International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

Therapeutic Approach For Essential Hypertension: A Brief Review.

Prof.J.S Venkatesh[1], Dr.Santosh Uttangi[2],Aadithya[3], Akhila K.R[4],Anagha T.J[5], Anjali Maria Thomas[6]

[1]*Professor,HOD,Department of Pharmacy Practice,S C S College of Pharmacy,Harapanahalli,Karnataka,India*
[2]*Asst.Professor,Department of Pharmacy practice,S C S College of Pharmacy,Harapanahalli,Karnataka,India*
[3-6]*Pharm D Interns,S C S College of Pharmacy,Harapanahalli,Karnataka,India*

Submitted: 10-02-2024 Accepted: 19-02-2024

ABSTRACT

With a prevalence of 15% globally, hypertension is one of the main causes of mortality and disability-adjusted life years. The majority of hypertension sufferers in high- and low-income nations do not obtain medical care. Most patients who undergo treatment continue to receive inadequate care and fall short of their blood pressure objectives. Consequently, in comparison to the previous guidelines, the new hypertension guidelines include more deliberate treatment options to maximise the likelihood of meeting the new, tight blood pressure objectives. For whom is hypertension treatment appropriate? Which antihypertensive drugs have the most compelling evidence to support them?Which therapy approaches have the best chance of effectively decreasing blood pressure? In this section, we go over hypertension medication in brief and address these queries along with a few other frequently asked questions about hypertension care.

INTRODUCTION

It is anticipated that 1.2 billion individuals worldwide suffer from hypertension in 2019—twice as many as in 1990.[1] One of the biggest global causes of death and disability-adjusted life years is hypertension, which also continues to be a major modifiable risk factor for coronary artery disease, stroke, and chronic kidney disease.[2-4] According to studies, for every 20 mm Hg increase in systolic or 10 mm Hg increase in diastolic blood pressure (BP), the risk of fatal cardiovascular events doubles.[5] It is simple to diagnose hypertension, and there are numerous low-cost treatments available to successfully manage it.[1,6]

Reducing hypertension is linked to fewer deaths and unfavorable cardiovascular outcomes,[7] and therapy for the condition requires both pharmaceutical and non-pharmacological

approaches.[8]Non-pharmacological measures should be used during the course of treatment. These include cutting back on sodium in the diet, eating more fruits and vegetables, eating a high-protein, low-carb diet, and losing weight.

Thiazide diuretics, the first class of drugs to be the subject of a clinical trial and the first to be used to treat hypertension, established pharmacological interventions for the first time in the late 1950s.[13, 14] Many other trials were carried out after thiazide diuretics produced positive results, demonstrating the effectiveness of other BP-lowering drugs in reducing hypertension and averting associated problems.[15–24] The groundbreaking Treatment of Mild Hypertension Study—the first to evaluate the effectiveness of several classes of blood pressure-lowering drugs—showed that a number of antihypertensive drugs significantly drop blood pressure with little variation between classes.[25] Based on the results of these seminal research, we continue to treat hypertension in our daily medical practice with

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

the majority of these recognized blood pressure drugs.[8] This article covers the pharmacologic treatment of essential hypertension and provides a quick overview of the various drug classes' uses and indications.

UNVEILING HYPERTENSION: NAVIGATING THE ONSET OF PHARMACOTHERAPY

Major hypertension guidelines employ varying blood pressure thresholds to characterize hypertension and its phases; nonetheless, they all base their recommendations on a combination of patient risk factors, such as the likelihood of developing atherosclerotic cardiovascular disease (ASCVD), and blood pressure level). Normal blood pressure is defined as less than 120/80 mm Hg in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines. For raised blood pressure (120-129/<80 mm Hg) and stage 1 hypertension (130-139/80-90 mm Hg) in the absence of clinical ASCVD or a 10-year ASCVD risk of less than 10%, non-pharmacological therapy is advised. For individuals with stage 1 hypertension who have symptomatic ASCVD or a 10-year ASCVD risk of 10% or less, as well as for all patients with stage 2 hypertension (BP ≥ 140/90 mm Hg), non-pharmacological plus pharmacological therapy is advised.[8]
The criterion for medication of hypertension is somewhat higher in the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines[27] and the 2020 International Society of Hypertension (ISH) Global Hypertension Practice Guidelines,[26] Patients with grade 1 hypertension (BP > 140-159/90-99 mm Hg), clinical ASCVD, high risk of ASCVD, chronic renal disease, diabetes mellitus, or hypertension-mediated organ damage should start medication right away, according to the 2020 ISH Global Hypertension Practice Guidelines.

Regardless of risk or comorbidities, pharmacotherapy is recommended for all patients with grade 2 hypertension, which is defined as blood pressure ≥ 160/100 mm Hg.[26] In patients with grade-1 hypertension (BP 140-159/90-99 mm Hg), renal impairment, high risk of ASCVD, or hypertension-mediated organ damage, the 2018 ESC/ESH guidelines advise starting medication right away. Pharmacotherapy is necessary for both grade 2 (BP 160-179/100-109 mm Hg) and grade 3 (BP ≥ 180/110 mm Hg) hypertension, irrespective of comorbidities or ASCVD risk.[27]

CHOOSING THE CLASS OF DRUGS

For patients with essential hypertension, it is generally advised to start treatment with one of three drug classes: thiazide diuretics, angiotensinconverting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs), or calcium channel blockers (CCBs).[8]

Numerous studies have demonstrated that there are not plenty of variations between drug classes in the effectiveness of various BP-lowering drugs in treating hypertension and preventing itsconsequences.[25,28,31]Reducing blood pressure was associated with fewer major cardiovascular events, revealed to a meta-analysis of 31 randomised trials. When patients were split into two age groups (those under 65 or more than 65), this effect persisted, demonstrating that treating hypertension will benefit both older and younger persons.Although after looking at the data for patients on beta blockers, ACEi, ARBs, CCBs, and diuretics, the study found insufficient proof that choosing one type of antihypertensive drugs over another significantly improved outcomes.29A year later, 147 papers that were released between 1966 and 2007 were included in another meta-analysis that examined data for 464,164 patients. It revealed that all antihypertensive drug classes were linked to a comparable drop in coronary artery disease or stroke, even though beta blockers were linked to a decreased risk of coronary heart disease events if taken soon after a myocardial infarction and CCBs were attributed to a slightly lower risk of stroke. Once more, the findings of this investigation supported the significance of blood pressure control in many age groups, irrespective of the utilised medications

For every 10 mm Hg drop in systolic blood pressure, there was a significant decrease in major cardiovascular events and mortality, according to a new meta-analysis and systematic review involving 123 studies and 613,815 participants. This study

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

demonstrated that diuretics were better in preventing heart failure, CCBs were outstanding in eliminating stroke and inferior in preventing heart failure, and beta blockers were inferior in preventing such adverse effects.[31] According to a recent Cochrane systematic review article, those suffering from moderate-to-severe essential hypertension may benefit equally from low-dose thiazide diuretics, ACEi, or CCBs as initial treatment in terms of lowering mortality and morbidity, while patients with high-dose thiazide diuretics or beta blockers may benefit less from such interventions.[32] Ultimately, major guidelines suggest treating hypertension rather than choosing a pharmaceutical class to meet the goal of lowering major cardiovascular events even if there is no specific indication for an antihypertensive drug.[8, 26, 27]

SINGLE OR MULTIDRUG RECOMMENDATIONS

Recent guidelines propose introducing two blood pressure-lowering medications simultaneously in the majority of patients, not withstanding prior guidelines' recommendation to start treatment with monotherapy and gradually raise dosage before moving with another class of medication or adding a second medication if necessary.[8,26,27] Nonetheless, studies indicate that about 60% of hypertension patients lack treatment. This finding holds true for all countries, from those with low to high incomes.

Significantly, out of the 40% of individuals who obtain treatment, almost 65% do not meet the 140/90 mm Hg goal.[33] Furthermore, over the past many years, the BP goal has decreased, which makes it more difficult for monotherapy to meet the new, more stringent objectives. A single medication's dose increase has little incremental effect on decreasing blood pressure and may even raise the likelihood of adverse effects. It's significant to note that the majority of patients who took part in the published clinical studies either required multidrug therapy to begin or were treated with multiple BP-lowering medications during the trial.[29–32] Therefore, most patients with hypertension should begin treatment with more than one blood pressure-lowering medication, according to new guidelines.[8, 26,27]

According to the 2018 ESC/ESH recommendation, patients with high normal blood pressure (130-139/85-89 mm Hg) may find that monotherapy is adequate if their blood pressure is near to the 140/90 mm Hg threshold and alternative therapies have not been able to lower blood pressure. If not, it suggests that the majority of patients who fit the therapeutic criteria outlined above begin on two distinct classes of drugs.[27] For patients with hypertension who need pharmacotherapy, the 2020 ISH Global Hypertension Practice Guideline suggests starting low doses of two discrete medication classes.26 Patients with stage 2 hypertension (BP ≥ 140/90 mm Hg) ought to start therapy with two firstline medicines from distinct classes, according to the 2017 ACC/AHA guideline. Patients with hypertension in stage 1 (BP = 130-138/80-90 mm Hg) may benefit from monotherapy with higher doses of medication to reach the target blood pressure of less than 130/80 mm Hg, and if necessary, increasing the dose.[8]

INDICATIONS AND CONTRAINDICATIONS FOR COMMONLY USED ANTIHYPERTENSIVE MEDICATION

Understanding the indications and contraindications for commonly used antihypertensive medications is paramount in tailoring treatment strategies. Thiazide diuretics, beneficial in conditions associated with edema such as Heart Failure with Reduced Ejection Fraction (HFrEF) and Heart Failure with Preserved Ejection Fraction (HFpEF), should be used cautiously in cases of hyperuricemia, hyponatremia, hypercalcemia, and sulfa allergy. Angiotensin-Converting Enzyme Inhibitors (ACEi) and Angiotensin II Receptor Blockers (ARB) are indicated in conditions like HFrEF and Chronic Kidney Disease (CKD) with proteinuria but should be avoided in pregnancy, severe hyperkalemia, bilateral renal artery stenosis, and cases of angioedema related to ACE inhibitors. Calcium Channel Blockers (CCB), whether dihydropyridine or non-dihydropyridine, find utility in various conditions, including prior stroke, stable angina, Raynaud phenomenon, atrial fibrillation/flutter, and migraine headaches. However, non-dihydropyridine CCBs should be avoided in cases of heart

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

failure with reduced ejection fraction (HFrEF) in class 3 or 4, 2nd- or 3rd-degree atrioventricular (AV) nodal block, bradycardia, and sick sinus syndrome. Aldosterone antagonists are indicated for HFrEF and resistant hypertension but should be avoided in the presence of severe hyperkalemia. This comprehensive understanding of medication classes, along with their indications and contraindications, assists healthcare professionals in making informed decisions tailored to individual patient needs.

AM, PM, OR BID DOSING

Around 15% less blood pressure is often found at night than during the day. A negative correlation exists between non-dipping phenomenon and unfavourable cardiovascular events. Non-dipping phenomenon is defined as the inability of blood pressure to drop by at least 10% of its baseline value during sleep. Reorganising the schedule of blood pressure medication dosages to the evening may help diminish the non-dipping phenomena, according to certain research.[35–38] Patients who take blood pressure-lowering drugs in the morning or the evening do not exhibit any appreciable differences in their BP readings, in accordance with numerous further clinical research.[38–41]21 randomised controlled trials and 1,993 hypertensive patients' data were examined in a Cochrane systematic review. It demonstrated that when taking blood pressure medicine in the evening as opposed to the morning, better blood pressure control may result. The relevance of this improved blood pressure control is yet unknown, nonetheless, as none of the trials included clinically meaningful end measures, such as mortality or cardiovascular events.[42] Critically, 21,104 those involved were randomised to receive their blood pressure medication in the morning or the evening in the recently published TIME (Treatment In Morning versus Evening) research. According to the results of this randomised clinical research, patients can take their blood pressure-lowering drugs whenever it is most convenient for them throughout the day, as there was no discernible difference in major cardiovascular events between the study groups.[42]. Significantly, 21,104 patients were randomised to receive their BP prescriptions in the morning or the evening in the recently published TIME (Treatment In Morning versus Evening) research. Patients can take their blood pressure-lowering drugs whenever it's convenient for them during the day, according to the results of this randomised clinical research, which found no significant difference in major cardiovascular events across the study groups.[43]While boosting the number of daily doses of blood pressure-lowering drugs may appear to reduce variations in blood pressure, it has been linked to a decrease in long-term medication adherence and an increase in treatment failure.[44, 45] To increase medicine adherence and lower the risk of treatment failure, once-daily dose is advised over multiple daily dosing in all three of the 2018 ESC/ESH, 2020 ISH, and 2017 ACC/AHA Global Hypertension Practice Guidelines. In order to further increase the likelihood of drug adherence, they also suggest a single pill strategy (one pill that includes two distinct medications) for the first treatment of hypertension. They do not, however, offer any particular advice regarding whether to take the drugs in the morning or at night.[8, 26, 27]

PATENTED MEDICATIONS VERSUS OFF BRAND

The use of generic medications offers prospective benefits in terms of healthcare cost savings and, consequently, treatment availability for a wider population, given the worldwide incidence of hypertension and the considerable expenses involved with treatment. Despite the fact that recommendations based on the concept of bioequivalency and drug approval procedures do not distinguish in this way, clinicians' and patients' uncertainties about the efficacy and safety of generic medications can on occasion impede their adoption.[47–48] However, current regulations, which centre on biologic equivalency in order to infer comparable clinical efficacy, do not require studies that directly compare clinical efficacy, and thus are infrequent.

Although the included studies frequently concentrated on assessing bioequivalency and are therefore characterised by small sample sizes, brief follow-up, and the inclusion of largely young, healthy persons, meta-analyses have

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

attempted to offer some assistance. There was no proof that innovator medications were better than generic ones in an initial lengthy systematic review and meta-analysis of 47 publications, 38 of which were randomised clinical trials, on brand-name and generic medications used to treat cardiovascular illnesses (beta blockers, diuretics, CCBs, and ACEi).[49] The safety of generic drugs was further reinforced by a more recent meta-analysis that was published by Manzoli et al. in 2016 and which essentially corroborated the same conclusions.[50] Extensive recent population datasets support this notion. Ti et al. compared the hazard ratios for major adverse cardiac and cardiovascular events, all -cause death, and 17 branded versus generic pharmaceutical substances for the treatment of hypertension/heart failure, hyperlipidemia, and diabetes mellitus in an observational retrospective study involving a dataset of 9,413,620 insured individuals.[51] According to the study's findings, generic drugs were on par with branded ones, if not better. In a Chinese surrounding area, two sizable community-based randomised controlled trials conducted recently tracked 29,000 hypertension patients whose propensity score matched for brand-name versus generic medicine use.The data either revealed higher hospitalisation rates for CVD in patients started on some of the branded drugs analysed, potentially indicating a difference in medication adherence in the brand prescription groups, or they showed no difference in the mean reduction in systolic blood pressure, hypertension control rate, or CV outcomes[51,52] It should come as unsurprising that using generic medications resulted in lower prescription prices in both instances.In a recent open crossover randomised controlled trial conducted in France, hypertension patients were assigned to receive their regular antihypertensive treatment with brand-name medications solely for six weeks, followed by a switch to generics for an additional six weeks, or in the opposite sequence.[54] Twenty-four hour ambulatory blood pressure monitoring showed no discernible distinction in the effects of using branded versus generic medications (mean 24-hour average blood pressure of 129/77 vs 128/77 mm Hg for brand versus generic pharmaceuticals, respectively). When considered in combination, these results provide credence to the safety and effectiveness of generic drugs in the management of BP, with potential benefits in terms of efficacy due to the reduced financial burden on patients.

NON-PHARMACOLOGICAL APPROACHES TO HYPERTENSION

Non-pharmacological approaches play a crucial role in the comprehensive management of hypertension. A multifaceted strategy encompasses attention to diet, salt, and alcohol reduction, along with an emphasis on regular physical activity. For optimal blood pressure control, individuals are advised to limit the consumption of processed and packaged foods, carefully check labels for salt content, and incorporate the use of spices to enhance flavor while reducing salt intake to less than 1.5 grams per day. A targeted goal involves aiming for a daily reduction of 1,000 mg in salt intake. Engaging in physical activity is also vital, with a recommended 150 minutes per week of moderate-intensity exercise. Weight management is emphasized, encouraging the maintenance or achievement of a normal Body Mass Index (BMI). For those who are overweight, a goal of a 1 kg reduction is recommended. Adopting a healthy diet, such as the Dietary Approaches to Stop Hypertension (DASH) pattern, which includes a rich intake of fruits, vegetables, whole grains, and low-fat dairy products while reducing saturated and total fat, is pivotal. Moderation of alcohol intake is advised, with a limit of two drinks daily for men and one drink daily for women. In summary, a holistic non-pharmacological approach addressing these lifestyle factors should be an integral part of the therapeutic strategy for all patients managing hypertension.

PHARMACOLOGICAL APPROACH TO RESISTANT HYPERTENSION

Resistant hypertension is characterized by elevated clinic blood pressure (BP) levels (>140/90 mm Hg) despite undergoing treatment with three antihypertensive medications that have complementary mechanisms of action, including a diuretic.[57]Guidelines specifically state that these three medications should

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

consist of optimal doses of an ACE inhibitor or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a diuretic. It is crucial to handle patients with challenging hypertension carefully, ensuring accurate diagnosis and ruling out secondary hypertension or pseudo-resistance. Pseudo-resistance may result from improper BP measurement techniques, white coat hypertension, medication nonadherence, intolerance to certain drugs, and concurrent use of substances or medications with hypertensive effects, such as excessive dietary sodium.

Pseudo-resistance poses a significant and often overlooked challenge, underscoring the importance of considering and ruling it out to accurately identify individuals with genuine resistant hypertension. High salt intake remains prevalent in the general population, leading to elevated blood pressure (BP) levels and serving as a substantial obstacle in managing hypertension. A study conducted in Italy, utilizing 24-hour urinary sodium excretion in patients suspected of having resistant hypertension, revealed that only 27% of them adhered to recommended salt consumption guidelines.[58] Decreasing salt intake has been linked to lower BP, especially in hypertensive patients compared to normotensive individuals.[10] Furthermore, adhering to prescribed medications is a crucial factor in achieving and sustaining BP control, thereby preventing cardiovascular diseases (CVD). Assessing adherence is challenging due to cumbersome and costly methods for objective confirmation, compounded by various factors influencing a patient's willingness and ability to adhere to a chronic treatment regimen.[45] Physicians managing hypertension must be aware of these factors and the associated risks of nonadherence, highlighting them in discussions with patients as integral components of an effective hypertension management strategy.[59]

Identifying secondary causes of hypertension, such as renal arterial stenosis, hyperaldosteronism, obstructive sleep apnea, and pheochromocytoma, is essential because they require distinct treatment approaches aimed at tackling the root cause.[8] It's noteworthy that the prevalence of these conditions varies significantly, and so does the probability of hypertension completely resolving once the underlying disease is treated. For instance, a surgical removal of a rare pheochromocytoma can reasonably be expected to normalize blood pressure values. However, in more common cases like patients with obstructive sleep apnea, the use of continuous positive air pressure may address respiratory issues, but the persistence of underlying comorbidities associated with this condition makes it likely that ongoing hypertension treatment will be necessary.[60]

The exact pathophysiology of true resistant hypertension remains inadequately understood. Nonetheless, a widely accepted hypothesis implicates disrupted sodium homeostasis and improper kidney-mediated sodium retention. The PATHWAY-2 (Optimum Treatment for Drug-Resistant Hypertension) study, a double-blind placebo-controlled crossover trial, investigated the effectiveness of medications targeting this system to enhance blood pressure (BP) control in resistant hypertension. The study conclusively demonstrated the superiority of spironolactone over alpha and beta blockers.[61]A total of 230 patients successfully completed all treatment phases, involving 12 weeks of once-daily administration of spironolactone, bisoprolol, doxazosin, and placebo in addition to their baseline BP treatment. Patients receiving spironolactone experienced the most significant reduction in BP, with a mean reduction of 8.7 mm Hg compared to 4.03 mm Hg for doxazosin and 4.26 mm Hg for bisoprolol.

Spironolactone has emerged as the preferred medication in this scenario and is currently recommended as the fourth-line option to be added to the standard hypertension treatment.[57] This recommendation particularly applies to patients with normal potassium levels (K < 4.5 mEq/L), considering the limited but existing risk of hyperkalemia observed in the PATHWAY 2 trial. For patients with elevated potassium levels, it is advised to double the thiazide diuretic dose. If spironolactone is not well-tolerated, alternative potassium-sparing diuretics such as amiloride and eplerenone may be considered. The ACC guidelines, while somewhat less explicit, suggest utilizing spironolactone while maximizing diuretic

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1404-1415 www.ijprajournal.com ISSN: 2249-7781

dosage and introducing "other agents with different mechanisms of action" to achieve blood pressure (BP) control in resistant hypertension. Regarding these alternative options, the PATHWAY 2 trial supports the effectiveness of bisoprolol and doxazosin in improving BP control in the context of resistant hypertension, although the reduction achieved is somewhat less compared to spironolactone.[61]

Clonidine has been investigated in this context, as demonstrated in the ReHOT (Resistant Hypertension Optimal Treatment) trial, where 187 patients were randomly assigned to receive either clonidine or spironolactone as the fourth drug for blood pressure (BP) control.[62]Although clonidine showed inferior 24-hour BP reduction, both systolic and diastolic, compared to spironolactone, it achieved comparable rates of BP control. However, the use of clonidine is impeded by significant side effects, and safer alternatives are available. Some data also exist supporting the use of hydralazine and minoxidil in this clinical setting.[63] Nevertheless, their infrequent usage is attributed to notable side effects such as fluid retention and tachycardia.[27]

Considering the significant evidence linking autonomic nervous system activity to the pathophysiology of hypertension, device-based treatment approaches have been assessed.[64] Randomized clinical trials investigating renal denervation and chronic baroreceptor stimulation have produced unfavorable or conflicting results, accompanied by safety concerns. Consequently, these approaches are currently not recommended.[65,66]

CONTEMPORARY UPDATES

Through a variety of mechanisms, including natriuresis, osmotic diuresis, and a drop in sympathetic tone, the selective sodium -glucose cotransporter-2 (SGLT2) receptor inhibitors (empagliflozin, canagliflozin, and dapagliflozin) have been shown to have BP-lowering effects.The 67 In a meta-analysis assessment of the available standardised clinical trials, the degree of actual blood pressure drop was measured between 2 and 3 mm Hg, which is a small but significant influence.[38] The long-standing cardiovascular benefits of these drugs, particularly in the management and prevention of heart failure, should be taken into account when creating a tailored treatment plan for each patient.[69]In addition to the anticipated advantages associated with weight loss on hypertension, glucagon-like peptide 1 receptor agonists (GLP1-RA), ground-breaking medications for the medical treatment of obesity, have a number of additional beneficial effects on the level of blood pressure. Indeed, the early onset of treatment observed in research investigations with GLP1-RA led to a drop in blood pressure before significant weight loss, indicating that these drugs exerted independent effects on hypertension.[70]

The impact is substantial; in key standardised clinical studies, liraglutide and semaglutide showed a drop in systolic blood pressure in the range of 3.5 to 5.6 mm Hg and 3.9 to 6.2 mm Hg, respectively.[71] The potential causes for these antihypertensive effects include natriuresis and increased urine production, direct vasodilation through specific blood vessel receptors, a reduction in sympathetic activity, or enhanced endothelial function by mitigating the detrimental effects of hyperglycemia.[72]These two groups may provide a significant auxiliary medical approach to enhance blood pressure regulation in high-risk individuals, wherein multiple states co-occurring conditions like obesity, type 2 diabetes, and metabolic syndrome might be effectively managed concurrently.[73]

I. CONCLUSION

One of the main causes of death and morbidity in the world is hypertension. About 15% of people worldwide suffer with hypertension, and the majority of these individuals either do not receive therapy at all or, if they do, do not reach their blood pressure targets. Numerous studies have demonstrated, and every major guideline consistently advises, that the primary factor lowering adverse cardiovascular events is the total degree of blood pressure reduction rather than the usage of a particular class of antihypertensive medications. Initially, using multiple drug therapy and implementing strategies to improve patient compliance, such as one-time dosing, using generic and less expensive

medications, or using well-tolerated medication, can be linked to more consistent blood pressure control and, consequently, a more significant reduction in future event.

ACKNOWLEDGEMENTS
Authors thank Dr Nagendra Rao, principal, SCS College of pharmacy, Harapanahalli, for his valuable suggestions and support.
CONFLICT OF INTEREST: None

REFERENCE

[1]. **NCD Risk Factor Collaboration.** Worldwide trends in hypertension prevalence and progress in treatment and control from1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021 Sep 11;398(10304):957-980. doi: 10.1016/S0140-6736(21)01330-1

[2]. **GBD 2016 Risk Factors Collaborators.** Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16;390(10100):1345-1422. doi: 10.1016/S0140- 6736(17)32366-8

[3]. **Forouzanfar MH, Liu P, Roth GA,** et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA. 2017 Jan 10;317(2):165-182. doi: 10.1001/jama.2016.19043

[4]. **Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D.** Predictors of new-onset kidney disease in a community-based population. JAMA. 2004 Feb 18;291(7):844-50. doi: 10.1001/jama.291.7.844

[5]. **Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Collaboration PS.** Age -specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002 Dec 14;360(9349):1903-1913. doi: 10.1016/s0140- 6736(02)11911-8

[6]. 6. **Carey RM, Muntner P, Bosworth HB, Whelton PK.** Prevention and Control of Hypertension: JACC Health Promotion Series. J Am Coll Cardiol. 2018 Sep 11;72(11):1278-1293. doi: 10.1016/j.jacc.2018.07.008

[7]. **Brunström M, Carlberg B.** Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018 Jan 1;178(1):28-36. doi: 10.1001/jamainternmed.2017.6015

[8]. **Whelton PK, Carey RM, Aronow WS,** et al. 2017 ACC/AHA/ AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19):e127-e248. doi: 10.1016/j.jacc.2017.11.006

[9]. **Appel LJ, Moore TJ, Obarzanek E,** et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997 Apr 17;336(16):1117-24. doi: 10.1056/NEJM199704173361601

[10]. **Sacks FM, Svetkey LP, Vollmer WM,** 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 Jan 4;344(1):3-10. doi: 10.1056/NEJM200101043440101

[11]. **Appel LJ, Sacks FM, Carey VJ** et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 2005 Nov 16;294(19):2455-64. doi: 10.1001/jama.294.19.2455

[12]. 12. **Blumenthal JA, Babyak MA, Hinderliter A** et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE

study. Arch Intern Med. 2010 Jan 25;170(2):126-35. doi: 10.1001/archinternmed.2009.470

[13]. **Freis ED, Wanko A, Wilson IM, Parrish AE.** Treatment of essential hypertension with chlorothiazide (diuril); its use alone and combined with other antihypertensive agents. J Am Med Assoc. 1958 Jan 11;166(2):137-40. doi: 10.1001/jama.1958.02990020025004

[14]. **Effects of treatment on morbidity in hypertension.** Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967 Dec 11;202(11):1028-34. PMID: 4862069

[15]. **Effects of treatment on morbidity in hypertension.** II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970 Aug 17;213(7):1143-52. PMID: 4914579

[16]. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. JAMA. 1979 Dec 7;242(23):2562-71. PMID: 490882

[17]. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J (Clin Res Ed). 1985 Jul 13;291(6488):97-104. doi: 10.1136/bmj.291.6488.97

[18]. **Staessen J, Bulpitt C, Clement D,** et al. Relation between mortality and treated blood pressure in elderly patientswith hypertension: report of the European Working Party on High Blood Pressure in the Elderly. BMJ. 1989 Jun 10;298(6687):1552-6. doi: 10.1136/bmj.298.6687.1552

[19]. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991 Jun 26;265(24):3255-64. PMID: 2046107

[20]. **Hansson L, Zanchetti A, Carruthers SG,** et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998 Jun 13;351(9118):1755-62. doi: 10.1016/s0140-6736(98)04311-6

[21]. **Dahlöf B, Sever PS, Poulter NR,** et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo- Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentrerandomised controlled trial. Lancet 2005 Sep 10-16;366(9489):895-906. doi: 10.1016/S0140-6736(05)67185-1

[22]. **Jamerson K, Weber MA, Bakris GL,** et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008 Dec 4;359(23):2417-28. doi: 10.1056/NEJMoa0806182

[23]. **Cushman WC, Evans GW, Byington RP,** et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1575-85. doi: 10.1056/NEJMoa1001286

[24]. **Wright JT Jr, Williamson JD, Whelton PK,** et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16. doi: 10.1056/NEJMoa1511939

[25]. **Neaton JD, Grimm RH Jr, Prineas RJ,** et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA. 1993 Aug 11;270(6):713-24. PMID: 8336373

[26]. **Unger T, Borghi C, Charchar F,** et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020 Jun;38(6):982-1004. doi: 10.1097/HJH.0000000000002453

[27]. **Williams B, Mancia G, Spiering W,** et al. 2018 ESC/ESH Guidelines for the

management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104. doi: 10.1093/ eurheartj/ehy339

[28]. **Materson BJ, Reda DJ, Cushman WC,** et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med. 1993 Apr 1;328(13):914-21. doi: 10.1056/NEJM199304013281303

[29]. **Turnbull F, Neal B, Ninomiya T,** et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008 May 17;336(7653):1121-3. doi: 10.1136/bmj.39548.738368.BE

[30]. **Law MR, Morris JK, Wald NJ.** Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009 May 19;338:b1665. doi: 10.1136/bmj.b1665

[31]. **Ettehad D, Emdin CA, Kiran A,** et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016 Mar 5;387(10022):957-967. doi: 10.1016/S0140- 6736(15)01225-8

[32]. **Wright JM, Musini VM, Gill R.** First-line drugs for hypertension. Cochrane Database Syst Rev. 2018 Apr 18;4(4):CD001841. doi: 10.1002/14651858.CD001841.pub3

[33]. **Chow CK, Teo KK, Rangarajan S,** et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013 Sep 4;310(9):959-68. doi: 10.1001/ jama.2013.184182

[34]. **Hermida RC, Ayala DE, Fernández JR, Calvo C.** Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. Hypertension. 2008 Jan;51(1):69-76. doi: 10.1161/HYPERTENSIONAHA.107.096933

[35]. **Szauder I, Csajági E, Major Z, Pavlik G, Ujhelyi G.** Treatment of Hypertension: Favourable Effect of the Twice-Daily Compared to the Once-Daily (Evening) Administration of Perindopril and Losartan. Kidney Blood Press Res. 2015;40(4):374-85. doi: 10.1159/000368513

[36]. **Hermida RC, Calvo C, Ayala DE,** et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects. Chronobiol Int. 2005;22(4):755-76. doi: 10.1080/07420520500180488

[37]. **Hermida RC, Ayala DE, Mojón A, Fontao MJ, Fernández JR.** Chronotherapy with valsartan/hydrochlorothiazide combination in essential hypertension: improved sleep-time blood pressure control with bedtime dosing. Chronobiol Int. 2011 Aug;28(7):601-10. doi: 10.3109/07420528.2011.589935

[38]. **Hermida RC, Ayala DE, Fontao MJ, Mojón A, Fernández JR.** Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing. Chronobiol Int. 2010 Jul;27(6):1287- 303. doi: 10.3109/07420528.2010.489167

[39]. **Zappe DH, Crikelair N, Kandra A, Palatini P.** Time of administration important? Morning versus evening dosing of valsartan. J Hypertens. 2015 Feb;33(2):385-92. doi: 10.1097/ HJH.0000000000000397

[40]. **White WB, Mansoor GA, Pickering TG,** et al. Differential effects of morning and evening dosing of nisoldipine ER on circadian blood pressure and heart rate. Am J Hypertens. 1999 Aug;12(8 Pt 1):806-14. doi: 10.1016/s0895-7061(99)00044-8

[41]. **Poulter NR, Savopoulos C, Anjum A,** et al. Randomized Crossover Trial of the Impact of Morning or Evening Dosing of Antihypertensive Agents on 24-Hour Ambulatory Blood Pressure.

Hypertension. 2018 Oct;72(4):870-873. doi: 10.1161/HYPERTENSIONAHA.118.11101

[42]. **Zhao P, Xu P, Wan C, Wang Z.** Evening versus morning dosing regimen drug therapy for hypertension. Cochrane Database Syst Rev. 2011 Oct 5;2011(10):CD004184. doi: 10.1002/14651858.CD004184.pub2

[43]. **Mackenzie IS, Rogers A, Poulter NR** et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet 2022;400:1417-1425. doi: 10.1016/S0140-6736(22)01786-X

[44]. **Schroeder K, Fahey T, Ebrahim S.** How can we improve adherence to blood pressure-lowering medication inambulatory care? Systematic review of randomized controlled trials. Arch Intern Med. 2004 Apr 12;164(7):722- 32. doi: 10.1001/archinte.164.7.722

[45]. **Burnier M, Egan BM.** Adherence in Hypertension. Circ Res. 2019 Mar 29;124(7):1124-1140. doi: 10.1161/ CIRCRESAHA.118.313220

[46]. **Cooper-DeHoff RM, Elliott WJ.** Generic drugs for hypertension: are they really equivalent? Cur Hypertens Rep. 2013 Aug;15(4):340-5. doi: 10.1007/s11906-013-0353-4

[47]. **Banahan BF 3rd, Kolassa E.** A physician survey on generic drugs and substitution of critical dose medications. Arch Intern Med. 1997 Oct 13;157(18):2080-8. PMID: 9382664

[48]. **Kjoenniksen I, Lindbaek M, Granas AG.** Patients' attitudes towards and experiences of generic drug substitution in Norway. Pharm World Sci. 2006 Oct;28(5):284-9. doi: 10.1007/s11096-006-9043-5

[49]. **Kesselheim AS, Misono AS, Lee JL,** et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008 Dec 3;300(21):2514-26. doi: 10.1001/jama.2008.758

[50]. **Manzoli L, Flacco ME, Boccia S,** et al. Generic versus brand-name drugs used in cardiovascular diseases. Eur J Epidemol. 2016 Apr;31(4):351-68. doi: 10.1007/s10654-015-0104-8

[51]. **Tian Y, Reichardt B, Dunkler D,** et al. Comparative effectiveness of branded vs. generic versions of antihypertensive, lipid-lowering and hypoglycemic substances: a population-wide cohort study. Sci Rep. 2020 Apr 6;10(1):5964. doi: 10.1038/s41598-020-62318-y

[52]. **Zhang SY, Tao LY, Yang YY,** et al. Evaluation of blood pressure lowering effect by generic and brand-name antihypertensive drugs treatment: a multicenter prospective study in China. Chin Med J (Engl). 2021 Jan 19;134(3):292- 301. doi: 10.1097/CM9.0000000000001360

[53]. **Huang T, Bai L, Wushouer H,** et al. Clinical Outcome and Medical Cost of Originator and Generic AntihypertensiveDrugs: A Population-Based Study in Yinzhou, China. Front Pharmacol. 2022 Feb 22;13:757398. doi: 10.3389/ fphar.2022.757398

[54]. **Dinic M, Maillard N, Bouiller M, Alamartine E, Mariat C.** Generic vs brand-name drugs for the treatment of hypertension. J Hypertens. 2018 Jun;36:e123. doi: 10.1097/01.hjh.0000539318.41572.12

[55]. **Dahlöf B, Devereux RB, Kjeldsen SE,** et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):995-1003. doi: 10.1016/S0140-6736(02)08089-3

[56]. **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 Dec 18;288(23):2981-97. doi:

10.1001/jama.288.23.2981

[57]. **Jones NR, McCormack T, Constanti M, McManus RJ.** Diagnosis and management of hypertension in adults: NICE guideline update 2019. Br J Gen Pract. 2020 Jan 30;70(691):90-91. doi: 10.3399/bjgp20X708053

[58]. **Galletti F, Barbato A, MINISAL-SIIA Study Group.** Prevalence and determinants of resistant hypertension in a sample of patients followed in Italian hypertension centers: results from the MINISAL-SIIA study program. J Hum Hypertens. 2016 Nov;30(11):703-708. doi: 10.1038/ jhh.2016.6. Epub 2016 Mar 3.

[59]. **Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J.** Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013 Aug;62(2):218-25. doi: 10.1161/HYPERTENSIONAHA.113.00687

[60]. **Salman LA, Shulman R, Cohen JB.** Obstructive Sleep Apnea, Hypertension, and Cardiovascular Risk: Epidemiology, Pathophysiology, and Management. Curr Cardiol Rep. 2020 Jan 18;22(2):6. doi: 10.1007/s11886-020-1257-y

[61]. **Williams B, MacDonald TM, Morant S,** et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015 Nov 21;386(10008):2059-2068. doi: 10.1016/ S0140-6736(15)00257-3

[62]. **Krieger EM, Drager LF, Giorgi DMA,** et al. Spironolactone Versus Clonidine as a Fourth-Drug Therapy for Resistant Hypertension: The ReHOT RandomizedStudy (Resistant Hypertension Optimal Treatment). Hypertension. 2018 Apr;71(4):681-690. doi: 10.1161/ HYPERTENSIONAHA.117.10662

[63]. **Liu G, Zheng XX, Xu YL, Lu J, Hui RT, Huang XH.** Effect of aldosterone antagonists on blood pressure in patients with resistant hypertension: a meta-analysis. J Hum Hypertens. 2015 Mar;29(3):159-66. doi: 10.1038/jhh.2014.64

[64]. **Sobotka PA, Mahfoud F, Schlaich MP, Hoppe UC, Böhm M, Krum H.** Sympatho-renal axis in chronic disease. Clin Res Cardiol. 2011 Dec;100(12):1049-57. doi: 10.1007/s00392- 011-0335-y

[65]. **Bhatt DL, Kandzari DE, O'Neill WW,** et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014 Apr 10;370(15):1393 -401. doi: 10.1056/NEJMoa1402670

[66]. **de Leeuw PW, Bisognano JD, Bakris GL,** et al. Sustained Reduction of Blood Pressure With Baroreceptor Activation Therapy: Results of the 6-Year Open Follow- Up. Hypertension. 2017 May;69(5):836-843. doi: 10.1161/ HYPERTENSIONAHA.117.09086

[67]. **Sanidas EA, Papadopoulos DP, Hatziagelaki E, Grassos C, Velliou M, Barbetseas J.** Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors Across the Spectrum of Hypertension. Am J Hypertens. 2020 Mar 13;33(3):207 -213. doi: 10.1093/ajh/ hpz157

[68]. **Mazidi M, Rezaie P, Gao HK, Kengne AP.** Effect of Sodium- Glucose Cotransport-2 Inhibitors on Blood Pressure in People With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of 43 Randomized Control Trials With 22 528 Patients. J Am Heart Assoc. 2017 May 25;6(6):e004007. doi: 10.1161/JAHA.116.004007

[69]. **Heidenreich PA, Bozkurt B, Aguilar D,** et al. 2022 AHA/ ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022 May 3;79(17):1757-1780. doi: 10.1016/j.jacc.2021.12.011

[70]. **Ryan D, Acosta A.** GLP-1 receptor agonists: Nonglycemic clinical effects in weight loss and beyond. Obesity (Silver Spring). 2015 Jun;23(6):1119-29. doi: 10.1002/oby.21107

[71]. **Taha MB, Yahya T, Satish P,** et al.

Glucagon-Like Peptide 1 Receptor Agonists: A Medication for Obesity Management. Curr Atheroscler Rep. 2022 Aug;24(8):643-654. doi: 10.1007/s11883-022-01041-7

[72]. **Sivertsen J, Rosenmeier J, Holst JJ, Vilsbøll T.** The effect of glucagon-like peptide 1 on cardiovascular risk. Nat Rev Cardiol. 2012 Jan 31;9(4):209-22. doi: 10.1038/nrcardio.2011.211

[73]. **Berra C, Manfrini R, Regazzoli D,** et al. Blood pressure control in type 2 diabetes mellitus with arterial hypertension. The important ancillary role of SGLT2-inhibitors and GLP1-receptor agonists. Pharmacol Res. 2020 Oct;160:105052. doi: 10.1016/j.phrs.2020.105052