REVIEW ARTICLE

Controversies in the management of patients with arterial hypertension

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KEY WORDS
classification, targets, single-pill combination, renal denervation, sodium

ABSTRACT
Every 5 to 6 years, international and national guidelines provide updated recommendations for the standard management of hypertension in adults. Thus, within the last 18 months, societies from Europe (European Society of Cardiology and European Society of Hypertension), America (American College of Cardiology and American Heart Association), and Great Britain (National Institute for Health and Care Excellence) published their new guidelines. Despite the fact that all of them are supposedly based on the most recent clinical evidence, there are always some discrepancies between recommendations due to different interpretation of clinical trials. The purpose of the present review is to discuss 6 issues that have generated some controversies, namely, the definition of hypertension, identification of patients who should be treated, target blood pressure, pertinence of reducing salt intake, mono- or combination therapy as first-line treatment, and the role of renal denervation in resistant hypertension.

Introduction Hypertension is the main risk factor of cardiovascular diseases worldwide, affecting more than 1 billion people globally. Reducing blood pressure (BP) in patients with hypertension is the most effective way to lower the mortality rates and target organ damages associated with hypertension.[1] Today, these 2 allegations are well accepted in the medical community, but this has not always been the case. Indeed, in the midst of the 20th century, many physicians deemed arterial hypertension a compensatory mechanism that did not deserve any treatment, whereas others were proposing drug treatments for those with an elevated BP without a strong support of clinical trials. This was probably the first important controversy in the management of essential hypertension. In the 1960s and 1970s, the first randomized controlled trials conducted by the Veterans Administration Cooperative Study Group confirmed the benefits of treating patients with elevated diastolic BP.[2,3] Consequently, in 1977, the first Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure published a strict recommendation to treat any patient with hypertension with diastolic BP higher than 115 mm Hg and to consider therapy in those with diastolic BP higher than 90 mm Hg depending on their cardiovascular risk.[4] In the same decade, the first guidelines for the management of hypertension were issued first by the World Health Organization (WHO) and the International Society of Hypertension (ISH), and thereafter by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure with the objective to help physicians in their clinical decisions.[5] The guidelines were written by hypertension experts and updated periodically. Until 2003, the ESH and ESC endorsed the WHO / ISH guidelines, but thereafter it was believed that these guidelines might not be representative because of the heterogenous accesses to health care, drug therapies, and economic resources of the countries. Therefore, they started to publish their own guidelines in 2003, introducing progressively evidence-based criteria. Simultaneously, several countries started to publish their own national recommendations.[6] The latter were sometimes, but not always, in accordance with the international guidelines coming from the United

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Received: September 29, 2019.
Accepted: September 30, 2019.
Published online: October 1, 2019.
Kardiol Pol. 2019; 77 (10): 902-907
doi:10.33963/KP.15002

States or Europe, leading to controversies with regard to the management of patients with hypertension. In this respect, the recently published guidelines by the ESC / ESH[7] in Europe and by the ACC / AHA[8,9] in the United States, and even more recently, the 2019 NICE guidelines in Great Britain[10] did not avoid the controversy, with some substantial differences generating animated discussion. The purpose of this article is to discuss some of the recent controversies in the diagnosis and management of hypertension in adults according to the most recent recommendations.

Definition of hypertension: is >140/90 mm Hg still correct? The major current controversy concerns the definition of hypertension. Hypertension in adults is defined as a BP of 140/90 mm Hg or higher with a special consideration for elderly patients with isolated systolic hypertension defined as a systolic BP of 140 mm Hg or higher but a diastolic BP of less than 90 mm Hg. These definitions have been accepted and applied worldwide for decades. In 2018, the ACC/AHA guidelines changed this definition putting the cut-off point between normotension and hypertension at 130/80 mm Hg[8,9] (TABLE 1). In addition, those with a systolic BP between 120 and 129 mm Hg and a diastolic BP of less than 80 mm Hg have an elevated BP. This major modification has generated many negative reactions for several reasons. Firstly, it increased by almost 15% the number of patients with hypertension in the population; secondly, it also increases the percentage of treated patients with uncontrolled hypertension; and, thirdly, it raises substantially the number of patients with low cardiovascular risk needing clinical management by general practitioners with the risk of inducing more adverse effects than clinical benefits. Interestingly, in the United States, the American Academy of Family Physicians and the American College of Physicians rejected this modification. Thus, we face a situation in which various definitions of hypertension exist, which might have direct consequences for the management of the disorder.[11]

TABLE 1 Hypertension categories according to the 2018 European Society of Cardiology and European Society of Hypertension guidelines[7] and the 2017 American College of Cardiology and American Heart Association guidelines[8,9]

Category	Systolic BP	and/or	Diastolic BP
ESC / ESH 2018			
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 Hypertension	140–159	and/or	90–99
Grade 2 Hypertension	160–179	and/or	100–109
Grade 3 Hypertension	≥180	and/or	≥110
Isolated systolic Hypertension	≥140	and	≤90
ACC / AHA 2017			
Normal	<120	and	<80
Elevated	120–129	and	<80
Stage 1	130–139	or	80–89
Stage 2	≥140	or	≥90

Values are presented as mm Hg.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension

The main reason why the ACC / AHA guidelines committee changed the definition of hypertension is the results of the SPRINT (Systolic Blood Pressure Intervention Trial) published in 2015.[12] In this trial, targeting a systolic BP of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and all-cause mortality. Moreover, the benefits of reaching the lower target were also observed in the elderly.[13] However, the method used to measure office BP in SPRINT was a major issue. Indeed, in contrast to all previous clinical trials on hypertension, SPRINT investigators used a different methodology combining an automated device with measurements done in a quiet room unattended or unobserved—that is, without an observer being present in the room.[14] Thus, the treatment arm including patients with systolic BP of less than 120 mm Hg in SPRINT very likely compares with higher systolic BP values when measured normally in a physician's office. This was actually demonstrated by Filipovski et al[15] who reported lower office BP (mean [SD] 8.5 [9.0]/3.0 [6.1] mm Hg) when measured unattended with an automated device as compared with the standard auscultatory method.

Considering these new information, what should practitioners do? Most national hypertension guidelines in Europe (including the very recent NICE guidelines) and Asia[16] have actually maintained the 140/90 mm Hg cut-off defining hypertension. This is also true for Poland.[6,17] This seems reasonable as long as office BP is measured using either auscultatory or oscillometric devices in the presence of a physician or a nurse. Physicians could apply the ACC / AHA definition only if they modify their habits and start measuring BP according to the SPRINT protocol, that is, with an automated device in a quiet room and without any healthcare professional in the room (unattended).

Who should be treated? So far, there has been no strict recommendation to treat patients with high-normal BP, that is, with BP values between 130 to 139 mm Hg systolic and 85 to 89 mm Hg diastolic. At best, guidelines suggest to follow such patients regularly and to implement lifestyle changes if necessary. In support of this attitude, the HOPE-3 (Heart Outcomes Prevention Evaluation–3) trial confirmed that drug therapy is not associated with lower rates of major cardiovascular events compared with placebo in patients with an intermediate risk and no cardiovascular disease unless systolic BP is higher than 143 mm Hg.[18] According to the 2017 ACC/AHA guidelines, these patients would be considered as hypertensive and should receive lifestyle recommendations and a medical treatment if BP remains higher than 130/80 mm Hg. The 2018 ESC/ESH guidelines have now made a step in the direction of American recommendations in that people with high-normal BP should receive drug treatment if their calculated cardiovascular risk is greater than 5% (patients with high and very high cardiovascular risk) or if they have renal disease or hypertension-mediated organ damage.[7] This novel attitude towards patients with borderline BP values emphasizes the need to estimate the cardiovascular risk profile of all patients in whom BP is measured more systematically. A specific cardiovascular risk assessment system and risk charts calibrated for the Polish population have been published in 2015.[19]

Treating hypertensive patients: how low should we go? In the majority of guidelines, the general recommendation is to lower BP below 140/90 mm Hg by implementing lifestyle changes first and then introducing drug therapies. Exceptions in treatment targets exist in some guidelines for the very elderly (<150/90 mm Hg) or patients with diabetes or chronic kidney disease and proteinuria (<130/80 mm Hg) or patients with coronary artery disease (<130 mm Hg). In coherence with their new classification, 2017 ACC/AHA guidelines recommend to lower BP below 130/80 mm Hg in all patients. This new approach is based, again, on the results of the SPRINT trial and some, but not all, meta-analyses have raised many issues. First, this low target will be difficult to achieve in many patients if one considers that today less than 50% of treated patients with hypertension achieve a target BP of less than 140/90 mm Hg. Therefore, this may become discouraging for both patients and physicians. Moreover, there is no evidence from randomized controlled trials to support a diastolic BP of less than 80 mm Hg. In addition, in some patients, like the elderly, a more intensive treatment to reach low targets may be rather harmful. Indeed, in the SPRINT trial patients randomized to the 120 mm Hg systolic BP target experienced hypotensive episodes and worsening of renal function more frequently.[12] Lastly, such a low target might increase the number of consultations needed to manage patients with hypertension and lead to overload of many general practitioners.

Therefore, it appears more reasonable to apply the target strategy from the ESC/ESH guidelines,[7] which recommend a range of targets to be achieved in 2 steps. The first is to bring BP below 140/90 mm Hg in all hypertensive patients. Then, BP can be lowered further to 130 to 140 mm Hg in most patients depending on their age, level of cardiovascular risk, tolerance to hypertensive therapy, and presence or absence of concomitant diseases.

Starting drug therapy: monotherapy or single-pill combinations first? Stepped-care drug therapy has been the standard of care in hypertension since the very first hypertension guidelines from the 1970s. Today, it remains the most recommended therapeutic strategy in most guidelines. Thus, the ACC/AHA guidelines recommend to start with monotherapy in patients with stage 1 hypertension, whereas in stage 2 hypertension initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended. A similar approach is proposed in the Polish guidelines.[17] According to the 2019 NICE guidelines, physicians should offer an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker monotherapy as step 1 to adults who have type 2 diabetes and are of any age or family origin, or are younger than 55 years of age but are not black African or African Caribbean. Patients should receive calcium channel blocker monotherapy as the first step in 1 antihypertensive treatment if they are aged 55 or older and do not have type 2 diabetes or if they are of any age, are African or African Caribbean, and do not have type 2 diabetes.[10]

The committee for ESC and ESH guidelines have decided to modify their therapeutic strategy for several reasons. Firstly, the stepped-care therapy has now been used for decades with a modest success rate in controlling hypertension. Indeed, in most European countries, the control rate of treated patients does not exceed 50%. Secondly, 40% to 50% of treated patients stop their antihypertensive therapy during the first year because of pill burden. Thirdly, many physicians do not adapt the therapy after the first prescription in patients with uncontrolled hypertension. Fourthly, the time needed to achieve an adequate BP control is often very long (>6 months). Thus, the objective in changing the strategy was to increase the BP lowering efficacy of the first step, reduce pill burden, and shorten the time to achieving BP control. To achieve these goals,

the ESC / ESH guidelines recommend to start antihypertensive treatment with a single-pill combination of 2 drug classes, that is, a renin–angiotensin system (RAS) blocker combined with a diuretic or a calcium channel blocker. The second set consists in prescribing a single-pill triple combination with a RAS blocker, diuretic, and calcium antagonist. This more aggressive initiation of therapy should enable to control BP in 50% to 60% of patients after the first prescription of a single pill. Yet, the use of a monotherapy as the first step is not completely abandoned but it is reserved to frail, very elderly patients or to younger patients with a modest elevation of BP. This new therapeutic approach was generally well received but its implementation may be challenging in some countries, as dual and triple single-pill combinations are not universally available or reimbursed.

Lifestyle changes: should sodium intake be reduced? To what level? Physiologically, sodium is one of the main determinants of BP. Several epidemiological surveys have demonstrated that the higher the salt intake in populations, the higher the BP and the risk of developing hypertension with age.[20-24] There is also a relationship between sodium intake and the risk of death and cardiovascular events.[20,24-27] However, some investigators found a linear correlation between sodium intake and cardiovascular events,[25,26] whereas others reported an increased risk of death and cardiovascular events at higher as well as at lower estimated levels of sodium intake, suggesting a U-shaped relationship.[27,28] Therefore, the authors of these latter observations do not support the recommendations made by the WHO, AHA, or ESC / ESH to reduce sodium intake in populations to 1.5 to 2.0 g sodium per day or 5 g sodium chloride per day. These apparently contradictory results caused a considerable controversy in the cardiovascular community, some supporting a general reduction in salt intake in populations and others suggesting no changes. For many years, the reasons for the discrepancy were not well understood except for the fact that spot urine samples rather than 24-hour urine collections were used to estimate sodium intake in studies reporting a U-shaped relationship. Very recently, He et al[29] reanalyzed the Trials of Hypertension Prevention follow-up data. They calculated sodium intake using the measured 24-hour urinary sodium excretion as well as the estimations from spot sodium concentrations using the Kawasaki, Tanaka, and INTERSALT (International Cooperative Study on Salt) formulas. Their analysis suggested that a U-shaped relationship is due to an artefact associated with the use of spot urine samples, which take into account sodium as well as creatinine.[29] Therefore, they concluded that inaccurate estimates of sodium intake (with formulas based on a spot urine tests) cannot be used in association studies, as variables used in the formulas per se seem to be related to mortality independent of sodium.[29] Whether this finding will close the dispute is unknown; however, it is unlikely.

Nevertheless, in most countries, salt consumption is high. The estimated mean level of global sodium consumption was 3.95 g per day (or 10 g sodium chloride per day) in a study by Mozaffarian et al,[24] but with regional mean sodium levels ranging from 2.18 to 5.51 g per day. In this study, countries from Central and Eastern Europe had the highest sodium intakes. Thus, it is wise to recommend a general reduction of sodium intake in these populations, including Polish populations. At this point it is useful to remember that in patients with hypertension, lowering salt intake is beneficial in several aspects: not only does it lowers BP and cardiovascular events but also increases the antihypertensive efficacy of RAS blockers and diuretics and lowers microalbuminuria. At the 2019 ESC meeting in Paris, Dr Jaime Miranda from Lima presented the results of their prospective study in Peru, in which they replaced the normal sodium chloride with a salt substitute containing 75% sodium and 25% potassium in the households of 6 Peruvian villages.[30] The salt substitution induced a modest decrease in BP in the population, but the most striking result was that it reduced the likelihood of developing hypertension by 51% compared with normal salt (hazard ratio, 0.49; 95% confidence interval, 0.34–0.71; P <0.001).[31] Thus, these data suggest that lowering salt intake may prevent the development of new cases of hypertension. Therefore, even though there may still be some controversy on the pertinence of reducing salt intake to 5 to 6 g a day, salt reduction appears to be a wise recommendation, at least in patients with hypertension.

Resistant hypertension and renal denervation: still alive? The development of device therapies such as renal denervation (RDN), baroreflex activation therapy, and endovascular baroreflex modulation has stimulated the clinical interest and research in the field of resistant hypertension. Indeed, these devices were originally designed to improve the management of patients with severe uncontrolled hypertension and this promoted much research on the prevalence and clinical characteristics of resistant hypertension.

Several surveys have been conducted to determine the prevalence of resistant hypertension.[32-35] Interestingly, large discrepancies were found in these studies with prevalence ranging from 5% to 30%. In fact, after excluding the cases of pseudo-resistant hypertension due

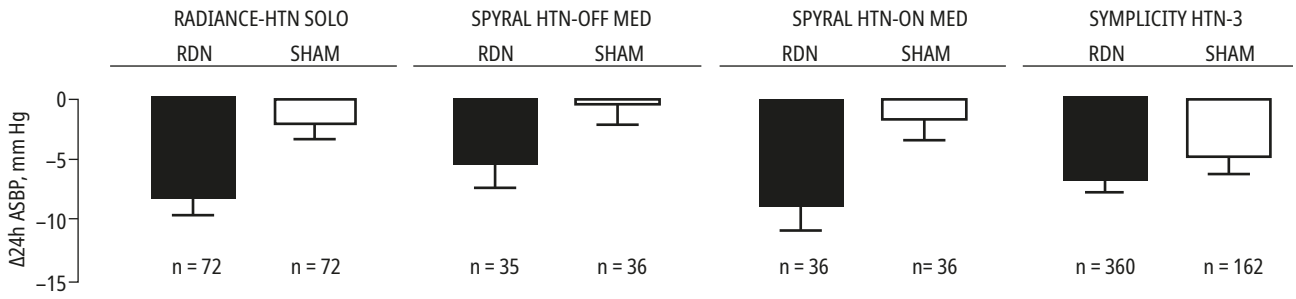

FIGURE 1 24-hour ambulatory systolic blood pressure reduction in RADIANCE-HTN SOLO, SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and SYMPLICITY HTN-3 randomized clinical trials (reproduced with permission from Lobo et al[42]).

Abbreviations: ASBP, ambulatory systolic blood pressure; HTN, hypertension; OFF MED, without medical treatment; ON MED, on medical treatment; RDN, renal denervation; SHAM, sham procedure

to nonadherence to drug therapy and white-coat hypertension, the prevalence of true resistant hypertension was much lower, below 5% in the general population and slightly higher in hypertension centers, where complicated cases are referred.[36] The second observation is that many patients with resistant hypertension can actually be conrolled using the prescription of spironolactone as the fourth-line therapy after diuretics, calcium antagonists, and RAS blockers.[37-40] Thus, the real need for an interventional therapy decreased significantly as more precise data on resistant hypertension were gathered.

The initial clinical and experimental studies using radiofrequency RDN to reduce BP in patients with resistant hypertension were quite promising,[41,42] but the enthusiasm faded after the publication of the negative results of SYMPLICITY HTN-3,[43] which lead to a drastic reduction in the number of procedures performed around the world. Nevertheless, some device companies did not stop their programs and even started new ones with revised objectives. New goals were to demonstrate that RDN indeed lowers BP in other groups of patients, to refine the technology in order to apply the denervation more distally in renal arteries, and to reduce the variability of the response to RDN improving the selection of patients who could benefit from the therapy. Two clinical programs should be cited, that is, the SPYRAL and the RADIANCE study programs. These programs addressed different populations, such as treatment-naive patients with hypertension, and new technologies, such as ultrasounds, as reviewed recently by Lobo et al.[44] Several of these studies confirmed the antihypertensive efficacy of RDN when compared with a sham procedure, as illustrated in FIGURE 1.[45-47] In addition to these studies, several registries were created to collect the multiple local experiences. The first results of these registries actually support the conclusions of the trials.[44] However, according to the 24-hour ambulatory BP data, the BP lowering effect of RDN appears to be modest, equivalent to the efficacy of 1 antihypertensive drug. Moreover, the response to RDN remains unpredictable and it is almost impossible to define good candidates for RDN a priori. Thus, taken together, these results confirm that RDN lowers BP but, at the present time, this approach cannot be recommended for routine use. However, it might be suggested to patients with severe hypertension despite a high number of prescribed drugs or to nonadherent patients who refuse antihypertensive drugs. However, in many of these patients, RDN per se will not be sufficient to control BP adequately. Several studies are still ongoing and physicians may have to wait for a better positioning of this approach in the management of patients with hypertension.

Conclusion This article briefly discusses 6 current major points of controversy from the field of arterial hypertension. On the last pages of the 2018 ESC / ESH hypertension guidelines, there is a list of 26 topics for which there are major gaps in evidence and additional studies are needed.[7] Each of these topics could represent a matter of controversial debate. In the absence of sufficient evidence, physicians have to make decision according to their own experience in the best interest of their patients. In this respect, the best interest of a patient with hypertension is often to have a well-controlled BP.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Burnier M. Controversies in the management of patients with arterial hypertension. Kardiol Pol. 2019; 77: 902-907. doi:10.33963/KP.15002

REFERENCES

1 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017; 389: 37-55.

2 Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967; 202: 1028-1034.

3 Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970; 213: 1143-1152.

4 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study. JAMA. 1977; 237: 255-261.

5 Kotchen TA. Developing hypertension guidelines: an evolving process. Am J Hypertens. 2014; 27: 765-772.

6 Tykarski A, Narkiewicz K, Gaciong Z, et al. 2015 guidelines for the management of hypertension. Recommendations of the Polish Society of Hypertension – short version. Kardiol Pol. 2015; 73: 676-700.

7 Williams B, Macia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018; 36: 1953-2041.

8 Whelton PK, Williams B. The 2018 European Society of Cardiology/European Society of Hypertension and 2017 American College of Cardiology/American Heart Association blood pressure guidelines: more similar than different. JAMA. 2018; 320: 1749-1750.

9 Whelton PK, Carey RM, Aronow WS, et al. 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. 2018; 71: 1269-1324.

10 Hypertension in adults: diagnosis and management. National Institute for Health and Care Excellende Guideline [NG136]. https://www.nice.org.uk/guidance/ng136/chapter/Recommendations. Accessed September 27, 2019.

11 Wójcik C, Shapiro MD. Bridging the gap between cardiology and family medicine. Circulation, 2019; 140: 709-711.

12 Wright JT Jr, Williamson JD, Whelton PK, et al. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015; 373: 2103-2116.

13 Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged >/=75 years: a randomized clinical trial. JAMA. 2016; 315: 2673-2682.

14 Kjeldsen SE, Lund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurements in the systolic blood pressure intervention trial: implications for entry and achieved blood pressure values compared with other trials. Hypertension. 2016; 67: 808-812.

15 Filipovský J, Seidlerová J, Ceral J, et al. A multicentre study on unattended automated office blood pressure measurement in treated hypertensive patients. Blood Pressure. 2018; 27: 188-193.

16 Ihm SH, Bakris G, Sakuma I, et al. Controversies in the 2017 ACC/AHA hypertension guidelines: who can be eligible for treatments under the new guidelines? An asian perspective. Circ J. 2019; 83: 504-510.

17 Czarnecka D, Jankowski P, Kopeć G, et al. Polish Forum for Prevention Guidelines on Hypertension: update 2017. Kardiol Pol. 2017; 75: 282-285.

18 Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016; 374: 2009-2020.

19 Zdrojewski T, Jankowski P1, Bandosz P, et al. A new version of cardiovascular risk assessment system and risk charts calibrated for Polish population [Polish]. Kardiol Pol. 2015; 73: 958-961.

20 Mente A, O'Donnell M, Rangarajan S, et al., Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. Lancet. 2018; 392: 496-506.

21 Mente A, O'Donnell M, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014; 371: 601-611.

22 Jackson SL, Cogswell ME, Zhao L, et al. Association Between urinary sodium and potassium excretion and blood pressure among adults in the United States: National Health and Nutrition Examination Survey, 2014. Circulation. 2018; 137: 237-246.

23 Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. BMJ. 1988; 297: 319-328.

24 Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. N Engl J Med. 2014; 371: 624-634.

25 Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation. 2014; 129: 981-989.

26 Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the trials of hypertension prevention. J Am Coll Cardiol. 2016; 68: 1609-1617.

27 O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med. 2014; 371: 612-23.

28 Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA. 2011; 305: 1777-1785.

29 He FJ, Ma Y, Campbell NR, et al. Formulas to estimate dietary sodium intake from spot urine alter sodium-mortality relationship. Hypertension. 2019; 74: 572-580.

30 Bernabe-Ortiz A, Diez-Canseco F, Gilman RH, et al. Launching a salt substitute to reduce blood pressure at the population level: a cluster randomized stepped wedge trial in Peru. Trials. 2014; 15: 93.

31 Community-based salt substitution programme lowers blood pressure [press release]. ESC Press Office. September 02, 2019. https://www.escardio.org/The-ESC/Press-Office/Press-releases/community-based-salt-substitution-programme-lowers-blood-pressure. Accessed October 9, 2019.

32 Calhoun DA, 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: 1403-1419.

33 de la Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011; 57: 898-902.

34 Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011; 57: 1076-1080.

35 Brambilla G, Bombelli M, Seravalle G, et al. Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. J Hypertens. 2013; 31: 2018-2024.

36 Carey RM, Calhoun DA, Bakris GL, et al. resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018; 72: e53-e90.

37 Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015; 386: 2059-2068.

38 Krieger EM, Drager LF, Giorgi DMA, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT Randomized Study (Resistant Hypertension Optimal Treatment). Hypertension. 2018; 71: 681-690.

39 Rosa J, Widimský P, Waldauf P, et al. Role of adding spironolactone and renal denervation in true resistant hypertension: one-year outcomes of randomized PRAGUE-15 Study. Hypertension. 2016; 67: 397-403.

40 Václavík J, Sedlák R, Jarkovský J, et al. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). Medicine (Baltimore). 2014; 93: e162.

41 Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010; 376: 1903-1909.

42 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: 1275-1281.

43 Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014; 370: 1393-1401.

44 Lobo MD, Sharp ASP, Kapil V, et al. Joint UK societies' 2019 consensus statement on renal denervation. Heart. 2019; 105: 1456-1463.

45 Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018; 391: 2335-2345.

46 Kandzari DE, Böhm M, Mahfoud F, et al. 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. 2018; 391: 2346-2355.

47 Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017; 390: 2160-2170.