

# A Novel Approach in Hypertension Management: A Review on Current Technologies

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## ABSTRACT

Systemic hypertension is the largest causes of morbidity and mortality in the world and is one of main causes that leading to increased risk of cardiovascular disease (CVD). Less than half of hypertensive patients are aware of their condition, despite it is currently undertreated, but the control of high blood pressure is successful. This will reduce the global burden of illness and death. The etiology of hypertension includes a genetic predisposition and a complex interaction of pathophysiological, genetic and environmental factors. Hypertensive patient needs to measurement of blood pressure (BP), studying of expected risk of atherosclerotic cardiovascular disease and other organ damage, or knowing of secondary reasons for hypertension. Lifestyle changes are effective in lowering blood pressure and stopping the consequences of hypertension and CVD, along with dietary adjustments and increased physical activity. Pharmacological treatment are efficient in controlling blood pressure and stopping the consequences of cardiovascular disease in the elderly patients. The first-line antihypertensive drugs consists of ACE inhibitor (angiotensin converting enzyme), angiotensin II receptor blocker, dihydropyridine calcium channel blocker, and thiazide diuretic.

**Keywords:** Cardiovascular, Chronic hypertension, Hypertension, New treatments.

## 1. Introduction

Blood pressure is the ratio of systolic blood pressure (pressure that blood exerts on the arterial wall when the heart contracts) and diastolic blood pressure (pressure when the heart relaxes), the hypertension depends on the method which used for measurement of Bp. The majority of hypertensive patients (90-95%) suffer from highly heterogeneous

"essential" or primary hypertension with multifactorial genetic environmental etiology. Positive family history is common in patients with hypertension, and heredity (due to genetic factor variation) is estimated to be 35% to 50% in most studies [1, 2] Secondary hypertension occurs if high blood pressure is due to other causes (example, aldosteronism, renal artery stenosis, neuroendocrine tumor of the adrenal glands with hypertension [3]. In treating

hypertension, it's miles critical to recollect a person's expected atherosclerotic CVD (ASCVD) chance extra than the extent of BP alone, as people with excessive CVD chance derive the best gain from BP reducing treatment [4].

## 2. Stages of hypertension

There are four categories of Blood Pressure: normal, mild, moderate and severe. Treatment depends on which category your pressure consistently falls in when readings are taken, see Table 1.

Table 1: The American College of Cardiology/American Heart Association Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017 Guideline) [5].

Normal	Systolic < 120 mmHg Diastolic < 80 mmHg
Elevated	Systolic: 120-129 mmHg Diastolic < 80 mmHg
Hypertension	Systolic: 130 mmHg or Higher Diastolic: 80 mmHg or Higher

## 3. Epidemiology

Since 1990 the number of hypertensive adults aged 30–79 years has increased to 1.28 billion within the last thirty years, despite that age is a proxy for the possibility in addition to environmental cause that boom BP over time, 1st high sodium diet, obesity, physical inactivity, and alcohol consumption.

However, as financial improvement progresses, high blood pressure first of all impacts people with a high socioeconomic status, financial improvement means the superiority of HT. The outcomes which are best in people with decrease socioeconomic status. Other factor genetic predisposition or damaging intrauterine (pre-eclampsia or gestational high blood pressure) have small but precise effects with excessive BP tiers in adulthood [6]. However, due to gaps in the diagnosis and treatment, so most of people with hypertension (41% of women and 51% of men) were unaware of their condition because they were not diagnosed [7].

## 4. Cardiovascular Disease Risk

The courting among BP and CVD is stated in each sex, at every age all through maturity and for all most important manifestations of cardiovascular and cerebrovascular diseases (including coronary heart diseases, myocardial infarction, and stroke) [8]. Stage of BP has confirmed to be a

chief aspect of CVD chance in all prediction models, CVD complication in people with high blood pressure generally tend to happen approximately 5 years in advance than in people with a decrease stage of BP [9].

According to study done by Hall ME et al in people of 40–69 years of age, a 20 mmHg upward thrust of systolic BP or a 10 mmHg upward thrust of diastolic BP.

is increase the chance of stroke or ischemic mortality by twice, while a systolic BP decrease of 5 mmHg can lower mortality rate 14% and CVD mortality through 9%. In elderly ( $\geq 80$  years), the corresponding relative risk is barely lower [10].

## 5. Pathophysiology of Hypertension

Blood pressure is decided with the aid of using numerous parameters of the cardiovascular, along with blood volume and cardiac output, arterial tone, the renin-angiotensin-aldosterone system (RAAS), the function of natriuretic peptides, the sympathetic nervous system (SNS) and the immunity. The mosaic principle of high blood pressure together with other environmental factors, such as excessive sodium consumption, extra alcohol consumption, and stress, will increase risk of hypertension [10].

Finally, aging will increase the possibility of growing high blood pressure, because of stiffening of the arterial vasculature, slowly growing in vascular collagen will increase incidence of atherosclerosis [11,12]. Immunological elements also can play a main part, especially at the history of autoimmune disease, infectious, inflammation together with rheumatoid arthritis [13].

### 5.1 Renin-Angiotensin-Aldosterone system and sodium homeostasis

The RAAS has complex consequences on BP regulation, balancing fluid and electrolyte levels, (result in reduced sodium reabsorption and extended sodium excretion), as well as regulating vascular resistance & tone [12].

The RAAS is multi-organ endocrine (hormone) system, regulates absorption of sodium and water in the kidney so affect the systemic blood pressure directly by assist adjust homeostasis within the kidney, when nutritional sodium will increase in normotensive individuals, compensatory haemodynamic adjustments consist of decrease in renal and peripheral vascular resistance to keep regular BP. Renin is synthesized were the function of renin is to cleave angiotensinogen to angiotensin I. Angiotensin-converting enzyme (ACE) convert angiotensin I to angiotensin II, Angiotensin II increase sodium reabsorption within the proximal tubule with the aid of aldosterone. In hypertensive patients Angiotensin II causing organ damage [10]. Aldosterone performs important part in hypertension by

binding to the mineralocorticoid receptor and enhances renal sodium reabsorption. [14].

## 6. Diagnosis of Hypertension

Since 2010, techniques to degree BP out- of workplace were more delivered to manual analysis and remedy of hypertension [15]. These consist of home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM). Evidence supports using digital oscillometric BP measurements within the workplace and out-of-workplace, the use of ABPM (commonly each 20–30 minutes) while HBPM (BP at ordinary durations) usually for the 24-hour duration diagnostic collection to corroborate accelerated BP readings carried out within the workplace or clinic to diagnose hypertension [15]. This was coincided with a study that was reported by Roush GC et al that identifying wonderful BP phenotypes, such as white coat or remoted hospital high blood pressure and masked or remoted ambulatory hypertension [16].

White coat high blood pressure is hypertension in which people exhibit accelerated blood pressure above the normal level in a clinic, however ordinary ABPM or HBPM readings. Introduction of 24-hour ambulatory blood strain monitoring (ABPM) which is the most popular diagnostic approach for hypertension, however has a few shortcomings in scientific exercise at the same time as scientific settings frequently lack enough gadgets to house of all sufferers with suspected hypertension. By contrast, masked high blood pressure is characterized via way of means of ordinary workplace readings however accelerated out-of-workplace readings (ABPM and HBPM) [17]. Self-monitoring and tele-monitoring to virtual clinics and artificial intelligence (AI)-assisted technology management which is a better predictor of end organ damage than clinic measurement. [18] Another technology for self-monitoring done by BP monitoring approaches such as smartphone and BP monitor by using the oscillometric signal [19].

A study by Omboni S et al support that Tele-monitoring is the transfer of data remotely-which also combined with the other parameters such as patient heart rate, oxygen saturations either from the patient's home or workplace to a professional healthcare such as hospital or clinic/surgery which is termed 'M-health' [20].

## 7. Prevention & Management

In maximum nations, were the age-associated growth in BP is common, while in remoted societies research suggest that excessive BP isn't always an inevitable outcome of growing older and that the upward thrust in BP is associated with adjustments in diet, reduced body weight and intake of alcohol [21,22]. Lifestyle changes (non-pharmacological) technique to reduce hypertension. The simplest one is weight loss, decreased Na<sup>+</sup> intake,[23,24], extended bodily activity, decreased intake of alcohol, and diets just like the Dietary Approaches to Stop Hypertension (DASH) diet. The DASH food plan is mainly successful whilst blended with different BP reducing interventions including a low sodium diet. Physical interest may be superior through making it less complicated for participants of the network to have interaction in exercising on a recurring basis [25].

## 8. Non-Pharmacological Management

Dietary guidelines recommended targeted nutritional low sodium consumption (preferably to <2.3 g in a day) can decrease the systolic Bp. [26] The maximum convincing proof is supplied via way of means of the Dietary Approaches to Stop Hypertension (DASH-sodium) trial, wherein the outcomes of three different kind of sodium intakes had been examined one after the other in mixture with diets: the DASH weight loss program, wealthy in fruit, vegetables, low-fats dairy products and decreased in saturated fats and cholesterol. As greater than 75% of nutritional salt comes from processed foods (in western countries). So far, best 3 countries (Japan, Finland and the United Kingdom) have efficaciously decreased populace salt intake [27]. Moderate alcohol intake - Keeping alcohol consumption ≤2 trendy drinks (~3.5 alcohol units) in line with day and ≤1 trendy drink (~1.75 alcohol units) can make a contribution to a 2–4 mmHg BP reduction [28,29]. Weight Loss - Excess weight commonly increases BP in prone individuals, [30] Lifestyle interventions, which includes hypocaloric diets and regular physical activity or exercise, are generally endorsed for sufferers with weight problems and high blood pressure [31], See Fig. 1.

## 9. Antihypertensive Pharmacotherapy

The common monotherapy agents used to treat HT were renin-angiotensin system blockers (RAS; either ACE inhibitors or angiotensin II receptor blockers).

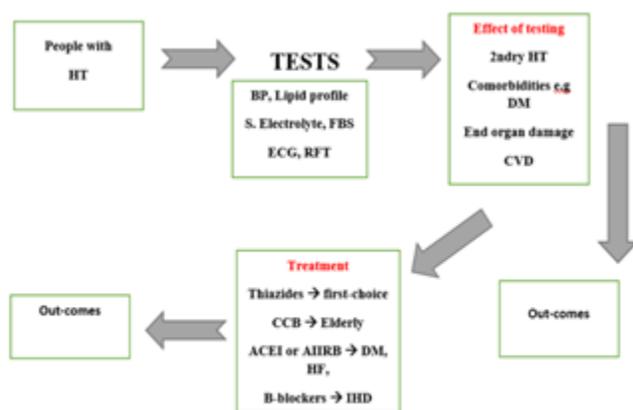


Fig. 1: Different explanation effect test and treatment on hypertension

Overall of diuretics, b-blockers, and calcium channel blockers (CCBs) most commonly used agents but with similar levels of usage. According to age and ethnicity, b-blockers were the second largely used agents for patients aged 55 years. Moreover, diuretics and CCBs are more frequently used than b-blockers in the older patients or African. The most commonly used double therapies are RAS blockers plus diuretics, RAS blockers with b-blockers, and RAS-blockers with CCBs. However commonly triple therapies also used is either RAS blockers, diuretics, and CCBs, or the alternative RAS blockers, diuretics, and b-blockers [32]. By contrast, combining ACE inhibitors and angiotensin II receptor blockers causes little BP reducing at the same time as growing the hazard for renal disorder and hyperkalemia (excessive blood potassium levels, that can cause cardiac arrhythmias). Similarly, combining RAS blockers with beta-blockers causes little BP reduction and indicated in patients suffering from acute myocardial infarction or coronary heart failure with decreased left ventricular ejection fraction [33].

Recently, hypertensive drugs such as mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, and agonists of natriuretic peptide receptor are proved more useful in preclinical or clinical developed non-hypertensive patients [34]. In obesity, hypertensive patient, these drugs ameliorate insulin resistance and in patients with heart failure, these drugs slow progression of diabetes mellitus type 2 [35].

Other drugs which are recently used for HT treatment is the vaso-peptidase inhibitors (Nepriylisin) or neutral endopeptidase which cause vasodilation, increase natriuresis, RAS inhibition and also cause breakdown of natriuretic peptides and end-organ damage. Indeed, greater anti-

hypertensive effects are obtained when it combined with other drugs like ACE inhibitor so it offers advantage to improve vasodilatation. On the other hand, this drug cause vasoconstriction, deterioration in the kidney functions & lead to organ damage [36]. The combined using of these drugs is discontinued due to higher incidence of angioedema for these drugs [37]. Ruilope LM et al illustrated that mineralocorticoid (Aldosterone) hormone control electrolyte and regulate volume homeostasis in the body. When elevated of aldosterone, the hypertension is developed. The main effector for action of this hormone is the mineralocorticoid receptor(MR) that present in the kidney. The activation of MR by aldosterone will enhance water and sodium reabsorption and increase loss of potassium; consequently it leads to hypertension.

Anti-aldosterone drugs inhibit the rate limiting step of aldosterone production;e.g finerenone drug decreases blood pressure by competing for aldosterone binding sites to treat hypertension mediated by aldosterone & reduces incidence of vascular disease. Mineralocorticoid receptor antagonist is recently discovered with high selectivity, better cardiac activity & organ protection without affecting kidney function adversely [39, 40]. However Anti-diabetic drugs have cardiovascular safety & lack of toxicity, so these drugs improve glycaemic control as a result it can decrease blood pressure & improve cardiovascular outcomes. Anti-diabetic drugs such as glucagon-like peptide 1 (GLP-1) analogue (e.g. liraglutide) can decrease blood pressure in diabetic hypertensive patients [41, 42].

## 10. Treatment of Resistant Hypertension

BP >140/90 is called resistant hypertension which can be treated with 3 or more antihypertensive drugs. However, predicted 12.8% of all people with hypertension within the United States and 15.3 % of these handled with antihypertensive satisfy the standards for drug resistant hypertension [34]. Adding a 4th or 5th drug ought to result in first-rate BP manipulate in those patients. The PATHWAY trial turned around sufferers with treatment resistant high blood pressure thru distinctive addition on treatment or placebo in a randomized trial [35]. All sufferers obtained a standardized antihypertensive routine comprising 3 drugs. In addition, the mineralocorticoid receptor antagonist (e.g. spironolactone) as a 4th drug is added [43]. Overall, mineralocorticoid receptor antagonism is an inexpensive desire in sufferers with tough to govern hypertension. Control

of potassium level in blood is required when these drugs are given. [44]

## 11. Device-based Treatments

Device-primarily based remedies had been more often introduced for hypertensive patients with non-control BP by antihypertensive drugs. Catheter-primarily based totally renal nerve ablation [45], electrical stimulation of carotid sinus [46], modulation of baroreflex transduction with a committed carotid stent, and deep mind stimulation [47] are idea to decrease BP via SNS inhibition. Creation of arteriovenous stent with tools lowers BP by the aid of using decreasing peripheral vascular resistance [48]. None of these has been to be efficacious in decreasing BP in randomized sham-managed medical trials [45].

## 12. Quality of life

Hypertension is one of the major risk factors for cardiovascular disease, which cause decrease the quality of life (QOL), especially in elderly patients [49]. There is an association between QOL and adherence to treatments. In the elderly patients, when the adherence level to treatments increases, the QOL also increases. Trevisol DJ et al reported that older age, longer duration of disease, polypharmacy, and lower educational status have negative effect on the adherence level [50]. Altered HRQoL in hypertensive patients are affected by several factors, such as the diagnosis, treatment, and alterations effects (each elevations and reductions) in BP [51].

## 13. Conclusions

According to WHO hypertension is a worldwide morbidity and mortality most identified risk factors, & according to Wolf-Maier K et al it is till now under-controlled disease although the wide range of presented treatment [52, 53].

Now a day's not only the traditional method for measuring Bp which is the cuff-based measurement of blood pressure, there is new devices, & methods to diagnose, screening & controlling HT, however they provide aspects of better results & accuracy, in addition to easily uses even by the patients themselves especially in the elderly (self-monitoring) such as smartphones & the health applications.

Until recently, the most appropriate method cannot have detected, the key evidence needed for the benefit of the health system to be effectively improved & avoid most fatal clinics mistakes & also reducing the elderly patients burden [54].

## References

1. Luft FC. Twins in Cardiovascular Genetic Research. *Hypertension*. 2001;37:350–356.
2. Fagard Rm et al. Heritability of Conventional and Ambulatory Blood Pressures: A Study in Twins. *Hypertension*. 1995;26:919–924.
3. Dominiczak A, Delles C and Padmanabhan S. Genomics and Precision Medicine for Clinicians and Scientists in Hypertension. *Hypertension* 69, e10–e13. 2017.
4. Sundström J, Arima H and Woodward M. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet*. 2014;384:591–598.
5. Health line. 2021. Types of Hypertension: Primary, Secondary, Causes, and More. [online] Available at: <<https://www.healthline.com/health/types-and-stages-of-hypertension>> [Accessed 21 Novmber 2021]
6. Poulter NR, Prabhakaran D and Caulfield M. *Hypertension*. *Lancet*. 2015;386:801–812.
7. Rapsomaniki E, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899–1911.
8. Stamler J, Stamler R and Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch. Intern. Med*. 1993;153:598–615.
9. Klag MJ, et al. Blood pressure and end-stage renal disease in men. *N. Engl. J. Med*. 1996;334:13–8.
10. Hall ME and Hall JE. Pathogenesis of Hypertension. *Hypertension: A Companion to Braunwald's Heart Disease*. 2018:33–51.
11. Whelton PK, et al. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase I of the Trials of Hypertension Prevention. *Trials of Hypertension Prevention Collaborative Research Group*. *Am. J. Clin. Nutr*. 1997;65:652S–660S.
12. Mikael L. de R, et al. Vascular Aging and Arterial Stiffness. *Arq. Bras. Cardiol*. 2017;109:253–258.
13. Harrison DG and Bernstein KE Inflammation and Immunity in Hypertension. *Hypertension: A Companion to Braunwald's Heart Disease*. 2018:60–69.
14. Zhou ZH & Bubien JK Nongenomic regulation of ENaC by aldosterone. *Am. J. Physiol. Cell Physiol*. 2001;281:C1118–30.
15. Dickson RC, Gaebel K, Zizzo A, et al. Self-reported physician adherence to guidelines for measuring blood pressure. *J Am Board Fam Med*. 2013;26:215-7.630
16. Roush GC, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13 844 patients with hypertension. *J. Hypertens*. 2014;32:2332–2340.

17. Stergiou GS, et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement. *J. Hypertens.* 2016;34:1665–1677.
18. Grant RW, Pandisisco JC, Pajolek H, Woulfe A, Pelletier A, Kvedar J, et al. Implementation of a web-based tool for patient medication self-management: the Medication Self-titration Evaluation Programme (Med-STEP) for blood pressure control. *Inform Primary Care.* 2012;20(1):57–67.
19. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Tele-monitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet.* 2010;376(9736):163–72.
20. Omboni S and Ferrari R. The role of telemedicine in hypertension management: focus on blood pressure telemonitoring. *Curr Hypertens Rep.* 2015;17(4):535.
21. He J, et al. Migration, blood pressure pattern, and hypertension: the Yi Migrant Study. *Am. J. Epidemiol.* 1991;134:1085–101.
22. Rosenthal T. The effect of migration on hypertension and other cardiovascular risk factors: A review. *J. Am. Soc. Hypertens.* 2014;8:171–191.
23. The effects of non-pharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA.* 1992;267:1213–20.
24. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. *Arch. Intern. Med.* 1997;157:657–67.
25. Sacks FM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N. Engl. J. Med.* 2001;344:3–10.
26. He FJ and Li J. Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ.* 2013;346:f1325.
27. He FJ and MacGregor GA. Reducing Population Salt Intake-Time for Global Action. *J. Clin. Hypertens.* 2014;17:10–13.
28. Xin X et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertens.* 1979; 38,1112–7.
29. Roerecke M, et al. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. *Lancet Public Heal* 2. 2017:e108–e120.
30. Börjesson M, Onerup A, Lundqvist S and Dahlöf B. Physical activity and exercise lower blood pressure in individuals with hypertension: narrative review of 27 RCTs. *Br. J. Sports Med.* 2016;50:356–361.
31. Stevens VJ. Long-Term Weight Loss and Changes in Blood Pressure: Results of the Trials of Hypertension Prevention, Phase II. *Ann. Intern. Med.* 2001;134:1.
32. Emanuela Falaschetti, Moushumi Chaudhury, Jennifer Mindell and Neil Poulter Continued Improvement in Hypertension Management in England: Results From the Health Survey for England 2006. *Hypertension.* 2009; 53: 480-486.
33. Oparil S & Schmieder RE New Approaches in the Treatment of Hypertension. *Circ. Res* 2015;116:1074–1095.
34. Jordan J et al. Improved Insulin Sensitivity With Angiotensin Receptor Neprilysin Inhibition in Individuals With Obesity and Hypertension. *Clin. Pharmacol. Ther.* 2016;101:254–263.
35. Williams B 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 (London, England).* 2015;386:2059–68.
36. Kostis JB, Packer M, Black HR, et al. : Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens.* 2004;17(2):103–11. 10.1016/j.amjhyper.2003.09.014
37. Packer M, Califf RM, Konstam MA, et al. : Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation.* 2002;106(8):920–6.
38. Ruilope LM. Aldosterone, hypertension, and cardiovascular disease: an endless story. *Hypertension.* 2008; 52:207–208.
39. Colussi G, Catena C and Sechi LA. Spironolactone, eplerenone and the new aldosterone blockers in endocrine and primary hypertension. *J Hypertens.* 2013;31:3–15.
40. Garthwaite SM and McMahon EG. The evolution of aldosterone antagonists. *Mol Cell Endocrinol.* 2004;217:27–31.
41. von Scholten BJ, Lajer M, Goetze JP, et al. : Time course and mechanisms of the anti-hypertensive andrenal effects of liraglutide treatment. *Diabet Med.* 2015;32(3):343–52.
42. Marso SP, Daniels GH, Brown-Frandsen K, et al. : Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311–22.
43. Calhoun DA, 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.
44. Sim JJ, et al. Characteristics of Resistant Hypertension in a Large, Ethnically Diverse Hypertension Population of an Integrated Health System. *Mayo Clin. Proc.* 2013;88:1099–1107.
45. Krum H et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet.* 2009;373:1275–1281.
46. Heusser K, et al. Carotid Baroreceptor Stimulation, Sympathetic Activity, Baroreflex Function, and Blood Pressure in Hypertensive Patients. *Hypertension.* 2010;55:619–626.
47. O’Callaghan EL et al. Chronic Deep Brain Stimulation Decreases Blood Pressure and Sympathetic Nerve Activity in a

- Drug- and Device-Resistant Hypertensive Patient. Hypertension. 2017;69, 522–528.
48. Lobo MD, et al. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet*. 2015;385:1634–1641.
49. Testa MA and Simonson DC Assessment of Quality-of-Life Outcomes. *N. Engl. J. Med.* 1996;334:835–840.
50. Trevisol DJ, Moreira LB, Kerkhoff A, Fuchs SC & Fuchs FD Health-related quality of life and hypertension: a systematic review and meta-analysis of observational studies. *J. Hypertens.* 2011;29:179–188.
51. Bardage C and Isacson DG Hypertension and health-related quality of life. an epidemiological study in Sweden. *J. Clin. Epidemiol.* 2001;54:172–81.
52. Organisation WH. World Health Organization (2013), A global brief on hypertension. Report. 2013 April 2013. Contract No.: WHO/DCO/WHD/2013.2.
53. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada and the United States. *Hypertension*. 2004;43(1):10–7.
54. Burke LE, Ma J, Azar KM, Bennett GG, Peterson ED, Zheng Y, et al. Current science on consumer use of Mobile health for cardio-vascular disease prevention: a scientific statement from the American Heart Association. *Circulation*. 2015;132(12):1157–213.