Original Article

Evaluation of Recent Updates Regarding the Management of Resistant Hypertension

Mahdi Abdulhadi Al Muammar[1]*, Ibrahim Abdu Alsubaihi[2], Mohammed Khalid S Alqahtani[2], Hajar Saad Dajam[2], Omar Abdullah M Alshanqiti[3], Naif Bandar bin Darwish[4], Almaali Mohammad Alrakha[5], Reema Faisal Aloufi[6], Majid Rashid H Alyami[7], Salman Farraj Alanazi[8]

[1] Department of Medical Science, Faculty of Medicine, Najran University, Najran, KSA. [2] Department of Medical Science, Faculty of Medicine, King Khalid University, Abha, KSA. [3] Department of Medical Science, Faculty of Medicine, Taibah University, Maddina, KSA. [4] Department of Medical Science, Faculty of Medicine, Shaqra University, Shaqra, KSA. [5] Department of Medical Science, Faculty of Medicine, Dar Al Uloom University, Riyadh, KSA. [6] Department of Medical Science, Faculty of Medicine, Taif University, Taif, KSA. [7] Ministry of Health, Rass Tanura General Hospital, Ras Tanura, KSA. [8] Department of Medical Science, Faculty of Medicine, Almaarefa University, Riyadh, KSA.

Abstract

Background: Resistant hypertension is believed to affect around 10% of the general hypertensive population. It is a dangerous condition that should not be neglected because it can cause severe target organ damage due to the persistently high blood pressure levels. The treatment of this subgroup must be aggressive and careful in order to control their blood pressure. Objective: This study was aimed to review the recent literature that has discussed resistant hypertension and its management. Methods: PubMed database was used for articles selection and the following keywords were used in the MeSH: resistant hypertension, and management of resistant hypertension. A total number of 50 papers were reviewed and included in the review. Conclusion: Since resistant hypertension is a complex condition, its management is also complicated due to its multifactorial etiology. Treatment depends on the identification of the underlying factors contributing to treatment resistance and reversing them. Choosing effective multi-drug regimens is important and lifestyle changes should be encouraged. Failure of one antihypertensive agent to lower blood pressure to target levels requires the dose to be increased, and/or further antihypertensive medications from these different drug classes to be added up to a maximum of three different drug classes. Aliskiren, which is a direct renin inhibitor, has also been found to be an effective add-on treatment. The addition of spironolactone allows in some patients for adequate control but its use can be limited because of the concerns regarding its potential adverse effects.

Keywords: Resistant Hypertension, Diagnosis, Management

Introduction

Hypertension is the most common chronic disease among adults in developed societies [1]. It is considered resistant when blood pressure remains outside the target values of 140 mmHg for systolic and 90 mmHg for diastolic blood pressure despite three full-dose antihypertensive drugs, one of which is a diuretic, in addition to non-pharmacological measures [2, 3].

Resistant hypertension is a clinical condition that needs special attention from the general practitioner and the hypertension specialist for many reasons. It is mostly caused by secondary causes [4]. Moreover, it can cause severe target organ damage because of persistently high blood pressure levels [5]. Thus, this condition leads to cardiovascular mortality and morbidity increase [6-8]. Patients with resistant hypertension usually have a long-standing history of poorly controlled and severe hypertension associated with other comorbidities, such as obesity, sleep apnea, diabetes, and chronic kidney disease [2, 7, 9, 10].

Resistant hypertension is believed to be present in around 10% of the general hypertensive population and in around 15% of individuals taking antihypertensive medications [11, 12]. This subgroup of hypertensive patients should be identified properly because of its clinical and economic consequences. The treatment of this subgroup should be

Address for correspondence: Mahdi Abdulhadi Al Muammar, Department of Medical Science, Faculty of Medicine, Najran University, Najran, KSA.
E-mail: mahdi5037@gmail.com

How to cite this article: Abdulhadi Al Muammar, M., Abdu Alsubaihi, I., Khalid S Alqahtani, M., Saad Dajam, H., Abdullah M Alshanqiti, O., Bandar bin Darwish, N. Evaluation of Recent Updates Regarding the Management of Resistant Hypertension. Arch Pharma Pract 2019;10(3):65-70.

aggressive and careful in order to control their blood pressure, which will decrease the subsequent risk of cardiovascular morbidity [13]. Therefore, we aimed in this article to review the recent literature that discussed resistant hypertension and its management.

Methodology

PubMed database was used for articles selection and the following keywords were used in the MeSH: resistant hypertension, and management of resistant hypertension. 50 papers were reviewed and included in the review.

Inclusion criteria: The articles were selected according to the relevance to the project, which should include resistant hypertension.

Exclusion criteria: All other articles that did not have a related aspect to resistant hypertension as their primary endpoint or repeated studies were excluded from the study.

Discussion

Hypertension is a prevalent condition and its prevalence is increasing worldwide [14]. Studies have found that resistant hypertension is associated with worse cardiovascular outcomes [15]. To lower the risk of adverse cardiovascular events in patients with hypertension, it is important to achieve optimal blood pressure control [16, 17]. However, despite the patient's awareness of blood pressure control importance, many of them cannot achieve their target blood pressure [15]. Many patients require multiple medications to control their blood pressure. However, only one or two antihypertensive drug classes are prescribed while their blood pressure still above their target blood pressure [16]. In the US, approximately 13% of treated hypertensive patients have apparent treatment-resistant hypertension [16, 18, 19].

Historically, in 1769, the priest and botanic, Stephen Hales was the first one who measured blood pressure. In fact, it was the blood pressure of a horse. In this process, a brass tube connected to a water column was inserted into the horse's carotid artery. The blood rose to about 8 feet, 8 inches, about 180 mmHg, and then sunk gradually to zero and accordingly the horse died. About 100 years later, the sphygmomanometer was invented for measuring blood pressure and this technique is still in use [20].

Holmqvist et al. [20] summarized the standardized way of measuring blood pressure in their paper. It should be in a way, which is after 5-10 minutes of rest and after avoiding coffee, tobacco, and heavy exercise 30 minutes before the measurement. The patient should be in a supine or seated position, resting his/her back and having the feet on the floor. The arm should be resting at the same level as the heart [21]. The width of blood pressure cuff around the arm should be appropriate in order to avoid any under- or overestimation [22, 23].

In the manual measurement of blood pressure, after filling the cuff with the air you release it slowly and use your stethoscope to listen for the Korotkoff sound in the brachial artery. What you hear is the turbulent flow in the artery when the pressure off the cuff is equal to the pressure that the left ventricle of heart, i.e. systolic blood pressure. As the pressure drops in the cuff when air is released, there will be repetitive pulse beats of turbulent blood flow until the cuff pressure is the same as the diastolic blood pressure and no turbulence is present [20, 24].

Automated blood pressure measurements performed in the clinic are suggested to replace manual office blood pressure since they seem to have a better correlation with the values of the out of office blood pressure [25]. The difference from standard office blood pressure measurement is that the patient is left alone in the examination room with an automated oscillometric blood pressure measurement device around the forearm. Repeated measurements are performed and a mean value of these readings is reported. The advantage of this technique is reduced artifact from the white-coat effect and hence reduced unnecessary treatment [20, 26].

Regarding pathophysiology, the process behind resistant hypertension is a complex process. It is featuring multiple overlapping biological systems affected by various factors, such as lifestyle and behavior. Renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) are the main systems regulating blood pressure in the body [27]. Moreover, there are other contributing factors, for example, sodium handling, endothelial function, and arterial stiffness. Hyperactivity of the SNS is a common feature of hypertension [28, 29].

If the activity of the SNS is increased, it will cause systemic vasoconstriction. This vasoconstriction stimulates renal tubules via sympathetic efferent nerves in order to increase water and sodium reabsorption and also trigger the release of renin hormone. Released renin activates the RAAS pathway, which ultimately contributes to an elevation in blood pressure [27, 30].

Moreover, hyperaldosteronism is also a common condition among hypertensive and resistant-hypertension patients [31]. Primary hyperaldosteronism is estimated to be in 10–20% of resistant hypertension patients [32]. Aldosterone function is to promote sodium reabsorption at the distal tubules in the nephron. It also acts peripherally to suppress endothelial nitric oxide production leading to blood pressure elevation because endothelial nitric oxide works as a vasodilator [33].

Unfortunately, persistent SNS hyperactivity or chronic hyperaldosteronism can have a detrimental effect on the heart. Aldosterone exerts pro-inflammatory actions and induces oxidative stress, which can result in the fibrosis of the myocardium [34]. Moreover, the increased sympathetic drive is associated with left ventricular hypertrophy, coronary vasoconstriction, and arrhythmias [35, 36].

Numerous lifestyle and biological factors have been identified to modulate RAAS and SNS activity, increase arterial stiffening, and impede endothelial function, which collectively contribute to develop resistant hypertension. In resistant-hypertension patients, mutations in genes regulating nitric oxide production, renal sodium handling, and enzymes responsible for metabolizing aldosterone have been identified [27, 37]. Increasing age is correlated with increased arterial stiffness and a higher prevalence of resistant hypertension [38]. Excessive dietary salt intake may promote fluid retention. This can lead to volume overload, which is a feature that appears in a majority of resistant hypertension patients [39]. The pathological mechanisms underlying salt-induced resistant hypertension include elevated RAAS and SNS activity and increased peripheral vascular fibrosis [40].

obesity is a strong factor contributing to hypertension in general and resistant hypertension. Adipocyte dysfunction can lead to systemic insulin resistance, hyperaldosteronism, and RAAS and SNS hyperactivity [41]. Pro-inflammatory autocrine and paracrine actions of adipose tissue also contribute to systemic and renal endothelial dysfunction, increasing arterial stiffness and disrupting sodium regulation in the kidney [42, 43].

Diabetes also exacerbates this vascular dysfunction, which increases arterial stiffness and serum aldosterone. Eventually, SNS activity will be elevated and blood pressure subsequently will be high [27, 40].

Management

Since resistant hypertension is a complex condition, its management is also complicated due to its multifactorial etiology. Treatment depends on the identification of the underlying factors contributing to treatment resistance and reversing them. Choosing effective multi-drug regimens is important. Lifestyle changes should be encouraged, for example, weight loss, regular exercise, ingestion of a low-fat, low-salt, high-fiber diet, and avoiding alcohol intake [32]. As clinically allowable, potentially interfering substances should down-titrated. Obstructive sleep apnea should also be treated if present [32].

Prescribed diets should be as simple as possible. They also should include the use of a long-acting combination of medications so that the number of prescribed pills taken daily can be reduced. This will maximize treatment adherence leading to better blood pressure control [32]. The adherence decreases with increasing the complexity of the dosing regimen, the number of pills, and out-of-pocket costs. In addition, adherence increases with more frequent clinic visits and by having the record of patients' home blood pressure measurements [32, 44]. To further improve the treatment, a multidisciplinary treatment approach can be used, such as nurse case managers, pharmacists, and nutritionists. This approach may lead to better results but in some countries, it can be labor-intensive and expensive [45]. The improvement of follow-up, as well as medication adherence, should be achieved by involving the patient by having him/her maintain a diary of home blood pressure values; while, family members' involvement will likely enhance persistence with recommended lifestyle changes [32].

- *Nonpharmacological measures*

Weight loss has a clear benefit in terms of reducing blood pressure and often allows for a reduction in the number of prescribed medications. Studies have shown that a 10-kg weight loss is associated with an average 6-mmHg reduction in systolic and a 4.6-mmHg reduction in diastolic blood pressure [46]. Moreover, the greatest benefit of weight loss was in the patients already receiving antihypertensive therapy at least for diastolic blood pressure reduction [47]. While difficult to achieve and even more difficult to maintain, weight loss should be encouraged in any patient with resistant hypertension who is either overweight or obese [32].

Restriction of dietary salt has shown a well-documented benefit in general hypertensive patients with diastolic and systolic blood pressure reduction of 2 to 6 and 5 to 10 mm Hg, respectively [48, 49]. Elderly patients and patients of black race tend to show larger benefit [49]. In the evaluation of patients whose blood pressure was uncontrolled on a combination of an ACE inhibitor and hydrochlorothiazide, decreased diastolic and systolic blood pressure was observed at a 1-month follow-up by 8 and 9 mmHg, respectively due to a reduced salt diet [50]. Therefore, all patients with resistant hypertension should have a salt-restricted diet. The ideal amount should be less than 100 mEq of sodium/24-hour [32].

Cessation of alcohol ingestion can significantly improve hypertension control. This improvement might be due to the improvements in medication adherence or due to the stoppage of negative physiological impacts of alcohol on the body [51].

Increased physical activity also showed a decrease in blood pressure. Kokkinos et al. [52] conducted a study on a small group of African-American men with severe hypertension. In this group of patients, diastolic blood pressure decreased by 5 mmHg and systolic blood pressure by 7 mmHg through a 16-week aerobic exercise regimen (stationary cycling 3 times/week) [52]. In addition, even with the withdrawal of some antihypertensive medications, reductions in diastolic blood pressure were maintained after 32 weeks of exercise. At least, a 30-min exercise should be fixed in the daily program of patients [32, 53].

Moreover, diet control seems to be an effective way of controlling blood pressure. Ingestion of a diet that is low in total saturated fats, high in low-fat dairy products, and rich in vegetables and fruits; calcium, magnesium, and potassium has shown a significant decrease in systolic and diastolic blood pressure [32, 54].

- *Pharmacological Interventions:*

Most guidelines recommend initial drug therapy to include either a thiazide-type diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker. Failure of one antihypertensive agent to reduce blood pressure to the target levels requires the dose to be increased, and/or further antihypertensive medications from these different drug classes to be added up to a maximum of three different drug classes. However, combining an ARB with an ACE is contraindicated [27].

In spite of taking drugs, many patients with resistant hypertension have a suppressed plasma renin activity, which usually results in renin activity increase [55]. Some physicians tend to increase the intensity of the diuretic regimen by switching from hydrochlorothiazide to chlorthalidone [56]. When renal function is reduced below 30 mL/min/1.73 m^2, it may help to add or substitute a loop diuretic, such as bumetanide (twice-daily dosing) or torsemide (once-daily dosing). Nevertheless, this maneuver has not been assessed significantly in the literature [13].

When working up a resistant hypertension patient, aldosterone excess should be considered. In this case, a low dose (12.5 to 50 mg/day) of the aldosterone receptor antagonist spironolactone has been found to be an effective addition to an existing three-drug regimen to treat hypertension. This has been so even without a diagnosis of aldosterone excess [57]. The addition of spironolactone allows some patients to decrease the number or dosage of other blood pressure medications needed for adequate control [58]. Nevertheless, spironolactone use can be limited because of the concerns regarding its adverse effects, for example, hyperkalemia. In patients with kidney disease or those who are concurrently on ACE-inhibitors or angiotensin receptor blockers, there is an increased risk of developing hyperkalemia while taking spironolactone [59]. In addition, aldosterone blockers have been found to be effective in treating heart failure and promoting repair of cardiac damage caused by hypertension when ACE inhibitor or ARBs are used concurrently [60, 61].

Aliskiren, a direct renin inhibitor, has also been found to be an effective add-on treatment [62]. In the USA, there have been no new major classes of antihypertensive drugs in the market since the introduction of aliskiren [13]. Therefore, aliskiren can be considered as the most appropriate add-on therapy for patients already managed medications being able to decrease cardiovascular risk.

Current drug development is aiming to target the renin-angiotensin-aldosterone system outside the renal parenchyma. One of these targets is in the brain, which mediates many of the mechanisms of blood pressure control [63]. One of these promising agents is endothelin antagonists. Endothelin antagonists have been approved in the US for the treatment of scleroderma-related ulcers and pulmonary hypertension. They are also powerful vasodilators that impact a pathway (mediated by Endothelin-1) implicated in hypertension and chronic kidney disease. Moreover, they appear to hold some benefits in treating diabetes and metabolic syndrome [64].

Conclusion

Since resistant hypertension is a complex condition, its management is also complicated due to its multifactorial etiology. Treatment depends on the identification of the underlying factors contributing to treatment resistance and reversing them. Choosing effective multi-drug regimens is important and lifestyle changes should be encouraged. With strict treatment decisions, resistant hypertension patients can achieve normotension. As mentioned earlier, treatment should consider both pharmacologic therapy and lifestyle modification. In order to maximize the treatment outcomes, the patient should be well educated regarding his disease and its complications. This will encourage the patient to consider the plans and regimens provided by the physician. Failure of one antihypertensive agent to lower blood pressure to the target levels requires the dose to be increased, and/or further antihypertensive medications from these different drug classes to be added up to a maximum of three different drug classes. Aliskiren has also been found to be an effective add-on treatment. The addition of spironolactone allows in some patients for adequate control as well but its use can be limited because of the concerns regarding its potential adverse effects.

References

1. Daryadokht, Masroor Roudsari, Mohammad Beigi Elahe, and Haghani Hamid. "Effect of Peer Education on the Medication Adherence and the Quality of Life of Hypertensive Patients." Pharmacophore, 2017; 8(3): 19-23.
2. Di Pilla, Marina, Rosa Maria Bruno, and Stefano Taddei. "Resistant Hypertension: An Incurable Disease or Just a Challenge For Our Medical Skill?." High Blood Pressure & Cardiovascular Prevention, 2016; 23(4): 347-353. https://doi.org/10.1007/s40292-016-0159-y.
3. Mancia, Giuseppe, Robert Fagard, Krzysztof Narkiewicz, Josep Redon, Alberto Zanchetti, Michael Boehm, Thierry Christiaens et al. "2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." Blood pressure, 2013; 22(4): 193-278. https://doi.org/10.1097/01.hjh.0000431740.32696.cc.
4. Pedrosa, Rodrigo P., Luciano F. Drager, Carolina C. Gonzaga, Marcio G. Sousa, Lílian KG de Paula, Aline CS Amaro, Celso Amodeo et al. "Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension." Hypertension, 2011; 58(5): 811-817. https://doi.org/10.1161/hypertensionaha.111.179788.
5. de la Sierra, Alejandro, Julián Segura, José R. Banegas, Manuel Gorostidi, Juan J. de la Cruz, Pedro Armario, Anna Oliveras, and Luis M. Ruilope. "Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring." Hypertension, 2011; 57(5): 898-902. https://doi.org/10.1161/hypertensionaha.110.168948.
6. Daugherty, Stacie L., J. David Powers, David J. Magid, Heather M. Tavel, Frederick A. Masoudi, Karen L. Margolis, Patrick J. O'Connor, Joe V. Selby, and P. Michael Ho. "Incidence and prognosis of resistant hypertension in hypertensive patients." Circulation, 2012; 125(3): 1635-1642. https://doi.org/10.1161/circulationaha.111.068064.

7. Dahmardeh, Haniyeh, and Mohammad Sedaghat. "Epidemiological Investigation Of Cardiovascular Diseases In Khatamol Anbia Hospital In Zahedan City In." Pharmacophore, 2017; 8(6): 60-63.
8. Ghamri, Kholoud A., Ranya A. Ghamri, and Ebtisam A. Alofi. "Knowledge of cardiovascular risk factors among medical students at king Abdulaziz university." Journal of Advanced Pharmacy Education & Research, 2017; 7(4): 525.
9. $ Taltia, Ankita, and Anitha Roy. "Orlistat-an anti-obesity drug-An overview." Journal of Advanced Pharmacy Education & Research, 2017; 7(3).
10. Saeed, Seham, Farida Islahudin, Mohd Makmor-Bakry, and Adyani Md Redzuan. "The practice of complementary and alternative medicine among chronic Kidney disease patients." Journal of Advanced Pharmacy Education & Research| Jul-Sep, 2018; 8(3): 31.
11. Smith, Steven M. "Epidemiology, prognosis, and treatment of resistant hypertension." Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2013; 33(10): 1071-1086. https://doi.org/10.1002/phar.1297.
12. Persell, Stephen D. "Prevalence of resistant hypertension in the United States, 2003–2008." Hypertension, 2011; 57(6): 1076-1080.. https://doi.org/10.1161/hypertensionaha.111.170308.
13. Maliha, George, and Raymond R. Townsend. "An Update on Treatment Options for Drug Resistant Hypertension." Current Cardiovascular Risk Reports, 2014; 8(8): 394. https://doi.org/10.1007/s12170-014-0394-5.
14. Benjamin, Emelia J., Michael J. Blaha, Stephanie E. Chiuve, Mary Cushman, Sandeep R. Das, Rajat Deo, J. Floyd et al. "Heart disease and stroke statistics-2017 update: a report from the American Heart Association." Circulation, 2017; 135(10): e146-e603. https://doi.org/10.1161/cir.0000000000000485.
15. Muntner, Paul, Robert M. Carey, Samuel Gidding, Daniel W. Jones, Sandra J. Taler, Jackson T. Wright Jr, and Paul K. Whelton. "Potential US population impact of the 2017 ACC/AHA high blood pressure guideline." Circulation, 2018; 137(2): 109-118. https://doi.org/10.1161/circulationaha.117.032582.
16. Patel, Kershaw V., Xilong Li, Nitin Kondamudi, Muthiah Vaduganathan, Beverley Adams-Huet, Gregg C. Fonarow, Wanpen Vongpatanasin, and Ambarish Pandey. "Prevalence of apparent treatment-resistant hypertension in the United States according to the 2017 high blood pressure guideline." In Mayo Clinic Proceedings, 2019; 94(5): 776-782. Elsevier. https://doi.org/10.1016/j.mayocp.2018.12.033.
17. Gu, Qiuping, Charles F. Dillon, Vicki L. Burt, and Richard F. Gillum. "Association of hypertension treatment and control with all-cause and cardiovascular disease mortality among US adults with hypertension." American journal of hypertension, 2010; 23(1): 38-45. https://doi.org/10.1038/ajh.2009.191.
18. Persell, Stephen D. "Prevalence of resistant hypertension in the United States, 2003–2008." Hypertension 2011; 57(6): 1076-1080. https://doi.org/10.1161/hypertensionaha.111.170308.
19. Egan, Brent M., Yumin Zhao, R. Neal Axon, Walter A. Brzezinski, and Keith C. Ferdinand. "Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008." Circulation, 2011; 124(9): 1046-1058. https://doi.org/10.1161/circulationaha.111.030189.
20. Dahlén Holmqvist, Lina. "Clinical hypertension-from early prediction to prevalence, treatment adherence and outcome of resistant hypertension." (2017). https://gupea.ub.gu.se/handle/2077/49483.
21. Mancia, Giuseppe, Robert Fagard, Krzysztof Narkiewicz, Josep Redon, Alberto Zanchetti, Michael Boehm, Thierry Christiaens et al. "2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." Blood pressure, 2013; 22(4): 193-278. https://doi.org/10.1097/01.hjh.0000431740.32696.cc.
22. Pickering, Thomas G., John E. Hall, Lawrence J. Appel, Bonita E. Falkner, John Graves, Martha N. Hill, Daniel W. Jones, Theodore Kurtz, Sheldon G. Sheps, and Edward J. Roccella. "Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research." Hypertension, 2005; 45(1): 142-161. https://doi.org/10.1161/01.hyp.0000150859.47929.8e.
23. O'brien, Eoin, Roland Asmar, Lawrie Beilin, Yutaka Imai, Jean-Michel Mallion, Giuseppe Mancia, Thomas Mengden et al. "European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement." Journal of hypertension, 2003; 21(5): 821-848. https://doi.org/10.1097/00004872-200305000-00001.
24. O'Brien, Eoin, Gareth Beevers, and Gregory YH Lip. "ABC of hypertension: blood pressure measurement: Part III—Automated sphygmomanometry: ambulatory blood pressure measurement." BMJ: British Medical Journal, 2001; 322(7294): 1110. https://doi.org/10.1136/bmj.322.7293.1043.
25. Myers, Martin G., Marshall Godwin, Martin Dawes, Alexander Kiss, Sheldon W. Tobe, F. Curry Grant, and Janusz Kaczorowski. "Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomised parallel design controlled trial." Bmj 342 (2011): d286. https://doi.org/10.1136/bmj.d286.
26. Staessen, Jan A., Geert Byttebier, Frank Buntinx, Hilde Celis, Eoin T. O'Brien, and Robert Fagard. "Antihypertensive treatment based on conventional or ambulatory blood pressure measurement: a randomized controlled trial." Jama, 1997; 278(13): 1065-1072. https://doi.org/10.1001/jama.278.13.1065.
27. Prosser, Hamish CG, Cynthia Gregory, Dagmara Hering, Graham S. Hillis, Greg Perry, Johan Rosman, Carl Schultz, Mark Thomas, Gerald F. Watts, and Markus P. Schlaich. "Preferred fourth-line pharmacotherapy for resistant hypertension: are we there yet?." Current hypertension reports, 2017; 19(4): 30. https://doi.org/10.1007/s11906-017-0728-z.
28. Grassi, Guido, and Venkata S. Ram. "Evidence for a critical role of the sympathetic nervous system in hypertension." Journal of the American Society of Hypertension, 2016; 10(5): 457-466. https://doi.org/10.1016/j.jash.2016.02.015.
29. Grassi, Guido, Gino Seravalle, Gianmaria Brambilla, Claudio Pini, Marina Alimento, Rita Facchetti, Domenico Spaziani, Cesare Cuspidi, and Giuseppe Mancia. "Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension." International journal of cardiology, 2014; 177(3): 1020-1025. https://doi.org/10.1016/j.ijcard.2014.09.138.
30. Oliva, Raymond V., and George L. Bakris. "Sympathetic activation in resistant hypertension: theory and therapy." In Seminars in nephrology, 2014; 34(5): 550-559. WB Saunders. https://doi.org/10.1016/j.semnephrol.2014.08.009.
31. Egan, Brent M., and Jiexiang Li. "Role of aldosterone blockade in resistant hypertension." In Seminars in nephrology, 34(3): 273-284. WB Saunders, 2014. https://doi.org/10.1016/j.semnephrol.2014.04.004.
32. Calhoun, David A., Mari K. Nishizaka, Mohammad A. Zaman, Roopal B. Thakkar, and Paula Weissmann. "Hyperaldosteronism among black and white subjects with resistant hypertension." Hypertension, 2002; 40(6): 892-896. https://doi.org/10.1161/01.hyp.0000040261.30455.b6.
33. Nishizaka, Mari K., M. Amin Zaman, Sharon A. Green, Kerry Y. Renfroe, and David A. Calhoun. "Impaired endothelium-dependent flow-mediated vasodilation in hypertensive subjects with hyperaldosteronism." Circulation, 2004; 109(23): 2857-2861. https://doi.org/10.1161/01.cir.0000129307.26791.8e.
34. Brown, Nancy J. "Aldosterone and end-organ damage." Current opinion in nephrology and hypertension, 2005; 14(3): 235-241. https://doi.org/10.1097/01.mnh.0000165889.60254.98.
35. Schlaich, Markus P., David M. Kaye, Elisabeth Lambert, Marcus Sommerville, Flora Socratous, and Murray D. Esler. "Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy." Circulation, 2003; 108(5): 560-565. https://doi.org/10.1161/01.cir.0000081775.72651.b6.
36. Schlaich, Markus P., Flora Socratous, Sarah Hennebry, Nina Eikelis, Elisabeth A. Lambert, Nora Straznicky, Murray D. Esler, and Gavin W. Lambert. "Sympathetic activation in chronic renal failure." Journal of the American Society of Nephrology, 2009; 20(5): 933-939. https://doi.org/10.1681/asn.2008040402.
37. El Rouby, Nihal, and Rhonda M. Cooper-DeHoff. "Genetics of resistant hypertension: a novel pharmacogenomics phenotype."

Current hypertension reports, 2015; 17(9): 71.https://doi.org/10.1007/s11906-015-0583-8.
38. Sarafidis, Pantelis A., and George L. Bakris. "State of hypertension management in the United States: confluence of risk factors and the prevalence of resistant hypertension." The Journal of Clinical Hypertension, 2008; 10(2): 130-139. https://doi.org/10.1111/j.1751-7176.2008.07309.x.
39. Graves, John W., Robert L. Bloomfield, and Vardaman M. Buckalew Jr. "Plasma volume in resistant hypertension: guide to pathophysiology and therapy." The American journal of the medical sciences, 1989; 298(6): 361-365. https://doi.org/10.1097/00000441-198912000-00001.
40. Townsend, Raymond R. "Pathogenesis of drug-resistant hypertension." In Seminars in nephrology, 34(5):506-513. WB Saunders, 2014. https://doi.org/10.1016/j.semnephrol.2014.08.004.
41. DeMarco, Vincent G., Annayya R. Aroor, and James R. Sowers. "The pathophysiology of hypertension in patients with obesity." Nature Reviews Endocrinology, 2014; 10(6): 364. https://doi.org/10.1038/nrendo.2014.44.
42. Rao, Akhilesh, Vishwam Pandya, and Adam Whaley-Connell. "Obesity and insulin resistance in resistant hypertension: implications for the kidney." Advances in chronic kidney disease, 2015; 22(3): 211-217. https://doi.org/10.1053/j.ackd.2014.12.004.
43. Tanner, Rikki M., David A. Calhoun, Emmy K. Bell, C. Barrett Bowling, Orlando M. Gutiérrez, Marguerite R. Irvin, Daniel T. Lackland, Suzanne Oparil, David Warnock, and Paul Muntner. "Prevalence of apparent treatment-resistant hypertension among individuals with CKD." Clinical Journal of the American Society of Nephrology, 2013; 8(9): 1583-1590. https://doi.org/10.2215/cjn.00550113.
44. Ogedegbe, Gbenga, and Antoinette Schoenthaler. "A systematic review of the effects of home blood pressure monitoring on medication adherence." The Journal of Clinical Hypertension, 2006; 8(3): 174-180. https://doi.org/10.1111/j.1524-6175.2006.04872.x.
45. Goessens, B. M. B., F. L. J. Visseren, J. K. Olijhoek, B. C. Eikelboom, and Y. Van der Graaf. "Multidisciplinary vascular screening program modestly improves the medical treatment of vascular risk factors." Cardiovascular drugs and therapy, 2005; 19(6): 429-435. https://doi.org/10.1007/s10557-005-6127-8.
46. Aucott, Lorna, Amudha Poobalan, W. Cairns S. Smith, Alison Avenell, Roland Jung, and John Broom. "Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review." Hypertension, 2005; 45(6): 1035-1041. https://doi.org/10.1161/01.hyp.0000165680.59733.d4.
47. Neter, Judith E., Bianca E. Stam, Frans J. Kok, Diederick E. Grobbee, and Johanna M. Geleijnse. "Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials." Hypertension, 2003; 42(5): 878-884. https://doi.org/10.1161/01.hyp.0000094221.86888.ae.
48. He, Feng J., Nirmala D. Markandu, and Graham A. MacGregor. "Modest salt reduction lowers blood pressure in isolated systolic hypertension and combined hypertension." Hypertension, 2005; 46(1): 66-70. https://doi.org/10.1161/01.hyp.0000171474.84969.7a.
49. Vollmer, William M., Frank M. Sacks, Jamy Ard, Lawrence J. Appel, George A. Bray, Denise G. Simons-Morton, Paul R. Conlin et al. "Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial." Annals of internal medicine, 2001; 135(12): 1019-1028. https://doi.org/10.7326/0003-4819-135-12-200112180-00005.
50. Singer, D. R., Nirmala D. Markandu, A. Louise Sugden, Michelle A. Miller, and Graham A. MacGregor. "Sodium restriction in hypertensive patients treated with a converting enzyme inhibitor and a thiazide." Hypertension, 1991; 17(6): 798-803. https://doi.org/10.1161/01.hyp.17.6.798.
51. Chobanian, Aram V. "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood PressureThe JNC 7 Report." Jama, 2003; 289(19): 2560. https://doi.org/10.1001/jama.289.19.2560.
52. Kokkinos, Peter F., Puneet Narayan, John A. Colleran, Andreas Pittaras, Aldo Notargiacomo, Domenic Reda, and Vasilios Papademetriou. "Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension." New England Journal of Medicine, 1995; 333(22): 1462-1467. https://doi.org/10.1056/nejm199511303332204.
53. Whelton, Seamus P., Ashley Chin, Xue Xin, and Jiang He. "Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials." In Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. Centre for Reviews and Dissemination (UK), 2002. https://doi.org/10.7326/0003-4819-136-7-200204020-00006.
54. Appel, Lawrence J., Thomas J. Moore, Eva Obarzanek, William M. Vollmer, Laura P. Svetkey, Frank M. Sacks, George A. Bray et al. "A clinical trial of the effects of dietary patterns on blood pressure." New England journal of medicine 1997; 336(16): 1117-1124. https://doi.org/10.1056/nejm199704173361601.
55. Egan, Brent M., Jan N. Basile, Shakaib U. Rehman, Phillip B. Davis, Curt H. Grob III, Jessica Flynn Riehle, Christine A. Walters et al. "Plasma renin test–guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial." American journal of hypertension 2009; 22(7): 792-801. https://doi.org/10.1038/ajh.2009.63.
56. Acelajado, Maria Czarina, and David A. Calhoun. "Resistant hypertension, secondary hypertension, and hypertensive crises: diagnostic evaluation and treatment." Cardiology clinics, 2010; 28(4): 639-654. https://doi.org/10.1016/j.ccl.2010.07.002.
57. Chapman, Neil, Joanna Dobson, Sarah Wilson, Bjorn Dahlof, Peter S. Sever, Hans Wedel, and Neil R. Poulter. "Effect of spironolactone on blood pressure in subjects with resistant hypertension." Hypertension 2007; 49(4): 839-845. https://doi.org/10.1161/01.hyp.0000259805.18468.8c.
58. Ouzan, James, Catherine Pérault, A. Michael Lincoff, Evelyne Carré, and Michel Mertes. "The role of spironolactone in the treatment of patients with refractory hypertension." American journal of hypertension, 2002; 15(4): 333-339. https://doi.org/10.1016/s0895-7061 (01)02342-1.
59. Lane, Deirdre A., Sarah Shah, and D. Gareth Beevers. "Low-dose spironolactone in the management of resistant hypertension: a surveillance study." Journal of hypertension, 2007, 25(4): 891-894. https://doi.org/10.1097/hjh.0b013e328014954d.
60. Funder, John W. "Mineralocorticoid receptor antagonists: emerging roles in cardiovascular medicine." Integrated blood pressure control, 2013; 6: 129. https://doi.org/10.2147/ibpc.s13783.
61. Guichard, Jason L., David A. Calhoun Donald Clark III, and Mustafa I. Ahmed. "Aldosterone receptor antagonists: current perspectives and therapies." Vascular health and risk management, 2013; 9: 321. https://doi.org/10.2147/vhrm.s33759.
62. Yoshitomi, Yuji, Ken-ichi Kawanishi, Akihisa Yamaguchi, Shun-ichiro Sakurai, Kazuo Minai, Toshikazu Ishii, Yasuhiro Tarutani et al. "Effectiveness of the direct renin inhibitor, aliskiren, in patients with resistant hypertension." International heart journal, 2013; 54(4): 88-92. https://doi.org/10.1536/ihj.54.88.
63. Monge, Matthieu, Aurélien Lorthioir, Guillaume Bobrie, and Michel Azizi. "New drug therapies interfering with the renin–angiotensin–aldosterone system for resistant hypertension." Journal of the Renin-Angiotensin-Aldosterone System, 2013; 14(4): 285-289. https://doi.org/10.1177/1470320313513408.
64. Moorhouse, Rebecca C., David J. Webb, David C. Kluth, and Neeraj Dhaun. "Endothelin antagonism and its role in the treatment of hypertension." Current hypertension reports, 2013; 15(5) 489-496. https://doi.org/10.1007/s11906-013-0380-1.