HHS Public Access

Author manuscript

Nat Rev Nephrol. Author manuscript; available in PMC 2016 July 29.

Published in final edited form as:

Nat Rev Nephrol. 2016 February ; 12(2): 70–72. doi:10.1038/nrneph.2015.199.

Hypertension in 2015: Treatment of resistant hypertension: Impact and evolving treatment options

Lilach O. Lerman, MD, PhD and **Stephen C. Textor, MD**

The Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

Abstract

Arterial hypertension elevates the risk of adverse renal and cardiovascular outcomes, which can be decreased by maneuvers that lower blood pressure (BP). However, a combination of multiple antihypertensive drugs at optimal doses fails to achieve BP control in up to 15% of the hypertensive population. This has led to a relentless search for novel therapeutic alternatives in order to achieve satisfactory control of BP levels. Several prominent studies published in 2015 have shed light on the risks imposed by uncontrolled or partially treated hypertension, and evaluate new therapeutic modalities designed to address the unmet needs of the treatment-resistant hypertensive individual.

Arterial hypertension substantially elevates the risk for adverse cardiovascular and renal outcomes, including end-stage renal disease (ESRD), ischemic cardiac and cerebrovascular events, accelerated atherosclerosis, congestive heart-failure (CHF), and all-cause mortality. Most of these can be decreased by maneuvers that lower blood pressure (BP). However, recognition that some hypertensive individuals are “treatment-resistant” is becoming a major issue in the area of nephrology and hypertension. Combinations of multiple antihypertensive drugs at optimal doses fail to achieve goal BP levels in at least 15% of the hypertensive population(1), often due to poor adherence or intolerance to antihypertensive regimens. This motivated a relentless search for novel therapeutic alternatives to achieve more satisfactory control of BP. Several studies published in 2015 have shed light on the risk imposed by uncontrolled hypertension, and evaluated new approaches designed to address the unmet needs of the treatment-resistant hypertensive individual.

The risks inherent to uncontrolled- and difficult-to-control-hypertension are reinforced by a retrospective, longitudinal 5-year cohort study of Kaiser Permanente members(2). The authors examined the electronic health-records of a 3.4-million ethnically-diverse population, of whom BP data were available for 470,386 individuals(3). Resistant hypertension (RH) was defined for 60,327 (12.8%) individuals, with 4.9% having controlled (on ≥4 drugs) and 7.9% uncontrolled RH, based on a goal systolic BP of 140mmHg and/or diastolic BP of 90mmHg. Individuals were followed until they experienced any outcome or until the end of observation. These authors reported that individuals with resistant hypertension (RH) had a greater risk for ESRD, ischemic heart events, CHF, and

Correspondence: Lilach O. Lerman, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905. Lerman.Lilach@Mayo.Edu, Phone: (507)-266-9376, Fax: (507)-266-9316.

cerebrovascular accidents compared with those with non-RH, with multivariable adjusted hazard-ratios of 1.32, 1.24, 1.46, 1.14, and 1.06, respectively. Importantly, patients with uncontrolled RH had similar baseline rates of comorbidities compared to those with controlled RH, yet subsequently experienced increased risk for ESRD and cerebrovascular accidents by 25% and 23%, respectively.

Activation of the sympathetic nervous system participates in some forms of RH and target organ injury. Renal denervation (RDN) has emerged as a novel interventional approach to decrease in BP via attenuation of renal artery sympathetic nerve activity, but remains controversial. Two large clinical trials of RDN in patients with RH, Symplicity HTN-1(4) and Symplicity HTN-2(5), reported decrements in BP and established the overall safety of the procedure. However, Symplicity HTN-3(6), a prospective, single-blind, randomized, sham-controlled trial conducted in the United States, failed to meet pre-determined endpoints from RDN, attributed partly to technical confounders. Consequently, RDN remains “in-limbo” in the United States, although it is used extensively in Europe.

The Global SYMPLICITY registry (GSR) was established to address the questions of safety and cost/benefit related to BP reduction in a “real-world” uncontrolled population of patients undergoing RDN, primarily outside the United States(7). It was designed to include ≤5000 patients ≥18 years old eligible for RDN, as defined by local regulations. The GSR recommended a 5-year follow-up with collection of a 24-hour ambulatory measurement and 3 BP measurements in each visit. Recently, the GSR reported on the 6-month follow-up of almost 1,000 hypertensive patients included in 134 centers located in five continents. A “severe hypertension cohort” within the GSR comprised 323 patients with a pre-treatment ambulatory systolic BP >135mmHg despite at least 3 antihypertensive drugs. Office systolic BP for the severe cohort (179±16mmHg) fell by 20.3±20.8mmHg 6 months after RDN, and the 24-hour mean systolic BP by 8.9±16.9mmHg; 18.6% achieved an office systolic BP <140mmHg. After RDN there was a small reduction in the number of antihypertensive medications, and low rates (<1%) of complications. Therefore, RDN provided relatively safe BP reduction beyond that achieved by intensive pharmacological therapies in patients with RH in this mixed hypertensive population.

An alternative approach to treating drug-resistant hypertension was examined in a prospective trial undertaken by the British Hypertension Society. The PATHWAY Studies Group investigated the optimal choice of a fourth-line drug treatment for RH added to a regimen including an angiotensin-converting-enzyme inhibitor or an angiotensin-II receptor blocker, a calcium-channel blocker, and a thiazide-like diuretic. These investigators reasoned that if RH was primarily caused by sodium retention, then a diuretic drug would be effective, whereas if the underlying pathogenic mechanisms are heterogeneous, then drugs with alternative mechanisms would be equally effective and best stratified by use of biomarkers of sodium/volume status, such as plasma renin level(8). Therefore, they compared the selection of spironolactone (with diuretic action based on mineralocorticoid receptor antagonism) with an α1-adrenoceptor blocker (doxazosin) that reduces peripheral resistance, and a β1-adrenoceptor blocker (bisoprolol), which reduces renin release and cardiac output.

To this end, Williams et al performed a12-month double-blind, placebo-controlled, crossover phase-4 trial in the UK. Careful attention was given to establishing baseline medication adherence prior to randomization. Treatment cycles were initiated for 6 weeks at a low dose, and then double the dose for another 6 weeks. The intention-to-treat analysis comprised 314 patients, of whom 230 completed all treatment cycles. The average reduction in home systolic BP with spironolactone was superior to placebo by −8.70mmHg, to doxazosin by −4.03mmHg, and to bisoprolol by −4.48mmHg. Spironolactone controlled BP in 58% of patients, and induced a greater fall in BP even in patients controlled by doxazosin or bisoprolol. The degree of home systolic BP fall with spironolactone showed a generally inverse relation with plasma renin levels that was superior to bisoprolol and doxazosin across most of the plasma renin distribution. Thus, spironolactone was a well-tolerated and an effective 4th line treatment for patients with RH. These findings also implicate sodium retention as the predominant pathophysiological mechanism underlying RH.

Beaussier and colleagues(9) formally evaluated the role of medication adherence on BP control and target organ injury in participants of a previously published 12-week, single-center, prospective, randomized, open-blinded endpoint trial performed in Paris, France. The primary study examined the role of sequential nephron blockade (SNB), which was more effective than sequential renin–angiotensin-system blockade (SRASB) for controlling BP in patients with RH(10). Patients whose BP was not adequately controlled by a 4-week triple-therapy regimen were randomized to SNB (spironolactone, furosemide, and amiloride) or SRASB (ramipril and bisoprolol).

The investigators evaluated adherence by means of plasma irbesartan level measurements, urinary N-acetylseryl-aspartyl-lysyl-proline/creatinine (AcSKDP/cr) ratio <4nmol/mmol (as a measure of ramipril effect), last medication intake before visit >24h, and detailed pill counts at each visit (taking <80% of theoretical intake as a marker of poor adherence). The results indicate that low medication adherence was prevalent (18.3%) among RH patients, and impacted the differential effect of drug regimens. The fall in systolic BP was greater with SNB than with SRASB (by −11.5mmHg) only for patients with acceptable medication adherence, as were changes in pulse-wave velocity and left-ventricular mass. Hence, optimizing diuretic therapy by SNB was the most effective strategy for controlling BP and decreasing target organ damage.

Taken together, studies in 2015 advanced our understanding of the prevalence and clinical significance of treatment resistant hypertension. These also better delineate the pathophysiology underlying RH and strategies to improve BP control, the need for which was reinforced by the potential risks of uncontrolled RH. In patients with RH in a “real-world” setting, RDN reduced BP effectively, despite predominant underlying excess sodium retention. Spironolactone was found to be an effective 4th-line BP-lowering treatment, but clearly, medication adherence is critical for adequate BP control and decreasing target organ damage.

Acknowledgments

Partly supported by NIH grants DK100081, DK73608, HL123160, and DK102325.

References

1. Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res. 2015; 116:1074–95. [PubMed: 25767291]
2. Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. Kidney Int. 2015; 88:622–32. [PubMed: 25945406]
3. Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun DA, McGlynn EA, Kalantar-Zadeh K, Jacobsen SJ. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. Mayo Clin Proc. 2013; 88:1099–107. [PubMed: 24079679]
4. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009; 373:1275–81. [PubMed: 19332353]
5. Symplicity HTNI. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010; 376:1903–9. [PubMed: 21093036]
6. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL, Investigators SH. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014; 370:1393–401. [PubMed: 24678939]
7. Bohm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, Ruilope L, Schlaich MP, Schmieder RE, Whitbourn R, Williams B, Zeymer U, Zirlik A, Mancia G, Investigators GSR. First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Hypertension. 2015; 65:766–74. [PubMed: 25691618]
8. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ, British Hypertension Society's PSG. 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
9. Beaussier H, Boutouyrie P, Bobrie G, Frank M, Laurent S, Coudore F, Azizi M. True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence. J Hypertens. 2015
10. Bobrie G, Frank M, Azizi M, Peyrard S, Boutouyrie P, Chatellier G, Laurent S, Menard J, Plouin PF. Sequential nephron blockade versus sequential renin-angiotensin system blockade in resistant hypertension: a prospective, randomized, open blinded endpoint study. J Hypertens. 2012; 30:1656–64. [PubMed: 22728905]

Key advances

- Uncontrolled resistant hypertension carries important risks for renal, cardiac, and cerebrovascular complications.
- Endovascular renal denervation may reduce blood pressure effectively, particularly in patients with high baseline systolic blood pressure.
- Spironolactone is an effective 4th-line antihypertensive drug.
- Even in carefully controlled treatment trials, poor medication adherence (identified in nearly 20% of participants) prevents effective BP control and regression of target organ damage.