International Journal of Advances in Medicine
Garg R. Int J Adv Med. 2023 Aug;10(8):647-652
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20232150

Review Article

Individualization of hypertension treatment: an expert review

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Received: 28 June 2023
Accepted: 03 July 2023

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ABSTRACT

Management of hypertension is complex in patients with comorbid conditions and in those who are at high cardiovascular risk. Multiple guidelines recommend different treatment goals and therapeutic approaches for hypertension. In this review, we take an individualized management approach for hypertension with comorbidities mainly diabetes and chronic kidney disease (CKD), coronary artery disease, and for young patients and the elderly. Current evidence indicates a blood pressure goal of <130/80 mmHg for most patients with comorbidities except for the elderly aged >75 years in whom systolic pressure of 130-139 mmHg and diastolic pressure of 70-80 mmHg may be considered. For patients with diabetes and CKD, renin angiotensin aldosterone system (RAAS) inhibitors remain the initial choice of agents whereas in the young or elderly, any class including RAAS inhibitors, calcium channel blockers, and thiazide diuretics may be preferred. Special consideration is necessary for the elderly concerning the possible side effects of each drug class. In the presence of additional risk factors, an individualized approach is necessary to tailor the most effective therapy as per patient needs. Thus, in treating hypertension, a multipronged but individualized approach is necessary to optimize blood pressure control and clinical outcomes in the real-world setting.

Keywords: Hypertension, Diabetes mellitus, Chronic kidney disease, Elderly

INTRODUCTION

Hypertension is a significant cardiovascular risk factor that contributes to substantial morbidity and mortality. Globally, approximately 1.3 billion people aged 30 to 79 years suffer from hypertension.[1] Estimates from 2019 indicate that over a billion people with hypertension belong to low- and middle-income countries.[2] In India, hypertension affects nearly one out of three individuals, with a higher prevalence in urban versus rural populations.[3] The management of hypertension is determined by multiple factors such as blood pressure levels, age and comorbidities. Recent estimates indicate one out of eight individuals aged 20 to 40 years are diagnosed with hypertension.[4] The prevalence of hypertension is significantly higher in the elderly aged above 60 years as compared to younger patients (65.6% versus 28.7%).[5] Diabetes often coexists with hypertension. In the South-East Asian region, the co-prevalence of diabetes and hypertension was reported to vary from 20.6% in India to 78.4% in Thailand.[6] Similarly, renal dysfunction indicated by microalbuminuria is observed in over 50% of individuals with hypertension.[7,8] In addition, dyslipidemia is commonly encountered in patients with hypertension, which adds to the existing cardiovascular risk.[9]

Besides these factors, cardiovascular risk is also an important consideration in managing hypertension. Treatment of hypertension significantly reduces the absolute cardiovascular risk. Adequate treatment of hypertensives with low cardiovascular risk is equally essential to prevent progression to higher cardiovascular risk.[10] High-risk individuals such as the elderly, those with diabetes or renal dysfunction or previous coronary heart disease (CHD), might remain in the high cardiovascular risk range despite the use of extensive concomitant therapies.[11] Thus, it is essential to analyze the concept of

cardiovascular risk in treating patients with hypertension. In India, hypertension prevalence is increasing substantially in younger age groups along with increasing comorbidities.[12] It is therefore extremely essential to manage hypertension effectively to lower residual cardiovascular risk in such patients with increased cardiovascular risk. There is a need to highlight the importance of different therapies in this context to assist primary physicians in effectively managing patients with hypertension. In this review, we take a case-based approach and discuss the most effective therapeutic intervention to effectively manage a patient with hypertension.

HYPERTENSION WITH DIABETES MELLITUS

Hypertension with diabetes adds to the increased morbidity and mortality. Strict blood pressure control is necessary to reduce the risk of major cardiovascular events (MACE) and all-cause deaths. Guidelines from the American Diabetes Association (ADA) and European Society of Cardiology and European Hypertension Society (ESC/ESH) recommend a target blood pressure of <140/90 mmHg for a patient with diabetes and hypertension.[13,14] However, some advocate stricter blood pressure goal of <130/80 mmHg in patients with diabetes.[15,16] It has been suggested that stricter blood pressure goal may be advised in younger patients (<50 years) and in those with the presence of target organ damage such as microalbuminuria and a goal of <140/90 mmHg may be optimal for the elderly (>80 years).[17]

In patients with hypertension and diabetes, renin-angiotensin-aldosterone system (RAAS) inhibitors are preferred as the initial choice compared with calcium channel blockers (CCBs) and thiazide-diuretics.[18] Hypertension in patients with diabetes also increases the risk of renal injury.[19] In such patients, American Diabetes Association (ADA) guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blocker (ARBs) at the maximum tolerated dose, as the first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g creatinine.[14] The use of ACEIs/ARBs reduces the incidence of acute myocardial infarction (MI), lowers the infarct size and reduces the incidence of stroke and MACE.[20] In patients with diabetes, a meta-analysis of 11 randomized controlled trials reported that both ACEIs and ARBs reduced cardiovascular mortality (odd ratio [OR 95% confidence interval {CI}]: 0.9 (0.8–1.0); p<0.01) and had a favorable impact on non-cardiovascular mortality (OR [95% CI]: 0.7 [0.9–1.0]; p=0.2) in comparison to placebo. Additionally, the incidence of new-onset diabetes was significantly reduced by both treatments.[21] However, ARBs have a better safety profile than ACEIs in terms of significantly lower risk of angioedema, cough, pancreatitis, and gastrointestinal bleeding.[22] Therefore, ARBs can be considered over ACEIs as the initial treatment of choice in patients with diabetes and hypertension.

In choosing an antidiabetic agent in a diabetic patient with hypertension, one should understand the effects of various oral antidiabetic drugs on blood pressure levels. Among various drugs, sodium-glucose cotransporter 2 inhibitors (SGLT2is) are most effective in systolic and diastolic blood pressure reduction. Among other antidiabetics, thiazolidinediones and glucagon-like peptide 1 (GLP-1) agonists reduce blood pressure, whereas other drugs may have an inconsistent effect on blood pressure.[23,24] Thus, SGLT2is and ARBs could be the choice of drugs for the management of glycemia and blood pressure in patients with hypertension and diabetes.

HYPERTENSION WITH CKD

In patients with CKD, hypertension is interlinked in a loop wherein increasing blood pressure levels lead to a progressive decline in renal function that further accentuates blood pressure.[25] The kidney disease Improving Global Outcomes (KDIGO) guidelines recommend a systolic blood pressure goal of <120 mmHg for patients with CKD. ACEIs or ARBs are the first choice of agents in treating hypertension in patients with CKD and severely increased albuminuria in both diabetics and non-diabetics. Monitoring of blood pressure every 2 to 4 weeks is advised. Dosage adjustments should undertake serum creatinine and potassium levels. If the drugs are well-tolerated (no rise in serum creatinine by >30%) for 4 weeks, they should be continued.[26]

Other agents such as thiazide diuretics and CCBs may be considered along with ACEIs/ARBs or may be added after their initial use. Mineralocorticoid receptor antagonists (MRAs) are effective in the management of refractory hypertension. Caution is advised for hyperkalemia or a reversible decline in kidney function.[26] In patients who have undergone renal transplants, ARBs and CCBs are recommended as the choice of treatment for the management of hypertension.[26]

Early identification of renal dysfunction is necessary to initiate treatment immediately. Screening for microalbuminuria should be done at regular intervals. Current literature indicates that the screening rates in patients with hypertension are low. In a cohort study from the US, the screening rates for albumin-to-creatinine ratio (ACR) were 35.1% and 4.1% in patients with diabetes and hypertension, respectively. However, the median prevalence of albuminuria (ACR ≥30 mg/g) was 32.1% in patients with diabetes and 21.8% in patients with hypertension.[27]

In India, a few studies have identified albuminuria prevalence to be 33.3-47% in patients with hypertension.[28,29] The American College of Physicians advises annual screening of albuminuria in patients who are diagnosed with hypertension. In patients who are already being treated with ACEIs/ARBs, monitoring of proteinuria may not be necessary.[30]

HYPERTENSION WITH ISCHEMIC HEART DISEASE

When considered as a risk factor for CAD, hypertension accounts for 25% and abnormal lipids account for 75% of overall cardiovascular risk.[31] Treatment of hypertension reduced the risk of CAD by 17%.[32] In patients with prior CAD or ischemic heart disease (IHD), the blood pressure goal is <130/80 mmHg.[15,16] One should exercise caution in lowering blood pressure levels as levels <120/70 mmHg may not prove further beneficial.[33]

RAAS inhibitors are frontline agents along with beta-blockers (BB) in patients who have had prior CAD. In the presence of anginal symptoms, CCBs can also be considered.[16] In the absence of anginal symptoms, thiazide diuretics or non-dihydropyridine CCBs should be considered for blood pressure control.[15] Studies indicate that in modern practice, ARBs but not ACEIs are used to manage hypertension in a substantial proportion of patients with stable CAD. ARBs do not differ from ACEIs in reducing the incidence of major cardiovascular outcomes.[34] In patients with CAD, thiazide-like diuretics, mainly chlorthalidone, are advocated if an additional blood-pressure lowering agent is necessary. Aldosterone antagonists are essential in CAD patients with HF.[35] Chlorthalidone is shown to reduce myocardial ischemia similar to diltiazem in the elderly population.[36] Thus, in such a high-risk population, chlorthalidone may be a preferred diuretic for control of hypertension in addition to existing therapy with ACEIs/ARBs.

Regular monitoring of blood pressure and cardiac function is necessary for patients with hypertension with CAD. Blood pressure check-up at regular intervals (e.g., every 3 months) can prove beneficial. It has been identified that the severity of CAD, reduced left ventricular function and uncontrolled blood pressure during follow-up are associated with adverse outcomes in such patients.[37] The adherence to therapy should be monitored. Compared to low adherence, high adherence to antihypertensive therapy is associated with lower risk of cardiovascular (CV) events.[38] Thus, adequate monitoring and control of blood pressure by maintaining high adherence to treatment are necessary for secondary prevention of MACE in patients with hypertension and CAD.

HYPERTENSION IN THE YOUNG AND ELDERLY

One out of eight individuals aged 20 to 40 years is known to have hypertension.[4] In India, the age-adjusted prevalence in persons aged between 15 and 49 was 11.3%.[39] Hypertension diagnosis remains lower in younger patients aged 18 to 31 years compared to elder patients aged >31 years. The slower diagnosis rate in young age individuals can be devastating in the long term.[40] It necessitates increasing awareness and hypertension detection rates in the primary care setting. In comparison, the prevalence of hypertension in the elderly is higher. Studies from India identified that hypertension prevalence in individuals >60 years is nearly 40%, whereas it increased to 83.5% in those aged >80 years.[41-43] Stricter blood pressure goals are advised in younger individuals. Control of blood pressure to <130/80 mmHg is necessary for younger adults, whereas in the elderly systolic blood pressure to the level of 130–139 mmHg and a diastolic value of <80 mmHg is advised.[16]

As an initial choice of therapy in hypertension without any comorbidities in young adults, any antihypertensive from RAAS inhibitors, CCBs, or thiazide-diuretics can be considered. A study from the UK identified no differences in achieved blood pressure levels after initiating CCBs or ACEIs/ARBs in younger patients.[44] In these individuals, not only the blood pressure values but also the overall CV risk should be considered while initiating treatment. Once secondary causes of hypertension are excluded, patients should undergo a complete evaluation for the presence of hypertension-mediated organ damage. Such patients need to be advised to follow lifestyle modification aggressively.[45] A recent study finds that despite continued elevated blood pressure and regular contact with primary care physicians, young adults had slower rates of antihypertensive medication initiation than middle-aged and older adults.[38] It is important to understand that a 5-mmHg reduction in blood pressure can reduce MACE incidence by 10%, irrespective of previous cardiovascular disease.[46] Therefore, every attempt should be made to aggressively treat young patients with hypertension.

In the elderly, RAAS inhibitors, CCBs and diuretics have an excellent safety profile and are generally well tolerated. Compared to younger subjects, intensive blood-pressure lowering strategy resulted in significant reduction in the primary cardiovascular endpoint (composite of nonfatal MI, acute coronary syndrome not resulting in an MI, nonfatal stroke, nonfatal acute decompensated heart failure and cardiovascular mortality).[47] However, avoiding hypotension and too rapid reduction in blood pressure may not be advisable. In frail patients, it may be wise to use a single agent initially and gradually increase the dosage as per tolerability. Though these patients have chances of various comorbidities, the use of loop diuretics or alpha-blockers should be avoided to reduce the risk of falls.[16] In frail patients who are at risk of orthostatic hypotension or falls, a strategy of medication reduction may also be practiced. In the short term, there may not be any difference in blood pressure levels. However, long-term clinical outcomes are not studied with this strategy.[48]

Renal function assessment is a necessary consideration in the elderly population. Increased systolic and diastolic BP beyond 140/80 mmHg increases the risk of proteinuria in the elderly.[49] As age increases, there is a gradual decline in renal function and this may accelerate in patients with uncontrolled BP. In elderly patients, the rate of decline in renal function is associated with the occurrence of apparent treatment-resistant hypertension.[50] Monitoring of renal function may be necessary at least on a yearly basis in elderly individuals with hypertension. The presence of renal dysfunction also increases the risk of hypokalemia with the use of diuretics. As observed in the systolic hypertension in the elderly program trial, the presence or absence of hypokalemia does not affect cardiovascular

outcomes.[51] Low-dose regimens may help mitigate the risk of hypokalemia with diuretics. Diuretics need to be avoided in patients with a history of gout.[52]

Isolated hypertension in young and older adults should not be ignored. Compared to younger patients with normal blood pressure, young adults with isolated hypertension have nearly twice the risk of cardiovascular disease-related mortality. Treatment of such patients with existing therapies offer protection.[53] Figure 1 shows the individualized treatment choices for managing hypertension among various comorbidities.

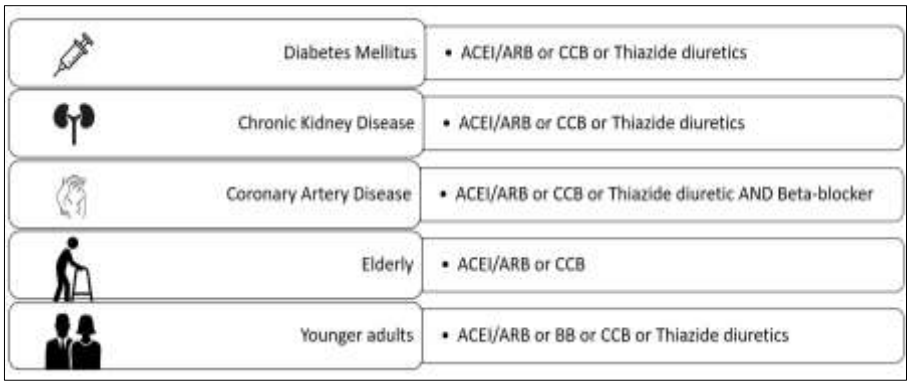

Figure 1: Antihypertensive treatment choices in various comorbid conditions.

CONCLUSION

Today, the management of hypertension in the real-world setting is complex. Multiple factors need to be considered in every patient who is diagnosed with hypertension. Individualization of treatment considering the age, comorbidities such as diabetes, CKD, CV risk and medication tolerability is necessary. In the current scenario, a blood pressure goal of <130/80 mmHg can be applied to most patients with hypertension except for the elderly where a target of <140/90 mmHg may be most feasible. Preference for ACEIs/ARBs is observed especially in diabetes and CKD. In younger patients, an aggressive approach to blood pressure reduction with an emphasis on lifestyle modification is necessary even in cases with mild hypertension. In the elderly, a more cautious approach is necessary to optimize treatment considering efficacy and tolerability.

Thus, in the current era, individualization of hypertension therapy is the need of the hour and necessitates the adoption of this approach in the real-world setting.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Vijay Katekhaye for his assistance in drafting, editing, and reviewing the manuscript.

Funding: Writing support was funded by Abbott Healthcare Pvt Ltd.
Conflict of interest: The author received speaker's honorarium from Abbott for participation in advisory board meetings. The author is a member of Association of Physicians of India, LSI, Paediatric Cardiological Society of India, ECHO Cardiology Society of India, and Asia Pacific Society of Interventional Cardiology
Ethical approval: Not required

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Cite this article as: Garg R. Individualization of hypertension treatment: an expert review. Int J Adv Med 2023;10:647-52.