

# Clinical Profile and Management Approach of Patients Diagnosed with Resistant Hypertension in the Philippine General Hospital

Gelza Mae A. Zabat, MD\* | Janellen L. Quiambao, MD\* | Ela C. Villaverde, MD\* | Christine Lorraine D. Balibadlan, MD\* | Raymond V. Oliva, MD†

\*Department of Medicine, Philippine General Hospital, Manila, Philippines

†Division of Hypertension, Department of Medicine, Philippine General Hospital, Manila, Philippines

## Abstract

**INTRODUCTION:** Resistant hypertension is blood pressure (BP) that remains above target despite treatment with maximum doses of three antihypertensive drugs, which may include a diuretic. The prevalence of resistant hypertension is unknown, and there are no local studies in the Philippines concerning this condition.

**METHODS:** A retrospective descriptive cohort study was conducted in the Hypertension Clinic of the Section of Hypertension of the Philippine General Hospital. A total of 51 patients were diagnosed with resistant hypertension, and charts were reviewed and analyzed.

**RESULTS:** Majority of the patients were female (31 [60.8%]), with a mean age of 56.3 years. All of them presented with symptoms; the most common presenting symptoms were headache, exertional dyspnea, nape pain, dizziness, and easy fatigability. Of the 51 patients, 45% also had diabetes mellitus, 11.8% had dyslipidemia, and 7.8% had a previous history of preeclampsia. Approximately 35% of these patients were smokers. The average BP before referral to the section was 167/94 mm Hg. By this time, most patients will either be on a four-drug regimen (42.1%) or a three-drug regimen (36.8%). The median number of visits in the Hypertension Clinic before control of BP was three follow-ups, with the average BP being 119/71 mm Hg. The regimens of the patients with controlled BP are three-drug combination (36.4%), four-drug combination (36.4%), and five-drug combination (27.3%).

**CONCLUSION:** Early referral to a hypertension specialist may benefit a patient with resistant hypertension, decreasing the number of follow-up visits to control a patient's BP. Patients with resistant hypertension may require four- to five-drug regimens, which may be needed to adequately control a patient's BP.

**KEYWORDS:** drug combination, elevated blood pressure, hypertension, resistant hypertension

## INTRODUCTION

Resistant hypertension (RH) is defined as a blood pressure (BP) that remains above goal despite the concurrent use of three antihypertensive agents of different classes. Ideally, one of the agents is a diuretic. The medications are prescribed at maximal doses.<sup>1</sup> This also includes patients with controlled BP, who are on four or more medications.<sup>2</sup> The prevalence of RH is unknown<sup>2,3</sup>; however, there are small studies that have shown a prevalence range of 5% to 50%. Unfortunately, these studies cannot estimate the prevalence of RH in the general population because these require large, diverse sample sizes that may not be feasible.<sup>4,5</sup>

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) provides relevant data on the prevalence of hypertension, with some insight on RH.<sup>6</sup> Approximately 50% of participants needed three or more antihypertensive drugs to maintain their target BP goals. However, these values may not be a precise estimate as the study excluded patients with a history of uncontrolled hypertension with more than two drugs during sample selection. Several patient characteristics were also determined to contribute to RH. These include older age, high baseline BP, obesity, increased dietary salt intake, chronic kidney disease (CKD), diabetes mellitus (DM), left ventricular hypertrophy, black race, female sex, and residence in southeastern United States.<sup>7,8,9</sup>

Pseudo-RH should be ruled out first before labeling a patient with RH. Several factors contribute to pseudoresistance, including improper BP measurements, arteriosclerotic arteries common among the elderly, white coat effect, poor adherence to medications, inadequate dosing or improper combination of antihypertensive agents, and physician inertia.<sup>8-19</sup>

Thus, management of RH, as recommended by both the American College of Cardiology and American Heart Association (AHA), is a two-step approach. First is to establish the diagnosis of RH by ruling out possible causes of pseudoresistance. Second is to identify factors that may contribute to treatment resistance.<sup>2,3</sup> These include drugs, such as nonsteroidal anti-inflammatory drugs, sympathomimetics, excess alcohol intake, volume overload, obesity, old age, DM, and secondary causes of hypertension. Once pseudo-RH and secondary causes are ruled out, the American College of Cardiology/AHA recommend aggressive treatment with appropriate doses and combinations of antihypertensive agents according to patient characteristics in a stepwise approach and referral to a hypertension specialist if BP is still uncontrolled.<sup>2,3</sup>

There are no published articles on the prevalence of RH and outcome articles on hypertension treatment, and the demographics of such patients have not yet been established in the Philippines. This study is designed to answer these questions, as well as to describe the approach to management of patients with RH here in the country, which may eventually help in creating local guidelines in the management of this condition in our hypertensive patients.

This study aims to determine the clinical profile of patients diagnosed to have RH. These demographic data can provide an insight on the possible risk factors of patients who are prone to develop RH.

A descriptive analysis of the management approach of physicians on RH can provide an insight on how primary physicians manage this illness and adherence to existing guidelines. This can pave way to possible local clinical guidelines in the management of RH and improvements to care and management in patients with this illness.

## METHODS

This is a retrospective, descriptive cohort study conducted at the Hypertension Clinic of the Philippine General Hospital, a tertiary care university training hospital. Inclusion criteria were adult patients 19 years or older, diagnosis of RH, and referred to the Hypertension Clinic from 2008 to 2012. Exclusion criteria included those who are not diagnosed with RH or who do not meet the criteria to be diagnosed with RH, diagnosed with secondary hypertension, and who were not referred to the Hypertension Clinic. The definition of RH was the one used by the AHA<sup>1</sup> as mentioned previously.

A total of 93 charts in the Hypertension Clinic were screened and reviewed by the authors. Of these, only 51 charts fulfilled the inclusion and exclusion criteria and were included in the study. Data including age; sex; referring department; medical history of hypertension or related illness and other comorbidities; personal and social history, such as vices and drug use; BP on admission and succeeding follow-ups; medications initiated, maintained, and discontinued; order of initiation of medications; and initial and last working diagnosis were extracted. The data gathered were tabulated on Microsoft Excel spreadsheets (Microsoft Inc, Redmond, Washington) and analyzed.

The data extracted were expressed as percentage of all the patients diagnosed with RH seen in the Hypertension Clinic. Each outcome was expressed as percentages of all patients included in the study. Mean and median measurements of the BPs were also computed. The medications used were tabulated and expressed as percentages and standard deviation if appropriate. We included all individuals diagnosed with RH referred to the Hypertension Clinic during the study period.

## RESULTS

In this cohort of patients with RH, 60.8% (n = 31) were female. Mean age of the patients was 56.3 years (57.8 years for male and 55.3 years for female patients). Their most common presenting symptoms were headache, exertional dyspnea, nape pain, dizziness, and easy fatigability. Majority of the patients with RH were also diagnosed with diabetes (n = 23 [45.1%]). Other significant comorbidities were dyslipidemia and history of preeclampsia. There were more nonsmokers (n = 20 [39.2%]) compared with smokers (n = 18 [35.3%]) (Table 1).

**Table 1.** Demographics and Baseline Patient Characteristics (N = 51)

	n	%
Male	20	39.2
Female	31	69.8
Mean age, y	56 ± 4 (56.3)	
Mean age for males, y	57 ± 3 (57.8)	
Mean age for females, y	55 ± 4 (55.3)	
Smoker	18	35.3
Nonsmoker	20	39.2
<b>Symptoms</b>		
Headache	15	29.4
Exertional dyspnea	7	13.7
Nape pain	6	11.8
Dizziness	6	11.8
Easy fatigability	6	11.8
Weakness	5	9.8
Orthopnea	4	7.8
Nausea and vomiting	3	5.9
Blurring of vision	3	5.9
Chest pain	2	3.9
Bipedal edema	2	3.9
Paresthesia	2	3.9
<b>Comorbidities/Past Illness</b>		
Diabetes mellitus	23	45.1
Dyslipidemia	6	11.8
Preeclampsia	4	7.8
Chronic kidney disease	4	7.8
Myocardial infarct	3	5.9
Pulmonary tuberculosis	3	5.9
Cataract	1	2.0
Others	13	25.5

Most of the referrals to the section came from the general medicine service (27.5%). Other referrals were from endocrinology, rehabilitation medicine, cardiovascular section, obstetrics and gynecology, and family medicine (Table 2).

Thirty-eight charts were retrieved, and the average initial BP

upon consult with their primary physicians was 170/97 mm Hg. Patients had a median number of six follow-ups before referral to the section. There was a skewed distribution of the number of consults among the patients because most patients were seen by their primary physician years before the establishment of the Hypertension Clinic in 2008. Median was used as

**Table 2.** Sources of Referrals to the Hypertension Clinic (N = 51)

Department	n	%
General medicine	14	27.5
Endocrinology	3	5.9
Rehabilitation medicine	1	2.0
Cardiology	1	2.0
Family medicine	1	2.0
Obstetrics and gynecology	1	2.0
Neurology	1	2.0

a measure of central tendency to take into account this discrepancy. The average BP before referral to the section was 167/94 mm Hg (Table 3).

Of the 51 patients with RH, 21.6% (11) already had a BP of less than 130/90 mm Hg. The median number of visits before control of BP was three follow-ups, and the average BP was 119/71 mm Hg (Figure 1).

Most of the primary physicians started with a two-drug combination in managing hypertension in these patients (n = 16 [42.1%]). The most used combination drugs were that of calcium-channel blocker (CCB) plus a  $\beta$ -blocker, followed by an angiotensin receptor blocker plus a thiazide diuretic and an angiotensin-converting enzyme inhibitor plus a CCB. However, a number of physicians also started with monotherapy (n = 12 [31.6%]). Their initial drug of choice was a  $\beta$ -blocker, particularly metoprolol, followed by an angiotensin-converting enzyme inhibitor, often enalapril (Figure 2).

Before referral to the Hypertension Clinic, most patients will be on either a four-drug regimen (42.1%), often combination of angiotensin receptor blocker, CCB,  $\beta$ -blocker, and a thiazide diuretic, or a three-drug regimen (36.8%) (Figure 3).

After an average of three consults in the Hypertension Clinic, BPs of patients were controlled with a three-drug combination (36.4%) and a four-drug combination (36.4%). The change was the use of vasodilating  $\beta$ -blockers (eg, carvedilol), maximizing thiazide diuretics, and the use of spironolactone in patients on four- to five-treatment regimen. Thirty-six percent of patients (36%) with RH are on spironolactone.

## DISCUSSION

In the latest Prevalence Study on Hypertension of the Philippine Heart Association (PRESYON-4),<sup>20</sup> approximately 13% of the cohort may be considered as having RH. It is important for physicians to identify, appropriately diagnose, and manage these patients as they may have a higher risk for cardiovascular events, may require more aggressive treatment, and may need specialized interventions to control their BP. They are most

**Table 3.** Blood Pressure Measurements and Number of Consults

	Mean	Median
BP on first consult with a primary physician	170/97	
No. of consults with a primary physician before referral to the Hypertension Clinic	25	6 $\pm$ 2
BP on last consult with a primary physician before referral to the Hypertension Clinic	167/94	
No. of consults at the Hypertension Clinic seen with controlled BP	3	3 $\pm$ 1
Controlled BP at the Hypertension Clinic	119/71	

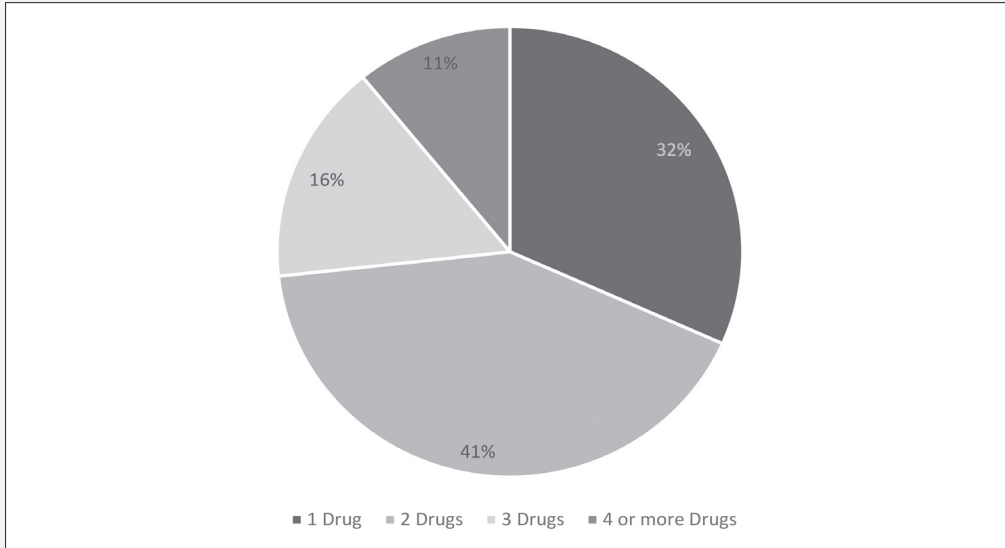
BP=blood pressure.

likely to have a secondary cause of hypertension, which may be partly reversible.<sup>21,22</sup>

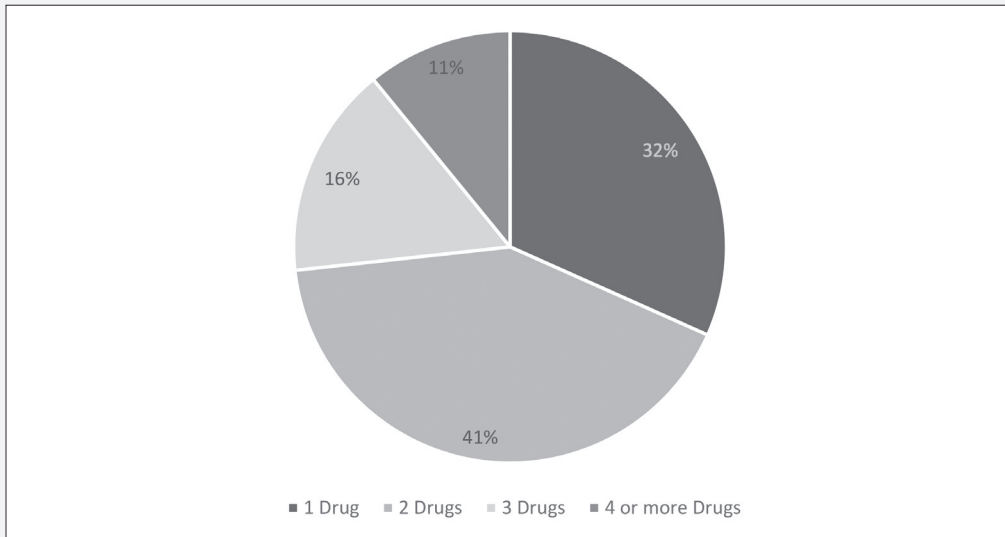
Several population-based studies have identified risk factors that may predict difficult-to-control elevation of BP. These include a higher systolic BP, presence of left ventricular hypertrophy in echocardiogram, older age, obesity, race, CKD, and DM.<sup>23</sup> We saw in our small cohort that most of our patients with RH are female and of older age and have a high systolic BP and presence of DM. These characteristics may predict the risk for RH. It is interesting to note that a history of preeclampsia may be a risk factor for RH. Studies indicate that hypertension develops faster in female patients with gestational hypertension compared with normotensive pregnancies. They may also develop earlier onset of cardiovascular risk factors and events.<sup>24</sup>

Treatment with nonpharmacologic and pharmacologic therapies should be advocated for patients with RH. Lifestyle changes should be encouraged, such as weight loss; regular exercise; low-fat, low-salt, high-fiber diet; and moderate alcohol intake.<sup>25</sup> In prescribing medications, the physician must ensure to give the drugs at full dosage. A triple combination of a renin-angiotensin-aldosterone inhibitor, a CCB, and a long-acting diuretic is often tolerated by most patients. An appropriate diuretic remains the cornerstone of management, as persistent volume expansion contributes to RH.<sup>26</sup> Chlorthalidone is preferred over hydrochlorothiazide but is not readily available in the country. Indapamide, another thiazide diuretic, may be a good alternative. However, we need to monitor serum electrolytes, especially in the elderly.<sup>27</sup>

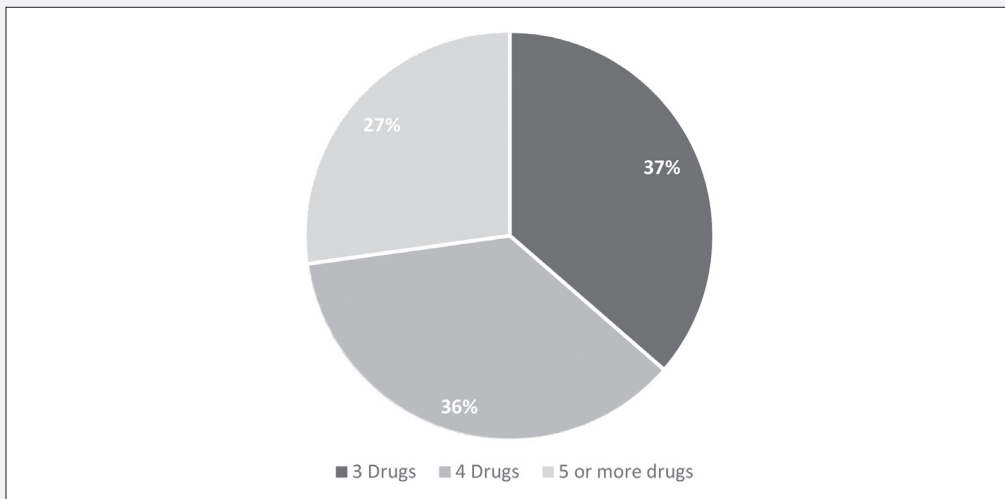
Adding aldosterone antagonists, such as spironolactone or eplerenone, provides a significant benefit to existing drug regimens in patients with RH.<sup>28</sup> If the patient is still hypertensive, additional medications are added sequentially. Possible agents that may be used include  $\beta$ -blockers, centrally acting agents, and vasodilators. Vasodilating  $\beta$ -blockers, such as labetalol,



**Figure 1.** Initial antihypertensive medications on first consult with a primary physician.



**Figure 2.** Antihypertensive medications before referral to the Hypertension Clinic.



**Figure 3.** Antihypertensive medications used in the Hypertension Clinic to control blood pressure.

carvedilol, or nebivolol, may provide more antihypertensive benefits with fewer adverse effects compared with traditional  $\beta$ -blockers.<sup>29</sup> If a centrally acting agent is required, long-acting drugs such as guanfacine or clonidine transdermal patch are added to the regimen. Lastly, potent vasodilators, such as minoxidil or hydralazine, can be very effective, particularly at higher doses.<sup>29</sup>

Experimental therapies such as renal denervation and surgical implantation of a device that will stimulate the carotid sinus baroreflex system have been tested in patients with RH. However, there were procedure-related adverse events causing some of these devices to be discontinued.<sup>30,31</sup> Future therapies may include the use of antisense oligonucleotides and small interfering RNA targeting the angiotensinogen.<sup>32</sup>

The use of three or more combination drugs must be individualized, taking into consideration prior benefit, risk for adverse events, and contributing factors including concomitant diseases such as CKD and diabetes. It must be noted that a referral to a hypertension specialist is warranted if therapy has progressed to adding a fourth agent.

## CONCLUSIONS AND RECOMMENDATIONS

Based on this descriptive study, majority of patients with RH are older than 50 years, female, diabetic, and with BP in the range of hypertension stage II. Primary physicians would opt to manage patients with a single antihypertensive drug or using a two-drug combination, preferring  $\beta$ -blockers. After gradual titration of drugs, patients still with BPs in the range of hypertension stage II even on three- or four-drug combination are referred to a hypertension specialist. It will take an average of three consults with the specialist to control the BP of patients with RH, often with a three- or four- or even five-drug combination.

The authors recommend the following: (1) early referral to a hypertension specialist to lessen the time needed to control the BP; (2) combination therapy of four to five drugs to adequately control a patient's BP based on current guidelines; (3) further study on the knowledge, practices, and attitudes of physicians in the management of RH; and (4) further study on risk factors associated with development of RH, such as female sex, older age, diabetes, and stage II hypertension.

## DISCLOSURE OF CONFLICTS/SOURCE OF FUNDING

The authors have no conflicts of interest in this study.

## ETHICAL CONSIDERATIONS

Throughout the course of data gathering, there was no interaction with patients. The names of each patient were concealed, and their charts were solely identified by their patient codes assigned during data collection. All the data collected were kept confidential. This study was approved by the UPM Research Ethics Board PGH Review Panel for ethics.

## REFERENCES

1. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206–1252.
2. 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.
3. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol* 2008;52:1749–1757.
4. Kaplan NM. Resistant hypertension. *J Hypertens* 2005;23:1441–1444.
5. Sarafidis PA, Bakris GL. State of hypertension management in the United States: confluence of risk factors and the prevalence of resistant hypertension. *J Clin Hypertens (Greenwich)* 2008;10:130–139.
6. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
7. Moser M, Setaro JF. Clinical practice. Resistant or difficult-to-control hypertension. *N Engl J Med* 2006;355:385–392.
8. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. *J Hypertens* 2005;23:2101–2107.
9. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ* 2008;336:1114–1117.
10. Kaplan NM. Resistant hypertension. *J Hypertens* 2005;23:1441–1444.
11. Sarafidis PA, Bakris GL. State of hypertension management in the United States: confluence of risk factors and the prevalence of resistant hypertension. *J Clin Hypertens (Greenwich)* 2008;10:130–139.
12. Verdecchia P, Schillaci G, Borgioni C, et al. White coat hypertension and white coat effect. Similarities and differences. *Am J Hypertens* 1995;8:790–798.
13. Brown MA, Buddle ML, Martin A. Is resistant hypertension really resistant? *Am J Hypertens* 2001;14:1263–1269.
14. Redon J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998;31:712–718.
15. Pierdomenico SD, Lapenna D, Bucci A, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. *Am J Hypertens* 2005;18:1422–1428.
16. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *CMAJ* 1999;160:31–37.

17. Mazzaglia G, Mantovani LG, Sturkenboom MC, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. *J Hypertens* 2005;23:2093–100.
18. 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. *Circulation* 2008;117:e510–e526.
19. Pimenta E, Gaddam KK, Oparil S. Mechanisms and treatment of resistant hypertension. *J Clin Hypertens (Greenwich)* 2008;10:39–244.
20. Sison JA, Cawed-Mande RM, Oliva RV. Prevalence, awareness, and treatment profile of adult Filipino hypertensive individuals: Philippine Heart Association—Council on Hypertension report on survey of hypertension (PRESYON-4). *Phil J Cardiol* 2021:53–68.
21. De la Sierra, Banegas JR, Oliveras A, et al. Clinical differences between resistant hypertensives and patients treated and controlled with three drugs. *J Hypertens* 2012;30 (6):1211–1216.
22. Braam B, Taler SK, Rahman M, Fillaus JA, et al. Recognition and management of resistant hypertension [published online November 28, 2016]. *Clin J Am Soc Nephrol* 2017;12(3):524.
23. Mahapatra R, Anupriya K, Chinnakali P, et al. Prevalence and risk factors for resistant hypertension: cross-sectional study from a tertiary care referral hospital in South India. *Cureus* 2021;13(10):e18779.
24. Bortolotto MR, Francisco RP, Zugaib M. Resistant hypertension in pregnancy: how to manage. *Curr Hypertens Rep* 2018;20(63).
25. Aucott L, Rothnie H, McIntyre L, Thapa M, Waweru C, Gray D. Long-term weight loss from lifestyle intervention benefits blood pressure?: A systematic review. *Hypertension* 2009;54:756–762.
26. Czarina AM, Calhoun DA. Treatment of resistant hypertension. *Minerva Cardioangiol* 2009;57:787–812.
27. Khosla N, Chua DY, Elliott WJ, Bakris GL. Are chlorthalidone and hydrochlorothiazide equivalent blood-pressure-lowering medications? *J Clin Hypertens (Greenwich)* 2005;7:354–356.
28. Givens RC, Lin YS, Dowling AL, et al. CYP3A5 genotype predicts renal CYP3A activity and blood pressure in healthy adults. *J Appl Physiol* 2003;95:1297–1300.
29. Townsend RR, DiPette DJ, Goodman R, et al. Combined alpha/beta-blockade versus beta 1-selective blockade in essential hypertension in black and white patients. *Clin Pharmacol Ther* 1990;48:665–675.
30. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive with or without denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015;385:1957.
31. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 2011;58:765.
32. Ren L, Colafella KMM, Bovee DM, et al. Targeting angiotensinogen with RNA-based therapeutics. *Curr Opin Nephrol Hypertens* 2020;29(2):180–189. associated with myocardial infarction in Africa. *Circulation* 2005;112(23):3554–3561.