considered, including lifestyle factors such as obesity or alcohol consumption, as well as the intake of vasopressor or sodium-retaining substances such as oral contraceptives, nonsteroidal anti-inflammatory drugs and analgesics, cancer therapies, or steroids (10). When managing patients with RH, comorbidities, frailty, and contraindications for specific medications are to be considered (25).

Nonadherence is frequent in pseudo-RH and associates with poor clinical outcomes (26, 27). In a meta-analysis of 24 studies including patients with apparent RH, the mean prevalence of nonadherence was 31%, ranging from 3% to 86% (28). Variance in nonadherence rates was in part related to the method of adherence assessment used (28). Several direct and indirect methods for measuring drug adherence are available. These have advantages and limitations; none can be considered the gold standard (29). For example, urine monitoring, often used in clinical studies, is impacted by the long washout periods of certain antihypertensive drugs, exceeding 24 h (30). As adherence fluctuates over time (11, 31) and typically decreases over time (32), repeat measurements should be considered.

NONPHARMACOLOGICAL TREATMENT

Lifestyle modifications, including dietary adjustments, weight loss, physical activity, and limiting alcohol consumption, are the cornerstone of therapy in all patients with hypertension but should especially be reinforced in RH (7, 10).

Dietary Sodium Reduction

RAS: renin-angiotensin system

Data on sodium consumption in RH are scarce. In a small ($n = 12$) randomized controlled crossover trial in RH, a low- compared to high-salt diet (50 mmol/day versus 250 mmol/day for a week) reduced office systolic and diastolic BP by 22.7 and 9.1 mm Hg, respectively (33). Similarly, in patients with chronic kidney disease and hypertension (mean number of antihypertensive medications 3.15 ± 1.09), salt restriction reduced systolic and diastolic BP by 10 and 4 mm Hg, respectively (34).

Weight Loss

In overweight patients with hypertension, weight loss can reduce systolic BP by about 1 mm Hg per kilogram (35). Evidence on weight loss in RH is scarce. In a subanalysis of the GATEWAY trial, including patients with hypertension and a body mass index between 30 and 39.9 kg/m^2, the prevalence of RH significantly decreased following randomization to metabolic surgery (Roux-en-Y gastric bypass) (36). Importantly, the BP-lowering effects of metabolic surgery cannot fully be attributed to the weight reduction, as the postoperative BP drop preceded it (37). The underlying mechanisms most likely involve improvements in sympathetic nerve activity, baroreflex control, sodium and water homeostasis, and anti-inflammatory effects (38).

Physical Activity

Preserving or increasing cardiorespiratory fitness through regular exercise decreases the risk of incident hypertension (39). It is well established that exercise lowers BP (40). All types of exercise, including endurance and resistance training, effectively lower systolic BP (41). In a network meta-analysis, the size of the BP-lowering effect of exercise was comparable to that of renin-angiotensin system (RAS) blockers, beta blockers, and diuretics (41). For RH, only a few dedicated trials are available. The Exercise Training in the Treatment of RH (EnRicH) trial randomized patients with RH to a 12-week moderate-intensity aerobic exercise training program, consisting of three 40-min supervised sessions per week, or usual care (42). Compared with the control group, 24-h ambulatory systolic and diastolic BP in the exercise group were reduced by 7.1 and 5.7 mm Hg, respectively (42). Similarly, two small meta-analyses also show reductions in ambulatory BP following aerobic exercise in RH (43, 44).

Structured Diet and Exercise Programs

The Treating RH Using Lifestyle Modification to Promote Health (TRIUMPH) trial compared the BP-lowering effects of a 4-month combined diet and exercise intervention, delivered in a cardiac rehabilitation setting, to a single 1-h educational session (45). The dietary component, DASH (Dietary Approaches to Stop Hypertension), entailed restriction of sodium and caloric intake. Participants in the structured lifestyle intervention group had greater reductions in office (−12.5 mm Hg versus −7.1 mm Hg) and ambulatory (−7.0 mm Hg versus −0.3 mm Hg) BP than those in the control group (45). A key barrier to implementing the intervention in clinical practice is that it was delivered within an established cardiac rehabilitation program, which is cost prohibitive for many and is not widely available.

PHARMACOLOGICAL TREATMENT

Most patients with RH should be treated with a RAS blocker, calcium channel blocker, and diuretic, ideally as a single-pill combination. If patients are on individual agents, switching them to a single-pill combination should be considered because this results in greater BP reductions,

probably due to improved medication adherence and simultaneous targeting of different mechanisms (46, 47).

Diuretic Therapy

eGFR: glomerular filtration rate

Adjusting diuretic therapy is particularly important because RH is often linked to salt retention, volume excess, high sympathetic tone, or a combination thereof. Most single-pill combination therapies include hydrochlorothiazide as a diuretic. As some studies and meta-analyses demonstrated a higher antihypertensive effect and a longer duration of action of the thiazide-like diuretics indapamide and chlorthalidone compared with hydrochlorothiazide (48–50), some guidelines and consensus statements suggested switching the diuretic therapy from hydrochlorothiazide to long-acting thiazide-like diuretics (51). In contrast to previous meta-analyses showing that thiazide-like diuretics achieved a greater reduction in the risk for CV events and heart failure compared with thiazides (52, 53), a recent large observational comparative cohort study including 730,255 individuals (54) and a randomized trial of 13,523 patients (Diuretic Comparison Project) (55) did not demonstrate superiority in reducing CV events of chlorthalidone over hydrochlorothiazide at equipotent doses. Of note, the risk of hypokalemia (54, 55) and hyponatremia (54) was higher in the chlorthalidone group than in the hydrochlorothiazide group.

While there is concern for diminished natriuretic effect of hydrochlorothiazide below an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2, the double-blind Chlorthalidone in Chronic Kidney Disease (CLICK) trial demonstrated significant ambulatory BP reductions in patients with uncontrolled hypertension and stage 4 chronic kidney disease (eGFR 15–29 mL/min/1.73 m^2) treated with chlorthalidone independent of loop diuretic use (56). In the CLICK trial, the BP-lowering effects of chlorthalidone were also observed in the subgroup of patients with RH (57). In patients with end-stage renal disease with residual renal function or hypoalbuminemia, long-acting loop diuretics, such as torsemide, may be considered.

Mineralocorticoid Receptor Antagonists

Spironolactone is the standard of care for treating RH. In the Prevention and Treatment of Hypertension with Algorithm Based Therapy-2 (PATHWAY-2) trial, the BP-lowering effects of spironolactone (25–50 mg daily) were superior to those of doxazosin (5–10 mg daily) and bisoprolol (5–10 mg) for RH (58). More patients achieved BP control, defined as home systolic BP <135 mm Hg, during the spironolactone treatment phase (58%) than with any of the other drugs ($p < 0.001$) (58). In the open-label runout phase of the PATHWAY-2 trial, the potassium-sparing diuretic amiloride (10–20 mg daily) reduced clinic systolic BP by 20.4 mm Hg, compared with an 18.3 mm Hg reduction with spironolactone (25 mg daily) (22). In the RH Optimal Treatment (ReHOT) trial, spironolactone reduced 24-h BP more than clonidine (59). Subsequently, several meta-analyses confirmed the BP-lowering efficacy of spironolactone in both nonresistant hypertension (60) and RH (61, 62). In a secondary analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, patients with heart failure with preserved ejection fraction and with RH had a reduction of the composite of CV death, aborted cardiac arrest, or heart failure hospitalization compared with patients in the placebo arm (63). In RH and diabetes, spironolactone reduced BP and albuminuria (64). The use of spironolactone is limited by the risk of hyperkalemia, particularly in chronic kidney disease, and antiandrogenic side effects, including gynecomastia and erectile dysfunction in men and menstrual irregularities in women (65, 66). Caution is required when eGFR is <45 mL/min/1.73 m^2 or baseline potassium is ≥4.5 mmol/L (7). Based on kidney function and serum potassium, more than two-thirds of patients with RH are eligible for spironolactone, but only a few receive it (67). Due to the large body of evidence for spironolactone in hypertension and the more potent

antihypertensive effect compared with eplerenone (65, 68), spironolactone is the mineralocorticoid receptor antagonist (MRA) of choice for antihypertensive treatment. In patients not tolerating spironolactone, eplerenone (50–200 mg daily) can be used (69). Due to the shorter duration of action, eplerenone should be administered twice daily. Of note, eplerenone is not marketed for the treatment of hypertension in some countries. Recently, nonsteroidal MRAs, such as KBP-5074 (70), apararenone (71), and esaxerenone (72), have been developed and are currently under investigation for hypertension. Esaxerenone has been approved in Japan for treating hypertension. Finerenone has improved CV and kidney outcomes in diabetes with chronic kidney disease but has only modest BP-lowering effects (73, 74).

Beta Blockers

Most current hypertension guidelines no longer recommend beta blockers as a first-choice drug (6–9). In randomized controlled trials and meta-analyses, beta blockers reduced the risk of stroke, heart failure, and major CV events in hypertension (75). However, compared to the first-line drugs, beta blockers were less protective against stroke (75). Moreover, beta blockers might have higher discontinuation rates for side effects and are associated with an increased risk of new-onset diabetes (76). Of note, beta blockers are a heterogeneous drug class, and as seen in heart failure, there probably is no class effect (77). For some agents, such as bisoprolol, carvedilol, and nebivolol, which have been shown to improve outcomes in heart failure (78), there are no data on CV outcomes from randomized controlled trials in hypertension (77). However, beta blockers are still recommended as first-line therapy in many patients with a compelling indication, such as heart failure, chronic coronary syndrome with angina pectoris, or atrial fibrillation for rate control, and in women who are planning to become pregnant (6, 7).

Data on the efficacy of beta blockers as a fourth or fifth antihypertensive drug are scarce. In the PATHWAY-2 trial, bisoprolol lowered office and home BP to a lesser extent than spironolactone at 12 weeks (58). It remains unknown whether the larger reduction in BP translates into superiority in improving CV outcomes. In the absence of CV outcome data from randomized controlled trials, a real-world retrospective cohort study (using health insurance data) of 80,598 patients with apparent RH did not find a reduction in major CV events with the initiation of MRA ($n = 6{,}626$) compared with beta blockers ($n = 73{,}972$) (79). The risks of hyperkalemia, gynecomastia, and kidney function deterioration were increased with MRA. Importantly, this analysis has severe limitations, as pseudoresistance was not systematically excluded, and the outcome assessment was based on healthcare records (79).

Beta blockers might be particularly efficacious in patients in whom increased sympathetic output is the major driver of RH. Elevated heart rate, independent of BP control, is associated with reduced survival in hypertension (80) and might serve as a surrogate parameter to identify patients who benefit the most from beta blockers (77). In contrast to MRA, beta blockers are well tolerated in patients with advanced and end-stage kidney disease (25).

Angiotensin Receptor–Neprilysin Inhibitors

Sacubitril-valsartan was initially developed to treat hypertension (81). By inhibiting the catabolism of natriuretic peptides and blocking the angiotensin II type 1 receptor, sacubitril-valsartan results in systemic vasodilatation, increased diuresis and natriuresis, and RAS inhibition (81, 82). In patients with mild to moderate hypertension, sacubitril-valsartan (100 mg, 200 mg, or 400 mg daily) resulted in a greater BP reduction than placebo (83), valsartan (81), or olmesartan alone (84). In the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Measuring Arterial Stiffness in the Elderly (PARAMETER) trial,

sacubitril-valsartan reduced office and ambulatory brachial and central BP more than olmesartan in systolic hypertension with stiff arteries (85). In contrast to omapatrilat, an angiotensin-converting enzyme (ACE) inhibitor and neprilysin inhibitor, which reduced BP more than ACE inhibitors alone but increased the risk of angioedema, sacubitril-valsartan was shown to be safe (81, 86).

Evidence for sacubitril-valsartan in RH from large prospective randomized controlled trials is lacking. In a small randomized controlled trial in RH, patients treated with valsartan 80 mg daily either switched to sacubitril-valsartan (200 mg daily) or remained on valsartan (87). Compared with the control group, sacubitril-valsartan significantly reduced ambulatory BP (87). In a post hoc analysis of the Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF) trial, which investigated sacubitril-valsartan in heart failure with preserved ejection fraction, the reduction in systolic BP was greater with sacubitril-valsartan than valsartan alone in patients with apparent RH (systolic BP $\geq$140 mm Hg or $\geq$135 mm Hg in diabetes despite treatment with a calcium channel blocker, valsartan, and a diuretic) (88). Moreover, the BP-lowering effect of sacubitril-valsartan was also shown in patients with MRA-resistant hypertension (88).

More data from randomized controlled trials prospectively investigating sacubitril-valsartan in hypertension, particularly RH, are necessary. Currently, sacubitril-valsartan is indicated for hypertension only in a few countries, such as Japan, China, and Russia (89, 90).

Other Drug Classes

Direct vasodilators, such as hydralazine and minoxidil, should be avoided as they can cause fluid retention and increased sympathetic tone (7). If they are used, concomitant treatment with loop diuretics and beta blockers and multiple daily dosing are required (7).

Emerging Drug Classes

Several new agents are under investigation for hypertension, including aminopeptidase A inhibitors, endothelin receptor blockers, aldosterone synthase inhibitors, and RNA-based antisense therapies targeting angiotensinogen (91). In this section, we briefly discuss two recent trials of baxdrostat and aprocitentan.

In PRECISION, a blinded randomized phase III trial, the dual endothelin A and B receptor antagonist aprocitentan reduced office BP by approximately 4 mm Hg and 24-h BP by approximately 5 mm Hg compared with placebo at 4 weeks in RH (92). These BP-lowering effects were sustained until 40 weeks. Mild to moderate edema and fluid retention were the most frequently observed adverse events (9–18%) (92). The advantages of aprocitentan are the long half-life (44 h), requiring only once-daily dosing, and the low drug–drug interaction potential (93).

In the BrigHTN trial, a phase II placebo-controlled dose-ranging trial involving 275 patients with RH, the selective aldosterone synthase inhibitor baxdrostat reduced office systolic BP compared with placebo (94). Of note, no drug-related serious adverse events and no instances of adrenocortical insufficiency occurred. None of the patients discontinued the trial because of hyperkalemia (94). Before baxdrostat becomes available for broad use in clinical practice, the positive results of the BrigHTN trial have to be confirmed in larger phase III trials.

INTERVENTIONAL THERAPY

Several interventional treatments have been investigated for the treatment of hypertension. Of these, the largest body of evidence exists for catheter-based renal denervation (RDN). Approaches other than RDN require further investigation and are therefore not discussed in this review.

RDN interrupts afferent and efferent sympathetic nerves in the adventitia and perivascular tissue of renal arteries (95). On the one hand, efferent sympathetic nerve activation increases renin secretion and renal tubular sodium reabsorption and decreases renal blood flow (96). On the other hand, afferent mechanosensitive and chemosensitive afferent sympathetic nerves provide feedback to the central nervous system (96).

The 2018 ESC/ESH guidelines did not recommend the use of device-based therapies for routine treatment of hypertension outside the context of clinical studies and trials (7), based on the results of three sham-controlled trials that did not demonstrate BP-lowering effects of a mono-electrode radiofrequency catheter system in patients with severe RH (97–99). The most controversial and, to date, largest randomized sham-controlled trial in the field of RDN, the Symplicity HTN-3 trial, had several methodological limitations, including frequent medication changes, limited experience of the proceduralists, and likely incomplete circumferential ablation in most patients (97, 100). At the same time, the RDN for Hypertension (DENERHTN) trial showed a daytime ambulatory BP reduction following RDN using the same catheter system in addition to a standardized pharmacological therapy, compared with standardized pharmacological therapy alone, in patients with well-defined RH (101).

Meanwhile, several high-quality studies of RDN were published, including randomized sham-controlled trials, confirming both the BP-lowering efficacy and safety of radiofrequency and ultrasound RDN in a broad population with hypertension with and without concomitant antihypertensive medications (102). The RADIANCE-HTN TRIO trial investigated ultrasound RDN in patients with RH on a fixed-dose, triple-combination therapy. Office and ambulatory BP were significantly reduced 2 months after RDN compared with sham (103). Per protocol, standardized stepped-care antihypertensive treatment was initiated in patients whose hypertension remained uncontrolled 2 months after randomization. After 6 months, patients in the RDN group had a similar reduction in BP as the control group, despite receiving fewer additional medications (104). In contrast to pharmacological therapies, the BP-lowering effect of RDN is constant over the 24-h circadian cycle ("always-on") and is independent of pharmacokinetics, drug adherence, and dosing schemes (102).

Of note, patients with advanced kidney disease (eGFR <40 mL/min/1.73 m^2) were excluded from the current sham-controlled trials. Although data from open-label studies suggest that RDN is feasible and safe in patients with advanced chronic kidney disease (105), and even in those on long-term hemodialysis (106), its use cannot be recommended until further evidence becomes available.

Safety and long-term reliability are prerequisites for use in clinical practice for interventional procedures with an always-on effect. Notably, there was no safety signal in the first- and second-generation RDN trials exceeding the risk of other femoral arterial access procedures (102). A meta-analysis found no increase in the risk of renal artery stenosis requiring stenting following RDN (pooled annual incidence 0.2%) compared to the natural incidence of renal artery stenosis in hypertension (107). Long-term follow-up data from the sham-controlled trials indicate a sustained BP-lowering effect for up to 3 years (108–110). Nonrandomized studies and registries report sustained BP reductions for up to 10 years (111, 112).

As for all second-line antihypertensive drugs, including spironolactone, no CV outcome data following RDN from randomized controlled trials exist. In the absence of data from randomized controlled trials, and as outcome studies are not expected, the impact of RDN on CV outcome was derived from the Global Symplicity Registry, the largest RDN registry, including more than 3,000 patients to date. In the Global Symplicity Registry, patients with uncontrolled hypertension with a higher time in the therapeutic target range following RDN had a significantly lower rate of

major CV events from 6 to 36 months (113). A 10% increase in time in the therapeutic target range resulted in a 16% lower rate of major CV events (113). Of note, while RDN has been approved in Europe, it has not been approved for the treatment of hypertension in several other countries, including the United States.

PROPOSED TREATMENT ALGORITHM FOR RESISTANT HYPERTENSION

In patients with true RH without causes of secondary hypertension, BP control to target value is the ultimate goal. Existing antihypertensive therapy should be re-evaluated, and switched to a single-pill combination if this has not already been done. As in all patients with hypertension, lifestyle measures, including alcohol reduction, weight loss, and physical activity, should be reinforced. In most patients with RH, lifestyle modifications alone will not lead to BP control. In patients with uncontrolled RH, intensifying the antihypertensive therapy, either by adding additional BP-lowering medications or performing RDN, is required. For most patients, spironolactone and vasodilating beta blockers should be considered the fourth and fifth drugs. In the absence of CV outcome data, and as both spironolactone and RDN lower BP [a strong surrogate for CV morbidity and mortality (2)], we recommend including the preference of a well-informed and educated patient in a shared decision-making process (**Figure 1**) (102).

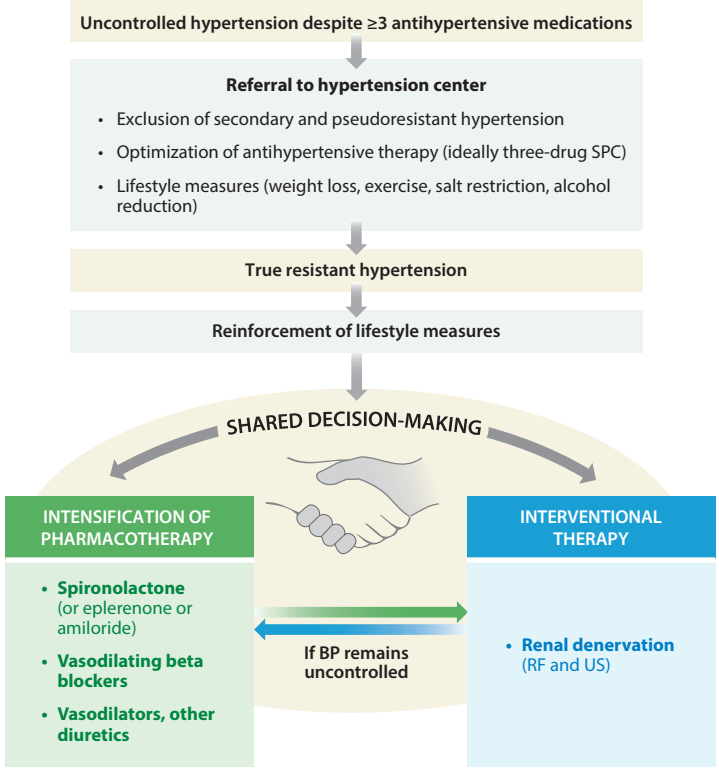

Figure 1

Management of resistant hypertension. Abbreviations: BP, blood pressure; RF, radiofrequency; SPC, single-pill combination; US, ultrasound.

SUMMARY

RH is an important risk factor for chronic kidney and CV disease. Although less than 10% of the patients with hypertension are resistant to treatment, the absolute number of patients with RH is high. Patients with RH should be treated by hypertension specialists capable of excluding causes for secondary RH and pseudo-RH. Lifestyle modifications are the foundation of treatment and should be reinforced. Intensifying antihypertensive treatment can include adding further antihypertensive drugs, usually spironolactone and vasodilating beta blockers, or RDN. This decision-making process should also involve the patient's preference.

DISCLOSURE STATEMENT

L.L. received speaker honoraria from ReCor Medical and Medtronic. F.M. is supported by Deutsche Gesellschaft für Kardiologie (DGK), Deutsche Forschungsgemeinschaft (German Research Foundation; SFB TRR219, project number 322900939), and Deutsche Herzstiftung. He has received scientific support from Ablative Solutions, Medtronic, and ReCor Medical and speaker honoraria/consulting fees from Ablative Solutions, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Inari, Medtronic, Merck, ReCor Medical, Servier, and Terumo. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; SFB TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Edwards, Medtronic, Novartis, Recor, Servier, and Vifor during the conduct of the study.

ACKNOWLEDGMENTS

We are grateful to Armin Schweitzer for technical and editorial help as well as artwork.

LITERATURE CITED

1. GBD 2019 Risk Factors Collaborators. 2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 396:1223–49
2. Thomopoulos C, Parati G, Zanchetti A. 2014. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *J. Hypertens.* 32:2285–95
3. Lv J, Ehteshami P, Sarnak MJ, et al. 2013. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *Can. Med. Assoc. J.* 185:949–57
4. NCD Risk Factor Collaboration. 2021. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 398:957–80
5. Aggarwal R, Chiu N, Wadhera RK, et al. 2021. Racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control in the United States, 2013 to 2018. *Hypertension* 78:1719–26
6. Whelton PK, Carey RM, Aronow WS, et al. 2018. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 71:1269–324
7. Williams B, Mancia G, Spiering W, et al. 2018. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur. Heart J.* 39:3021–104
8. Umemura S, Arima H, Arima S, et al. 2019. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens. Res.* 42:1235–481
9. Unger T, Borghi C, Charchar F, et al. 2020. 2020 International Society of Hypertension global hypertension practice guidelines. *J. Hypertens.* 38:982–1004

10. Mancia G, Kreutz R, Brunström M, et al. 2023. 2023 ESH guidelines for the management of arterial hypertension *The Task Force for the management of arterial hypertension of the European Society of Hypertension* Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J. Hypertens.* 41:1874–2071
11. Wunder C, Persu A, Lengele JP, et al. 2019. Adherence to antihypertensive drug treatment in patients with apparently treatment-resistant hypertension in the INSPiRED pilot study. *Blood Press.* 28:168–72
12. Noubiap JJ, Nansseu JR, Nyaga UF, et al. 2019. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. *Heart* 105:98–105
13. Smith SM, Gurka MJ, Winterstein AG, et al. 2019. Incidence, prevalence, and predictors of treatment-resistant hypertension with intensive blood pressure lowering. *J. Clin. Hypertens.* 21:825–34
14. Nazarzadeh M, Pinho-Gomes AC, Rahimi K. 2019. Resistant hypertension in times of changing definitions and treatment recommendations. *Heart* 105:96–97
15. Sim JJ, Bhandari SK, Shi J, et al. 2013. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin. Proc.* 88:1099–107
16. Cuspidi C, Macca G, Sampieri L, et al. 2001. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J. Hypertens.* 19:2063–70
17. Persell SD. 2011. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension* 57:1076–80
18. Georges CMG, Ritscher S, Pappaccogli M, et al. 2022. Psychological determinants of drug adherence and severity of hypertension in patients with apparently treatment-resistant versus controlled hypertension. *Blood Press.* 31:169–77
19. Kario K, Hoshide S, Narita K, et al. 2021. Cardiovascular prognosis in drug-resistant hypertension stratified by 24-hour ambulatory blood pressure: the JAMP study. *Hypertension* 78:1781–90
20. Taler SJ, Textor SC, Augustine JE. 2002. Resistant hypertension: comparing hemodynamic management to specialist care. *Hypertension* 39:982–88
21. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, et al. 2008. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Arch. Intern. Med.* 168:1159–64
22. Williams B, MacDonald TM, Morant SV, et al. 2018. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol.* 6:464–75
23. Siddiqui M, Calhoun DA. 2017. Refractory versus resistant hypertension. *Curr. Opin. Nephrol. Hypertens.* 26:14–19
24. Denker MG, Haddad DB, Townsend RR, Cohen DL. 2013. Blood pressure control 1 year after referral to a hypertension specialist. *J. Clin. Hypertens.* 15:624–29
25. Lauder L, Mahfoud F, Azizi M, et al. 2022. Hypertension management in patients with cardiovascular comorbidities. *Eur. Heart J.* 44:2066–77
26. Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. 2014. Non-adherence to cardiovascular medications. *Eur. Heart J.* 35:3267–76
27. Mazzaglia G, Ambrosioni E, Alacqua M, et al. 2009. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 120:1598–605
28. Durand H, Hayes P, Morrissey EC, et al. 2017. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. *J. Hypertens.* 35:2346–57
29. Kably B, Billaud EM, Boutouyrie P, Azizi M. 2020. Is there any hope for monitoring adherence in an efficient and feasible way for resistant hypertension diagnosis and follow-up? *Curr. Hypertens. Rep.* 22:96
30. Lauder L, Ewen S, Kunz M, et al. 2020. Adherence to antihypertensive drugs assessed by hyphenated high-resolution mass spectrometry analysis of oral fluids. *J. Am. Heart Assoc.* 9:e014180
31. Kandzari DE, Böhm M, Mahfoud F, et al. 2018. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 391:2346–55
32. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. 2012. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu. Rev. Pharmacol. Toxicol.* 52:275–301

33. Pimenta E, Gaddam KK, Oparil S, et al. 2009. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension* 54:475–81
34. McMahon EJ, Bauer JD, Hawley CM, et al. 2013. A randomized trial of dietary sodium restriction in CKD. *J. Am. Soc. Nephrol.* 24:2096–103
35. Neter JE, Stam BE, Kok FJ, et al. 2003. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 42:878–84
36. Schiavon CA, Ikeoka D, Santucci EV, et al. 2019. Effects of bariatric surgery versus medical therapy on the 24-hour ambulatory blood pressure and the prevalence of resistant hypertension. *Hypertension* 73:571–77
37. Ahmed AR, Rickards G, Coniglio D, et al. 2009. Laparoscopic Roux-en-Y gastric bypass and its early effect on blood pressure. *Obes. Surg.* 19:845–49
38. Pareek M, Bhatt DL, Schiavon CA, Schauer PR. 2019. Metabolic surgery for hypertension in patients with obesity. *Circ. Res.* 124:1009–24
39. Holmlund T, Ekblom B, Borjesson M, et al. 2021. Association between change in cardiorespiratory fitness and incident hypertension in Swedish adults. *Eur. J. Prev. Cardiol.* 28:1515–22
40. Cornelissen VA, Buys R, Smart NA. 2013. Endurance exercise beneficially affects ambulatory blood pressure: a systematic review and meta-analysis. *J. Hypertens.* 31:639–48
41. Naci H, Salcher-Konrad M, Dias S, et al. 2019. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. *Br. J. Sports Med.* 53:859–69
42. Lopes S, Mesquita-Bastos J, Garcia C, et al. 2021. Effect of exercise training on ambulatory blood pressure among patients with resistant hypertension: a randomized clinical trial. *JAMA Cardiol.* 6:1317–23
43. Dassanayake S, Sole G, Wilkins G, et al. 2022. Effectiveness of physical activity and exercise on ambulatory blood pressure in adults with resistant hypertension: a systematic review and meta-analysis. *High Blood Press. Cardiovasc. Prev.* 29:275–86
44. Saco-Ledo G, Valenzuela PL, Ruilope LM, Lucia A. 2022. Physical exercise in resistant hypertension: a systematic review and meta-analysis of randomized controlled trials. *Front. Cardiovasc. Med.* 9:893811
45. Blumenthal JA, Hinderliter AL, Smith PJ, et al. 2021. Effects of lifestyle modification on patients with resistant hypertension: results of the TRIUMPH randomized clinical trial. *Circulation* 144:1212–26
46. Webster R, Salam A, de Silva HA, et al. 2018. Fixed low-dose triple combination antihypertensive medication versus usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA* 320:566–79
47. Chow CK, Atkins ER, Hillis GS, et al. 2021. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. *Lancet* 398:1043–52
48. Dineva S, Uzunova K, Pavlova V, et al. 2019. Comparative efficacy and safety of chlorthalidone and hydrochlorothiazide-meta-analysis. *J. Hum. Hypertens.* 33:766–74
49. Roush GC, Ernst ME, Kostis JB, et al. 2015. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. *Hypertension* 65:1041–46
50. Roush GC, Holford TR, Guddati AK. 2012. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension* 59:1110–17
51. Carey RM, Calhoun DA, Bakris GL, et al. 2018. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 72:e53–90
52. Olde Engberink RH, Frenkel WJ, van den Bogaard B, et al. 2015. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis. *Hypertension* 65:1033–40
53. Chen P, Chaugai S, Zhao F, Wang DW. 2015. Cardioprotective effect of thiazide-like diuretics: a meta-analysis. *Am. J. Hypertens.* 28:1453–63
54. Hripcsak G, Suchard MA, Shea S, et al. 2020. Comparison of cardiovascular and safety outcomes of chlorthalidone versus hydrochlorothiazide to treat hypertension. *JAMA Intern. Med.* 180:542–51

55. Ishani A, Cushman WC, Leatherman SM, et al. 2022. Chlorthalidone versus hydrochlorothiazide for hypertension-cardiovascular events. *N. Engl. J. Med.* 387:2401–10
56. Agarwal R, Sinha AD, Cramer AE, et al. 2021. Chlorthalidone for hypertension in advanced chronic kidney disease. *N. Engl. J. Med.* 385:2507–19
57. Agarwal R, Sinha AD, Tu W. 2022. Chlorthalidone for resistant hypertension in advanced chronic kidney disease. *Circulation* 146:718–20
58. Williams B, MacDonald TM, Morant S, et al. 2015. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 386:2059–68
59. Krieger EM, Drager LF, Giorgi DMA, et al. 2018. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT randomized study (Resistant Hypertension Optimal Treatment). *Hypertension* 71:681–90
60. Bazoukis G, Thomopoulos C, Tsioufis C. 2018. Effect of mineralocorticoid antagonists on blood pressure lowering: overview and meta-analysis of randomized controlled trials in hypertension. *J. Hypertens.* 36:987–94
61. Chen C, Zhu XY, Li D, Lin Q, Zhou K. 2020. Clinical efficacy and safety of spironolactone in patients with resistant hypertension: a systematic review and meta-analysis. *Medicine* 99:e21694
62. Sinnott SJ, Tomlinson LA, Root AA, et al. 2017. Comparative effectiveness of fourth-line antihypertensive agents in resistant hypertension: a systematic review and meta-analysis. *Eur. J. Prev. Cardiol.* 24:228–38
63. Tsujimoto T, Kajio H. 2020. Spironolactone use and improved outcomes in patients with heart failure with preserved ejection fraction with resistant hypertension. *J. Am. Heart Assoc.* 9:e018827
64. Takahashi S, Katada J, Daida H, et al. 2016. Effects of mineralocorticoid receptor antagonists in patients with hypertension and diabetes mellitus: a systematic review and meta-analysis. *J. Hum. Hypertens.* 30:534–42
65. Parthasarathy HK, Menard J, White WB, et al. 2011. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J. Hypertens.* 29:980–90
66. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. 2014. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst. Rev.* 2014:CD007004
67. Egan BM, Li J. 2014. Role of aldosterone blockade in resistant hypertension. *Semin. Nephrol.* 34:273–84
68. Bazoukis G, Thomopoulos C, Tse G, Tsioufis C. 2018. Is there a blood pressure lowering effect of MRAs in heart failure? An overview and meta-analysis. *Heart Fail. Rev.* 23:547–53
69. Pitt B, Reichek N, Willenbrock R, et al. 2003. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation* 108:1831–38
70. Bakris G, Pergola PE, Delgado B, et al. 2021. Effect of KBP-5074 on blood pressure in advanced chronic kidney disease: results of the BLOCK-CKD study. *Hypertension* 78:74–81
71. Wada T, Inagaki M, Yoshinari T, et al. 2021. Apararenone in patients with diabetic nephropathy: results of a randomized, double-blind, placebo-controlled phase 2 dose-response study and open-label extension study. *Clin. Exp. Nephrol.* 25:120–30
72. Ito S, Itoh H, Rakugi H, et al. 2020. Double-blind randomized phase 3 study comparing esaxerenone (CS-3150) and eplerenone in patients with essential hypertension (ESAX-HTN Study). *Hypertension* 75:51–58
73. Bakris GL, Agarwal R, Anker SD, et al. 2020. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N. Engl. J. Med.* 383:2219–29
74. Pitt B, Filippatos G, Agarwal R, et al. 2021. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N. Engl. J. Med.* 385:2252–63
75. Thomopoulos C, Bazoukis G, Tsioufis C, Mancia G. 2020. Beta-blockers in hypertension: overview and meta-analysis of randomized outcome trials. *J. Hypertens.* 38:1669–81
76. Tsujimoto T, Sugiyama T, Shapiro MF, et al. 2017. Risk of cardiovascular events in patients with diabetes mellitus on beta-blockers. *Hypertension* 70:103–10

77. Esler M, Kjeldsen SE, Pathak A, et al. 2022. Diverse pharmacological properties, trial results, comorbidity prescribing and neural pathophysiology suggest European hypertension guideline downgrading of beta-blockers is not justified. *Blood Press.* 31:210–24
78. McDonagh TA, Metra M, Adamo M, et al. 2021. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* 42:3599–726
79. Desai R, Park H, Brown JD, et al. 2022. Comparative safety and effectiveness of aldosterone antagonists versus beta-blockers as fourth agents in patients with apparent resistant hypertension. *Hypertension* 79:2305–15
80. Julius S, Palatini P, Kjeldsen SE, et al. 2012. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. *Am. J. Cardiol.* 109:685–92
81. Ruilope LM, Dukat A, Böhm M, et al. 2010. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet* 375:1255–66
82. Wang TD, Tan RS, Lee HY, et al. 2017. Effects of sacubitril/valsartan (LCZ696) on natriuresis, diuresis, blood pressures, and NT-proBNP in salt-sensitive hypertension. *Hypertension* 69:32–41
83. Kario K, Sun N, Chiang FT, et al. 2014. Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Asian patients with hypertension: a randomized, double-blind, placebo-controlled study. *Hypertension* 63:698–705
84. Zhang Y, Zhao X, Huang H, Li M. 2022. Network meta-analysis of sacubitril/valsartan for the treatment of essential hypertension. *Clin. Res. Cardiol.* 112:855–67
85. Williams B, Cockcroft JR, Kario K, et al. 2017. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: the PARAMETER study. *Hypertension* 69:411–20
86. McMurray JJ, Packer M, Desai AS, et al. 2014. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N. Engl. J. Med.* 371:993–1004
87. Lyu TJ, Liu Y, Zhang H, et al. 2022. Clinical observation of sacubitril valsartan sodium in the treatment of resistant hypertension: a randomized clinical trial. *Front. Cardiovasc. Med.* 9:1099043
88. Jackson AM, Jhund PS, Anand IS, et al. 2021. Sacubitril-valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. *Eur. Heart J.* 42:3741–52
89. Zuo C, Li X, Fan L, et al. 2022. Effectiveness and safety of sacubitril/valsartan for patients with hypertension and heart failure in the real-world setting: a retrospective study in China. *J. Clin. Pharm. Ther.* 47:1539–47
90. Ohishi M. 2022. Sacubitril/valsartan—a new weapon for fighting the hypertension paradox. *Hypertens. Res.* 45:915–16
91. Salvador VD, Bakris GL. 2022. Novel antihypertensive agents for resistant hypertension: What does the future hold? *Hypertens. Res.* 45:1918–28
92. Schlaich MP, Bellet M, Weber MA, et al. 2022. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. *Lancet* 400:1927–37
93. Sidharta PN, Fischer H, Dingemanse J. 2021. Absorption, distribution, metabolism, and excretion of aprocitentan, a dual endothelin receptor antagonist, in humans. *Curr. Drug Metab.* 22:399–410
94. Freeman MW, Halvorsen YD, Marshall W, et al. 2023. Phase 2 trial of baxdrostat for treatment-resistant hypertension. *N. Engl. J. Med.* 388:395–405
95. Lauder L, Azizi M, Kirtane AJ, et al. 2020. Device-based therapies for arterial hypertension. *Nat. Rev. Cardiol.* 17:614–28
96. DiBona GF, Esler M. 2010. Translational medicine: the antihypertensive effect of renal denervation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 298:R245–53
97. Bhatt DL, Kandzari DE, O'Neill WW, et al. 2014. A controlled trial of renal denervation for resistant hypertension. *N. Engl. J. Med.* 370:1393–401
98. Desch S, Okon T, Heinemann D, et al. 2015. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 65:1202–8

99. Mathiassen ON, Vase H, Bech JN, et al. 2016. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. *J. Hypertens.* 34:1639–47
100. Kandzari DE, Bhatt DL, Brar S, et al. 2015. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur. Heart J.* 36:219–27
101. Azizi M, Sapoval M, Gosse P, et al. 2015. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 385:1957–65
102. Barbato E, Azizi M, Schmieder RE, et al. 2023. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *EuroIntervention* 18:1227–43
103. Azizi M, Sanghvi K, Saxena M, et al. 2021. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet* 397:2476–86
104. Azizi M, Mahfoud F, Weber MA, et al. 2022. Effects of renal denervation versus sham in resistant hypertension after medication escalation: prespecified analysis at 6 months of the RADIANCE-HTN TRIO randomized clinical trial. *JAMA Cardiol.* 7:1244–52
105. Marin F, Fezzi S, Gambaro A, et al. 2021. Insights on safety and efficacy of renal artery denervation for uncontrolled-resistant hypertension in a high risk population with chronic kidney disease: first Italian real-world experience. *J. Nephrol.* 34:1445–55
106. Scalise F, Sole A, Singh G, et al. 2020. Renal denervation in patients with end-stage renal disease and resistant hypertension on long-term haemodialysis. *J. Hypertens.* 38:936–42
107. Townsend RR, Walton A, Hettrick DA, et al. 2020. Review and meta-analysis of renal artery damage following percutaneous renal denervation with radiofrequency renal artery ablation. *EuroIntervention* 16:89–96
108. Bhatt DL, Vaduganathan M, Kandzari DE, et al. 2022. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. *Lancet* 400:1405–16
109. Mahfoud F, Kandzari DE, Kario K, et al. 2022. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet* 399:1401–10
110. Rader F, Kirtane AJ, Wang Y, et al. 2022. Durability of blood pressure reduction after ultrasound renal denervation: three-year follow-up of the treatment arm of the randomised RADIANCE-HTN SOLO trial. *EuroIntervention* 18:e677–85
111. Al Ghorani H, Kulenthiran S, Recktenwald MJM, et al. 2023. 10-Year outcomes of catheter-based renal denervation in patients with resistant hypertension. *J. Am. Coll. Cardiol.* 81:517–19
112. Sesa-Ashton G, Nolde JM, Muente I, et al. 2023. Catheter-based renal denervation: 9-year follow-up data on safety and blood pressure reduction in patients with resistant hypertension. *Hypertension* 80:811–19
113. Mahfoud F, Mancia G, Schmieder RE, et al. 2022. Cardiovascular risk reduction after renal denervation according to time in therapeutic systolic blood pressure range. *J. Am. Coll. Cardiol.* 80:1871–80