# HYPERTENSION
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## AIMS & SCOPE

**Hypertension Journal** is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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# Hypertension Journal

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# Contents

# *E*ditorial

# A Global Challenge in Need of a Global Strategy

Sabu Thomas, John D. Bisognano

Department of Medicine, Division of Cardiology, University of Rochester School of Medicine, Rochester, New York, United States

In ancient Indian Ayurvedic medicine, the quality of a patient's pulse was correlated with cardiovascular health. A "hard pulse" was probably synonymous with the modern term "hypertension." The history of hypertension of course would not be complete without describing Dr. Fredrick Akbar Mahomed's contributions in the late 19th century. This Irish-Indian physician working in London at the Guy's hospital first described conditions that later came to be known as "essential hypertension." Some of his other important contributions were the demonstration that high blood pressure could exist in apparently healthy individuals, that high blood pressure was more prevalent in the elderly, and that the heart, kidneys, and brain could be affected negatively by high arterial pressure.[1,2]

Welcome to this special edition of the Indian Journal of Hypertension in which authors from the University of Rochester explore eight areas in hypertension management that are commonly encountered by the treating clinician. Over the past several years, numerous professional societies have come up with guidelines that differ slightly in blood pressure goals for the general population and sometimes have specific goals for patients with diabetes, renal disease, or cardiovascular disease. There is profound agreement in the importance of intensive goal-directed treatment of hypertension, and rather than focus on the nuances of the guidelines, we focus on blood pressure measurement, pathophysiology, and different approaches to treatment that one may routinely encounter in special populations.

Worldwide, the prevalence of hypertension remains high with approximately 1 billion individuals affected and 7.1 million deaths attributed to hypertension each year.[3] Proper treatment of hypertension, therefore, is essential, particularly in populations at the highest risk of cardiovascular and renal disease, which will result in significant improvements in public health, adding life-years to the population and conserving limited health-care resources. Blood pressure management, in addition to lipid management and smoking cessation efforts, has entered a golden age of drug therapy with most medications being low cost with low side effects. However, all of these therapies should be used in addition to lifestyle modifications that include proper diet, moderation of sodium intake, frequent exercise, and efforts at achieving ideal body weight. Public health efforts that decrease the risk of heart attacks, heart failure, stroke, and renal disease include improving diet and educating patients regarding the dangers of smoking and a sedentary lifestyle. We hope that these articles will be helpful in improving your patients' health.

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**Address for correspondence:**
Sabu Thomas, Department of Medicine, Division of Cardiology, University of Rochester School of Medicine, Rochester, New York, United States.
E-mail: sabu_thomas@urmc.rochester.edu

# *R*eview *A*rticle

# Ambulatory Blood Pressure Monitoring

Janany Sabescumar, Erika R. Drury

Department of Medicine, Division of Nephrology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

## Abstract

Blood pressure measurements in the office are strongly associated with cardiovascular disease morbidity and mortality, but do not correlate well with 24 h blood pressure values. Ambulatory blood pressure monitoring (ABPM) is a powerful tool for investigating the true blood pressure burden in individual patients and currently accepted as the gold standard for diagnosing hypertension. ABPM can improve cardiovascular risk stratification for individual patients and evaluate for other abnormal blood pressure phenotypes. Here, we review the use of APBM, summarize data suggesting the superior predictive value of ABPM for cardiovascular disease, and practical applications for its clinical use.

**Key words:** Ambulatory blood pressure monitoring, hypertension, cardiovascular disease, masked hypertension

## Introduction

Accurate measurement of blood pressure is crucial for identifying and treating hypertension. Hypertension identified in a clinical setting is strongly associated with cardiovascular disease morbidity and mortality.[1] However, blood pressure fluctuates during the day, and office blood pressure readings do not correlate well with 24 h blood pressure values.[2] Therefore, out of office blood pressure measurement has been used to better characterize the true burden of hypertension and predict cardiovascular risk in individual patients. Ambulatory blood pressure monitoring (ABPM) captures out of office blood pressure values and more accurately reflects the total blood pressure load and variability in an individual patient. Here, we will review the predictive value and role of ABPM in clinical practice.

## Protocol for ABPM

Ambulatory blood pressure monitors are connected to a sphygmomanometer cuff on the upper arm and usually attached to a belt or pouch. Readings are measured every 15–30 min throughout the day and night and are typically blinded to the patient. Measurements are automatically downloaded onto a computer for processing while the patient monitors and logs their daily activities. There is no standard approach to determine an adequate or valid 24 h ABPM session. Guidelines suggest that greater than 70–80% of planned readings[3] or at least 10 readings during the daytime and at least 5 during the nighttime[4] are required.

Validation procedures for ABPM devices are available from several organizations[5,6] and an updated list of monitors validated for clinical use is readily found online (www.dableducational.org).

## Blood Pressure Treatment Thresholds

ABPM uses different thresholds for defining hypertension than office-based blood pressure measurements. Thresholds have been suggested based on data from European, Australian, Asian, and African-American populations.[7-10] These data have been summarized in the 2017 ACC/AHA guideline for blood pressure management, a summative statement on the prevention, identifying, evaluation, and treatment of high blood pressure in adults. In general, a clinic blood pressure of 140/90 mmHg generally corresponds to blood pressure at home of 135/85, 24 h ABP of 130/80 mmHg, daytime ABP of 135/85 mmHg, and nighttime ABP of 120/70 mmHg.[11] The precise relationships between office readings, home BP readings, and ABP readings

**Address for correspondence:**
Erika R. Drury, Department of Medicine, Division of Nephrology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue Box 675, Rochester -14642, New York, United States. E-mail: Erika_Drury@URMC.Rochester.edu

have not been classified in all populations, and therefore, these thresholds should be used as a general guide in individual patients.

## Association between Ambulatory Blood Pressure and Subclinical and Clinical Cardiovascular Disease

Several components of the ABP, including the 24 h mean ABP, daytime ABP, and nighttime ABP, have been shown to be superior to office blood pressure readings for predicting end-organ dysfunction.[12] Several studies have demonstrated stronger cross-sectional and longitudinal associations between ABP and left ventricular hypertrophy and dysfunction, proteinuria, the progression of CKD, atherosclerotic plaques, and cerebral infarcts or white matter lesions on MRI[13-16] than with OBP.

In a cross-sectional study of 108 patients, the 24 h mean BP predicted hypertensive target organ damage beyond casual BP measurements.[15] In a study of 74 hypertensive individuals, the 24 h mean ABP was significantly associated with the left ventricular mass and wall thickness even when accounting for clinic BP measurements.[17] In a study of 75 individuals with type 1 diabetes, an increase in sleep SBP was associated with incident microalbuminuria, whereas office measurements did not correlate with incident microalbuminuria.[18]

Considerable evidence exists suggesting that ABPM more strongly predicts cardiovascular disease than office blood pressure (OBP) measurements.[19] A landmark study by Perloff *et al.* first demonstrated that hypertensive patients with higher ABP had a greater cumulative frequency of fatal and non-fatal cardiovascular events than those with lower ABP.[20] In 1076 patients with essential hypertension with an average follow-up time of 5.1 years, there were 228 (21.2%) total clinical cardiovascular events. Patients with a mean ABP ≥ 10/6 mmHg higher than predicted based on the office BP had a statistically significantly higher cumulative incidence of a first clinical cardiovascular event than those with an ABP that was ≥ 10/6 mmHg lower than the office BP predicted.

Subsequent studies have shown the superiority of ABPM at predicting cardiovascular events[21-23] as well as cardiovascular mortality,[22,24,25] even after adjustment for conventional risk factors, most of which account for OBP measurements. Among patients with treated hypertension, ABP is superior to OBP for stratifying cardiovascular risk and predicting incident cardiovascular events.[26-28] In a study of 1963 patients with treated hypertension and median follow-up of 5 years, the baseline mean 24 h SBP and DBP independently predicted new cardiovascular events, even when adjusting for office BP.[26] The adjusted relative risk of a new cardiovascular event was 1.34 (95% CI 1.07–1.57) for 24 h ambulatory SBP and 1.21 (95% CI 1.01–1.46) for 24 h ambulatory DBP.

## Hypertension Phenotypes Defined by OBP and ABP Measurements

Four phenotypes of blood pressure can be defined by characterizing both OBP and ABP within individual patients: Normotension

(normal clinic and ABP measurements), hypertension (elevated clinic and ABP measurements), white coat hypertension (elevated clinic and normal ABP measurements), and masked hypertension (normal clinic and elevated ABP measurements).[11] ABPM can also reveal abnormal circadian variation of blood pressure. Blood pressure normally follows a diurnal pattern of variation, falling to its lowest levels during the first few hours of sleep (dipping) and rising to its highest levels early in the morning on awakening.[29] The normal nocturnal fall in BP is > 10%, but some persons have a blunted fall or an increase in BP with sleep, termed non-dipping and reverse dipping, respectively. The clinical significance of these phenotypes is described below.

### Masked hypertension

An estimated 15–30% of the general population have masked hypertension.[30] Estimates vary by geographic region,[31] the ABP periods used to define hypertension status,[32] demographics,[33] and comorbidities.[34,35] Specifically, high rates of masked hypertension have been demonstrated in African Americans[33] and in persons with chronic kidney disease.[34,35] Masked hypertension has been increasingly classified as a high-risk phenotype, strongly linked with an increased risk of hypertensive organ damage including increased left ventricular mass,[14] arterial stiffness and carotid intima-media thickness,[36] and albuminuria[37] as well as cardiovascular events.[38,39]

### White coat hypertension

White coat hypertension is suspected in persons with elevated clinic blood pressures but with normal home blood pressure readings and the absence of target organ dysfunction. It is generally accepted that persons with white coat hypertension have a similar risk of incident cardiovascular events compared to those with normotension, as demonstrated by a large meta-analysis (Fagard and Cornelissen, 2007). However, white coat hypertension may be associated with prevalent albuminuria[37] and an increased risk of future stroke.[40]

### Abnormal dipping

Abnormal nocturnal dipping can occur in both normotensive and hypertensive persons. In particular, reverse dipping is documented more frequently in persons with diagnosed hypertension, kidney disease, type 2 diabetes mellitus, and obstructive sleep apnea.[41] Both blunted and reverse dipping patterns, even when accounting for the office and daytime ABP, have been shown to be associated with a higher risk of coronary events, stroke, cardiovascular events, and all-cause mortality.[42,43] Reverse dipping has been linked to higher left ventricular mass in African Americans.[44] Abnormal dipping has also been associated with glomerular filtration rate decline[45] and kidney-associated death in patients with chronic kidney disease.[46]

## Evaluating Response to Treatment

Few studies have specifically evaluated the use of ABPM to guide treatment decisions and response to treatment in hypertension.

Staessen *et al.* showed that fewer antihypertensive drugs are prescribed when decisions are based on ABP rather than OBP measurements.[47] Whether treatment decisions based on ABP are superior to OBP in outcomes remain to be determined. In one study of 206 individuals with hypertension and left ventricular hypertrophy (LVH), there was a greater association between regression of LVH and a treatment-induced decline in ABP than with changes in OBP.[48] Nighttime dosing of antihypertensives may restore normal dipping, reduce nocturnal hypertension, and reduce cardiovascular events.[49-52] ABPM, therefore, would be useful to assess dipping response to therapy.

## Clinical Indications for ABP Monitoring

Practice guidelines and position papers including those from the European Society of Hypertension,[3] the American College of Cardiology/American Heart Association,[11] and the United States Preventive Services Task Force (USPSTF)[53] describe the recommended clinical use and applications of ABPM. The USPSTF, citing the consistent association between elevated ambulatory systolic BP and cardiovascular events independent of OBP, specifically recommends ABPM as the gold standard for confirming the diagnosis of hypertension.[53] However, adhering to this recommendation may not be feasible given the cost, burden, and often limited availability of ABPM devices. In general, ABPM is recommended for excluding white coat hypertension, monitoring the efficacy of antihypertensive treatment in individuals with borderline office BP values, evaluating for masked hypertension in individuals with hypertensive organ damage but normal OBP readings, and evaluation of diurnal patterns of blood pressure.[54] ABPM may also be helpful to assess labile blood pressures, hypotension, and elevated BP readings in the elderly and in pregnancy.[54]

## Conclusions

ABP monitoring is a powerful tool for investigating the true blood pressure burden in individual patients. It is widely accepted as the gold standard for the diagnosis of hypertension. It has been well-established that ABP values are better predictors of cardiovascular risk that OBP values. ABPM can assist in ruling out white coat hypertension, identifying masked hypertension, and abnormal diurnal BP patterns. However, the widespread use of ABPM may be limited by burden to patients, cost, and limited availability of monitoring programs. As most of the current treatment guidelines are based on results from large trials using in office BP readings, future studies are needed to understand the utility of ABPM to guide and modify treatment to decrease cardiovascular risks.

## Acknowledgments

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# $\mathcal{R}$eview $\mathcal{A}$rticle

# A Broad Review of Hypertension Pharmacology

Neil Gupta[1], Rebecca Schallek[2]

[1]Department of Internal Medicine, University of Rochester, Rochester, New York, United States, [2]Department of Internal Medicine, Division of Cardiology, University of Rochester, Rochester, New York, United States

## Abstract

Most patients who develop primary hypertension are treated with medications despite lifestyle changes. For providers, determining when to start medications can be confusing as guidelines frequently change and determining which medication to start can also be challenging. In general, medication is initiated after assessing a patient's risk for developing atherosclerotic cardiovascular disease using risk calculators as well as their medical comorbidities. Target blood pressure, time for follow-up, and initial medication(s) vary among patients. First-line agents include thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Second-line agents include beta-blockers, diuretics, alpha-1 antagonists, alpha-2 agonists, and direct-acting vasodilators. It is important to note that not all classes of blood pressure-lowering medications are considered equal and each patient's unique medical comorbidities should always be taken into account before initiating treatment. These medications have their own respective side effects and contraindications that providers should be aware of so that they can monitor for adverse reactions as well as council their patients.

**Key words:** Angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, atherosclerotic cardiovascular risk score, calcium channel blockers, hypertension, thiazide diuretics

Hypertension affects approximately 1.13 billion people worldwide, and these numbers continue to rise as the population gets older and the definition of hypertension continues to change. It has been shown repeatedly that controlling high blood pressure (BP) helps prevent developing cardiovascular (CV) disease, especially in the older population.[1,2] Every patient with hypertension should pursue lifestyle changes and non-pharmacological approaches to lower their blood pressure. These lifestyle changes generally include a healthy diet, regular exercise, minimal alcohol intake, and working toward a healthy weight.[3] However, when non-pharmacological approaches fail to achieve target blood pressure goals, antihypertensive medications can help patients to achieve the recommended targets. In this article, we will offer a broad review of the pharmacology of blood pressure-lowering drugs with their common indications, as well as common side effects.

## When to Start Medication and What is Our Target?

Before beginning a discussion on the hypertension pharmacological agents available, it is important to mention how target blood pressure goals continue to evolve, as evidenced by the 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.[4] The current recommendations favor an individualized approach based on one's personal CV risk factors. Once these CV risk factors and consequent target blood pressure goals are identified, pharmacological agents should be tailored toward a person's specific risk factors. For example, an individual with diabetes may benefit from one class of antihypertensives, while an individual who has known coronary atherosclerotic disease might do better with a different class. One tool that has been valuable in guiding blood pressure management is the atherosclerotic cardiovascular (ASCVD) risk score, which is available as an online calculator.[5] The ASCVD risk score helps determine an individual's 10-year and lifetime risk of developing atherosclerotic CV disease (including coronary death or non-fatal myocardial infarction [MI] and fatal or non-fatal stroke). It is used for primary prevention of developing atherosclerotic disease, and in recent guidelines, to establish goals in treating hypertension.[6]

Patients with an elevated ASCVD risk score > 10% or with known CV disease with Stage 1 hypertension (defined as a systolic blood pressure (SBP) ≥130 mmHg or a diastolic blood pressure (DBP) ≥80 mmHg) should initiate a BP-lowering medication, as well as continue non-pharmacological methods in reducing BP. Patients who have Stage 2 hypertension (defined as an SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg) without a known history of CV disease and with an estimated ASCVD risk score of <10% should use BP-lowering medications for the primary prevention of CV disease.[4] Patients who have Stage 2 hypertension will generally require at least two antihypertensive medications of different classes, in addition to following non-pharmacological approaches to lower BP. Furthermore, patients who have a systolic pressure 20 mmHg above target goal or a diastolic pressure 10 mmHg above goal will likely require at least two antihypertensive agents.[7]

Patients with an estimated ASCVD risk score of <10% with an elevated BP or Stage 1 hypertension should be managed with non-pharmacological methods and should have their BP rechecked in 3–6 months. Patients with normal BP of <120/80 mmHg should have yearly follow-up for BP checks and continue with lifestyle modifications.

Blood pressure reducing medications are also recommended for the prevention of recurrent CV events in patients with known CV disease with a goal SBP < 130 mmHg and a goal DBP < 80 mmHg. Ultimately, a goal BP of <130/80 mmHg should be obtained for patients with an ASCVD risk score >10% over 10 years, as well as those patients who have diabetes, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), chronic kidney disease (CKD), prior MI, or prior stroke.[4, 8-10]

Typically, clinicians should first follow standard treatment guidelines for patients with a history of known CV disease, HFrEF, prior MI, stable angina, and titrate the indicated medications to achieve a goal BP < 130/80 mmHg. For sole hypertension in the absence of other CV comorbidities, clinicians should increase the dose of one first-line antihypertensive medication until the goal BP is reached. If goal BP cannot be reached with maximal dosing, then a second first-line agent is added to the medication regimen. Patients should have monthly follow-ups if a medication is increased or if a new medication is added to their regimen to ensure adherence and to allow for monitoring of adverse events.[4,11] One major side effect of all antihypertensives is the potential to cause hypotension, which is why close monitoring is necessary when making changes.

## First-line Agents for Stage 1 Hypertension

### Thiazide diuretics

Thiazides are the most commonly used diuretics and are typically a first-line agent for treating hypertension.[12,13] These diuretics work by inhibiting the sodium chloride transporter in the distal convoluted tubule of the nephron, thus resulting in inhibition of sodium reabsorption and promoting water excretion.[14]

*Side effects*
Side effects are predominantly electrolyte disturbances, which include hyponatremia, hypomagnesemia, hypokalemia, hyperuricemia, hyperglycemia, hypercalcemia, and metabolic alkalosis. Side effects are typically dose dependent.[15,16]

*Comments*
Chlorthalidone is typically the preferred thiazide with its long half-life. It also has a well-established CV disease risk reduction in clinical trials. When starting a thiazide diuretic, clinicians should monitor for electrolyte disturbances with laboratories.[13]

### Calcium channel blockers

Calcium channel blockers (CCBs) reduce calcium flux into cells by binding to voltage-gated calcium channels located in vascular smooth muscle cells and cardiac myocytes, including the sinoatrial (SA) and atrioventricular (AV) nodes. In cardiac tissue (including the SA and AV nodes), these channels play an important role in cardiac inotropy and chronotropy.[17,18] These medications are offered in two different classes: Dihydropyridine CCBs and non-dihydropyridine CCBs. Dihydropyridine CCBs usually exhibit more vasodilation, causing a decrease in systemic vascular resistance (SVR) and are useful in decreasing blood pressure. Non-dihydropyridine CCBs work primarily by reducing chronotropy and inotropy in the SA/AV nodes and are useful in the management of supraventricular tachycardias.[19]

*Side effects*
Side effects include peripheral edema, flushing, headache, and constipation.[20]

*Comments*
A CCB from either class should generally be avoided in patients with HFrEF.[19,21] Non-dihydropyridine CCBs should be used with caution when combined with beta-blockers, as their concurrent use can increase the risk of heart block and symptomatic bradycardia.[4,22]

### Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers

Angiotensin is a peptide hormone important in regulating vasoconstriction. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) both work effectively in the same way on the angiotensin system. Both of these medications limit the systemic effects of angiotensin II; ACE inhibitors decrease the amount of angiotensin II, and ARBs block the binding of angiotensin II to its respected receptors, thereby decreasing vasoconstriction.[23-25]

*Side effects*
Hyperkalemia is the most common side effect. Dry cough, which usually begins 1–2 weeks after starting therapy, however, can develop up to 6 months after starting treatment and is much more common in ACE inhibitors than in ARBs. Angioedema is

a rare but potentially fatal complication that is associated with ACE inhibitors and is less likely to develop with ARBs.[25,26] If angioedema does occur, an ARB can be used for BP control only after discontinuation of the ACE inhibitor for 6 weeks. Furthermore, hypotension is seen more often in ARBs than in ACE inhibitors.[27]

*Comments*

ACE inhibitors and ARBs should never be used in conjunction with each other or in combination with a direct renin inhibitor. Both of these agents should be avoided in pregnancy and in patients with bilateral renal artery stenosis.[4,28-30] There is an increased risk of hyperkalemia in patients with CKD or when they are used in combination with potassium-sparing diuretics. These agents are typically the first-line antihypertensive agent in patients with CKD, HFrEF, and diabetics with albuminuria.[11,23,31]

## Secondary agents

Common secondary medications used for treating hypertension include beta-blockers, loop diuretics, potassium-sparing diuretics, aldosterone antagonists, and alpha-blockers. In specific medical comorbidities, some of these agents are used as first-line treatment for hypertension. For the most part though, they are used in adjunct with primary agents to control blood pressure.

Beta-blockers: Beta-blockers include a large class of medications that have variable affinities for beta and alpha receptors throughout the body, thus giving them diverse roles in treating different conditions. Depending on their target beta-receptor ( β-1 or β-2), certain beta-blockers have a significant role in metabolic activity and smooth muscle relaxation.[32] Beta-blockers are rarely used as initial therapy for hypertension list, a patient has a history of prior MI, coronary artery disease (CAD), or heart failure (HF).[33] In the case of CAD or HF, cardioselective beta-blockers are first-line agents in treating hypertension as they block the β-1 receptors in cardiomyocytes, leading to decreased chronotropy/inotropy and therefore cardiac oxygen demand.[34-36] Non-cardioselective beta-blockers should be avoided in patients with reactive airway disease. In general, practitioners should avoid abrupt cessation of beta-blockers as patients can exhibit beta-blocker withdrawal including symptoms of tachycardia, anxiety, and hypertension. Side effects of beta-blockers include fatigue, sexual dysfunction, impaired glucose tolerance, increased airway resistance (non-cardioselective), and bradycardia.[37]

## Diuretics

### Loop diuretics

Loop diuretics work by inhibiting the Na-K-2Cl transporter in the thick ascending loop of Henle. They can lead to the excretion of up to 20–25% of filtered sodium and thus decrease BP.[38] Loop diuretics are preferred in patients with moderate-to-severe CKD (GFR < 30 mL/min) over thiazide diuretics and

are used in patients with symptomatic heart failure. Side effects include hypokalemia, metabolic alkalosis, hyperuricemia, and hyponatremia.[38-40]

### Potassium-sparing diuretics

Potassium-sparing diuretics act in the collecting tubule by blocking sodium channels, thereby decreasing the reabsorption of sodium and thus decreasing the excretion of potassium. These agents are minimally effective at lowering blood pressure; however, they can be used in patients with hypokalemia on thiazide monotherapy. Side effects include hyperkalemia and metabolic acidosis and should be avoided in patients with GFR < 45 ml/min.[4,38]

Aldosterone antagonists: Aldosterone antagonists include eplerenone and spironolactone. These medications act by directly inhibiting the mineralocorticoid receptor, thus limiting the effects of aldosterone. This leads to a decrease in sodium reabsorption and potassium excretion in the collecting tubule. Eplerenone has a higher affinity for the mineralocorticoid receptor than spironolactone, therefore causing fewer endocrine side effects. These are primary agents when treating hyperaldosteronism and are also useful add-on therapies when treating resistant hypertension.[41] It has been proven that these agents reduce mortality in patients with HFrEF and an ejection fraction of <35%.[42] Side effects include hyperkalemia, gynecomastia, menstrual abnormalities, impotence, and decreased libido.[41]

### Alpha-1 blockers

These medications work by inhibiting the activation of alpha-1 receptors (located on the peripheral vasculature) by norepinephrine, thus leading to a decrease in BP.[43] They are often used in patients with benign prostate hypertrophy (BPH) and are typically considered second-line BP agents, often used in combination with other agents. They are associated with orthostatic hypotension and should be used with caution in the elderly.[4,44]

### Alpha-2 agonists

These agents work by stimulating alpha-2 receptors in the central nervous system (CNS), which reduces sympathetic outflow and causes a decrease in peripheral resistance, heart rate, and blood pressure. These agents are generally used as last line efforts to control blood pressure. Abrupt cessations of drugs like clonidine can lead to rebound hypertension and should, therefore, be tapered. Additional adverse reactions include sedation orthostatic hypotension, dry mouth, and sedation.[4,45]

### Direct-acting vasodilators

These agents include hydralazine, minoxidil, and nitrates. They work by relaxing the peripheral smooth muscles, causing vasodilation and a decrease in blood pressure. They are typically used in patients with angina to help control symptoms and blood pressure.[4,46] The combination of hydralazine and long-acting nitrates has been shown to decrease mortality in patients with

HFrEF and can be considered if patients cannot tolerate ACE inhibitor/ARB therapy.[4,47]

## Conclusion

Hypertension is a disease that affects a large portion of the world's population, and achieving target blood pressure goals is instrumental in preventing the development or recurrence of CV disease. Achieving these blood pressure goals can be both an art and a science, and hypertension guidelines recommend an individualized approach, taking a person's CV risk factors into account. There are a multitude of medications that can be used, but we generally recommend initiating therapy with a CCB, thiazide diuretic, or an ACE inhibitor/ARB as first-line therapy. A patient's medical comorbidities should help guide a clinician's choice of antihypertensive medication, and in some instances, secondary agents may be the preferred medication to initiate therapy.

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# Review Article

# Dysrhythmias and Hypertension

Timothy Byrnes, David Huang

Division of Cardiology, Department of Medicine, University of Rochester Medical Center, Rochester, New York, United States

## Abstract

More than a quarter of the population of both the United States and India have a diagnosis of hypertension (HTN). HTN can lead to multiorgan dysfunction, including hypertensive heart disease. Despite the well understood morbidity and mortality associated with HTN, only 48.3% of the United States' and 10.7–20.2% of India's hypertensive population are adequately treated. Hypertensive heart disease is the result of a complex interplay of several factors, which expose the patient to an increased risk of dysrhythmias and sudden cardiac death. Management of dysrhythmias in the setting of hypertensive heart disease is similar to normotensive patients, but with a focus on optimal blood pressure, which can often reverse the pathologic cardiac remodeling and reduce the burden of dysrhythmias.

**Key words:** Hypertension, Blood Pressure, Dysrhythmias, Arrhythmias, India, United States, US

## Background

Cardiovascular disease is the leading cause of death in the world,[1] as well as the United States and India for the past 80+ years[2] and 16 years,[3] respectively. The death rate per 100,000 population in the United States is 262.3[4] and India is 209.1.[5] There are a variety of risk factors for cardiovascular disease, but likely none more significant than hypertension (HTN).[6] More than a quarter of the population of both the United States (29.0%)[7] and India (29.8%)[8] have a diagnosis of HTN. Despite the well understood morbidity and mortality associated with HTN, only 48.3% of the United States'[7] and 10.7–20.2% of India's[8] hypertensive population are adequately treated. Historically, HTN has been defined as a blood pressure (BP) >140/90 mmHg,[9] but a change to >130/80 mmHg has been recommended[10] following the SPRINT Trial.[11] This is would result in a dramatic increase in the prevalence of HTN throughout the world, including up to 46% of the entire United States population.[12] The patients responsible for this increase in prevalence would primarily be younger,[13] which could be beneficial as several studies have shown that BP > 130/80 mmHg is associated with poorer outcomes in patients <65 years old.[14–16] In addition to ischemic heart disease, stroke, vascular disease, and renal insufficiency, HTN can cause hypertensive heart disease, even with BPs of 120–139/80–89 mmHg.[17,18]

## Hypertensive Heart Disease

Hypertensive heart disease is the result of a complex interplay of several factors, particularly mechanical stress, inflammation, and the renin angiotensin aldosterone system (RAAS), and is graded in four degrees of severity with a focus on the left ventricle (LV).[19]

1. Isolated LV diastolic dysfunction without hypertrophy
2. LV diastolic dysfunction with concentric hypertrophy
3. Clinical heart failure (HF) with preserved ejection fraction
4. Dilated cardiomyopathy with HF and reduced ejection fraction

Mechanical stress on the heart from increased afterload induces hypertrophy through parallel addition of sarcomeres.[20,21] In addition, this stress leads to increased intramyocardial pressure[22] and impaired cardiac perfusion. This issue is particularly present in subendocardial tissue, where the highest extravascular compressive forces occur.[23] Similar to cardiac tissue, coronary arterioles undergo medial hypertrophy, as well as intimal hyperplasia in response to HTN.[24] Cardiac and arterial hypertrophy exacerbate each other and result in ischemia, then eventually replacement fibrosis.[25]

Inflammation is also known to have a role in the pathogenesis of hypertensive heart disease. While it is uncertain

if inflammation is caused by HTN or vice versa,[26] it is well known that hypertensive patients have elevated markers of inflammation.[27] One explanation for the link is the frequent presence of inflammatory comorbidities (obesity, DM, etc.) in patients with HTN.[28,29] Inflammation causes hypertensive heart disease through several mechanisms. Titin, a large protein of the sarcomere, is an important regulator of cardiac stiffness[30] and inflammation is known to impair titin relaxation.[31] In addition, inflammation is known to promote endothelin-1 production from endothelial cells.[32] Endothelin-1 induces vasoconstriction, hypertrophy,[33] and generation of superoxide,[34] as well as endothelial to mesenchymal transition.[35] This transition leads to coronary microvascular disease (CMD) through vessel rarefaction and fibrosis,[36] which contributes to the ischemic process discussed earlier.

In addition, the renin–angiotensin–aldosterone system plays an important role in hypertensive heart disease, particularly in the setting of primary aldosteronism and renal artery stenosis.[10] Activation of systemic and/or local RAAS[37,38] induces interstitial fibrosis and endothelin-1 production.[39]

## Tachydysrhythmias

### Ventricular Dysrhythmias

While hypertensive heart disease causes ventricular dysfunction, it also predisposes patients to ventricular dysrhythmias in proportion to the degree of hypertensive heart disease.[40-43] These changes include prolongation of action potential duration due to remodeling of gap junctions[44] and resultant dispersion of repolarization.[45] These cellular derangements combined with tissue fibrosis and scar from CMD[41] may lead to arrhythmogenic impulse formation and abnormal electrical conduction patterns. The most common ventricular dysrhythmia in this population is premature ventricular beats (PVBs),[46] but patients can also experience non-sustained and sustained ventricular dysrhythmias.[47-49] In fact, patients with HTN have 30% higher risk of sudden cardiac death (SCD), which increases proportionally with degree of HTN.[50]

While optimal BP control has regularly been shown to reverse left ventricular hypertrophy (LVH), the impact on SCD risk is less consistent.[51,52] The explanation for this discordance is likely related to the type of antihypertensive medication as well as the degree of myocardial substrate alteration and presence of associated comorbidities (ischemic heart disease, etc.). While all antihypertensive medications can reverse LVH to varying degrees,[53] non-potassium-sparing diuretics, particularly thiazide diuretics, can increase the risk of SCD.[54,55] This is thought to be due to hypokalemia,[56] prolongation and dispersion of repolarization,[57,43] and associated electrogenic early and delayed after depolarizations.[58] Interestingly, potassium supplementation appears to negate this effect in loop diuretics, but not thiazide diuretics.[54,55]

When encountering a patient with ventricular dysrhythmias, medications should be reviewed for pro-arrhythmic potential, social history assessed for alcohol and/or stimulant use, blood work obtained (complete metabolic profile and thyroid function), a 12-lead electrocardiogram to assess baseline conduction, presence of LVH, and possibly determine the site(s) of origin of PVBs, a 24 h Holter to evaluate for potential dysrhythmias and/or ventricular ectopy burden, and a transthoracic echocardiogram to evaluate cardiac structure and function.[59] If there is concern for an infiltrative process or underlying ischemia, consider a cardiac MRI or ischemia evaluation (stress test and/or coronary angiography), respectively.[59]

Management of patients with HTN and ventricular dysrhythmias is similar to normotensive patients, but it is important to recognize special situations that preclude the use of certain medications. In the setting of reduced systolic function (degree 4 hypertensive heart disease), calcium channel blocking agents,[60-62] Class I agents,[63] sotalol,[64] and dronedarone[65] should be avoided. In addition, as hypertensive heart disease patients can have prolongation of cardiac repolarization, care should be taken when considering Class III antiarrhythmic agents due to associated risks of Torsades de Pointes, although this risk may less with amiodarone than other Class III agents.[66,67] In the past, Class I and non-amiodarone Class III antiarrhythmics have been contraindicated in the setting of significant LVH[68] due to a presumption that amiodarone had less risk of inducing dysrhythmias. However, an observational study of 537 patients with LV wall thickness >1.4 cm revealed that amiodarone actually had lower survival compared to Class I and non-amiodarone Class III agents.[69] In addition, ablation and defibrillator implant should be considered according to the established guidelines.[70,71] The indications for these treatment modalities are not affected by the presence or absence of HTN.[70,71]

### Atrial dysrhythmias

Although Messerli *et al.* focused on the impact of HTN on LV structure and function, HTN also impacts the atria.[19,72] In response to increased afterload, the atria initially hypertrophy (EHRAS Class I atrial cardiomyopathy), then experience collagen deposition as LV diastolic dysfunction develops (EHRAS Class II-III).[72] Ultimately, as a result of the hypertrophy, dilation, fibrosis, and gap junction remodeling, conduction velocity is slowed and cellular action potential duration is prolonged in a heterogeneous fashion,[73] which leads to increased risk of atrial dysrhythmias primarily through triggering focal ectopic automaticity and disruption of uniform impulse propagation.[44,72] In addition to an increased risk for premature atrial beats (PABs),[75] patients with HTN are at 1.8 and 3.4 times greater risk for atrial fibrillation[74] and supraventricular tachycardia (SVT),[47] respectively. Similar to the ventricle, optimal BP control can reverse the pathologic remodeling[76-78] and reduce atrial dysrhythmia burden[44,72,79,80] to vary degrees depending on the antihypertensive class of the

agent used and the underling degree of substrate. In general, the use of angiotensin receptor blockers as an antihypertensive appears to be associated with the most significant reduction in new-onset atrial fibrillation.[81-83] Overall, the management of these dysrhythmias is not different between normotensive and hypertensive patients and providers should be aware of the indications and contraindications for antiarrhythmic therapy and ablation.[68,94]

## Bradydysrhythmias

Patients with hypertensive heart disease are also at increased risk for bradydysrhythmias, including high-grade AV block and sinus node dysfunction.[84] Sinus node dysfunction and high-grade AV block in the setting of HTN are likely related to sclerosis of the sinus node artery[85] and possibly fibrosis, leading to exit block and disruption of the AV conduction system,[86] respectively. In addition, hypertensive patients are at increased risk for polypharmacy, which can lead to bradydysrhythmias, particularly with the combination of negative chronotropic effects of non-dihydropyridine calcium channel blockers and beta-blockers.[87,88] Management of bradydysrhythmias is independent of HTN, primarily focuses on removing reversible factors and implant a pacemaker if none are present.[71] It should be noted that implantation of a pacemaker is a well-accepted indication to allow for the continuation of aggressive antihypertensive medical therapy in patients with symptomatic bradycardia and difficult to control resistant HTN.

## Sleep Apnea

When evaluating a patients with HTN, consider an assessment for sleep apnea as 30% of patients with HTN have sleep apnea.[89] If unrecognized, sleep apnea can result in insufficient BP control and eventually dysrhythmias[90] due to transient periods of hypoxia and autonomic imbalance.[59] Up to 50% of patients with sleep apnea can experience nocturnal dysrhythmias, including sinus arrest, AV block, PVCs, NSVT, and atrial fibrillation. In addition, patients with sleep apnea are at 2.6 times greater risk of SCD.[91] Fortunately, proper treatment with positive airway pressure therapy in patients with obstructive sleep apnea can resolve nocturnal bradydysrhythmias if function is normal during awake periods[92] and reduce dysrhythmic events by 87%.[93] However, positive airway pressure therapy has variable and moderate impact on HTN,[59] so additional therapy is likely needed for optimal BP control.

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# Review Article

# Hypertension in End-Stage Renal Disease

Sonali Gupta, Scott E. Liebman

Department of Medicine, Division of Nephrology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

## Abstract

Hypertension is one of the leading causes of End Stage Renal Disease (ESRD) worldwide. The diagnosis and true prevalence estimates remain variable and challenging due the lack of a standardized definition. Most of the recommendations are based on expert opinions rather than high quality data. Ambulatory blood pressure measurement (ABPM) is the preferred method of diagnosing hypertension in this population but may not be readily available. Multiple factors are involved in the pathogenesis of hypertension ESRD including volume overload and impaired sodium balance, activation of the sympathetic nervous system and activation of the renin angiotensin aldosterone system. Management of hypertension in dialysis patients involves adjustment to dialysis prescription with meticulous attention to salt and water balance and dry weight. Pharmacological therapy is subsequently added if the blood pressure remains uncontrolled. There is no evidence supporting the use of one agent over another and the decision is generally individualized and made on the basis of any accompanying comorbidities. This review focuses on the current state of diagnosis and treatment of hypertension in ESRD patients.

**Key words:** Blood pressure, dialysis, end stage renal disease, hypertension

## Introduction

Hypertension is both a leading etiology of end-stage renal disease (ESRD) and a well-recognized cardiovascular risk factor in ESRD patients on dialysis. Despite this, hypertension remains highly prevalent and is often inadequately controlled in this population.[1,2] The prevalence estimates of hypertension in ESRD are quite variable, due to the lack of a standard definition for diagnosis as well as the setting and technique of blood pressure (BP) measurement. Hypertension and chronic kidney disease (CKD) are indeed closely interrelated clinical conditions such that sustained uncontrolled hypertension can cause worsening of renal function and vice versa. Here, we will consider the diagnosis and treatment of hypertension in ESRD patients on renal replacement therapy including both non-pharmacologic and pharmacologic approaches.

## Diagnosis of hypertension in ESRD

The diagnosis of hypertension in ESRD patients on dialysis is challenging due to the absence of an accepted definition and different methods of BP measurement. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest targeting a pre-dialysis BP of <140/90 mmHg and a post-dialysis BP of <130/80 mmHg.[3] However, this recommendation is expert opinion and not based on high-quality evidence. Improper measurement techniques may result in significantly higher BP readings both pre- and post-dialysis.[4] BP is highly dependent on extracellular fluid volume in hemodialysis (HD) patients in particular, and BP measurements can vary widely during and between HD treatments based on rapid changes in volume status.[5,6] As a result, before and after dialysis BP measurements might not be the best values on which to base a diagnosis of hypertension.

In one meta-analysis, Agarwal *et al.* showed that both pre- and post-dialysis BP readings have poor diagnostic accuracy and correlate poorly with mean interdialytic BP as determined through 44 h ambulatory BP monitoring (ABPM).[7] ABPM can also identify nocturnal non-dippers, a subgroup with a higher cardiovascular morbidity and mortality.[8] Although ABPM may

be the preferred method for the diagnosis of hypertension in HD patients, it is expensive, impractical, and may not be available to all patients.

Standardizing the technique of BP measurement may lead to more accurate BP readings in hemodialysis patients both pre- and post-dialysis.[4] Adding the average of intradialytic blood pressures to those obtained before and after treatment can improve reproducibility and accuracy compared with using either pre- or post-dialysis readings alone.[9] If ABPM is not feasible or available, home BP measurements may be a reasonable compromise. Home BP readings correlate better with 44 h ABPM compared with either pre- or post-dialysis values, with home BP readings ≥150 mmHg being the best predictor in diagnosing systolic hypertension in hemodialysis patients.[10] In addition, home readings may help recognize patients with masked and white coat hypertension-diagnoses which would be missed if one relied only on in-center BPs.[11]

Both ABPM and home measurements are especially useful in patients with large swings in dialysis unit BP measurements and can help to guide management. In general, it is suggested that home measurements should be performed for a week with two readings in the morning before medications and in the evening pre-dinner, although this has not been validated in the ESRD population.[12]

### Prevalence and control of hypertension in ESRD

The prevalence of hypertension in ESRD is difficult to define because of different definitions (i.e., at what level of BP is hypertension determined) and the fluctuation of BP with respect to timing of dialysis due to volume shifts and removal during the procedure. In a study involving 2535 adult HD patients, hypertension was reported in 86% when defined as use of antihypertensive medications or pre-dialysis average systolic and diastolic BP (SBP and DBP) of >150 mmHg and >85 mmHg, respectively.[13] Among these subjects, BP was adequately controlled in only 30%, untreated in 12%, and inadequately treated in the remaining 58%. A 2011 study by Agarwal examined BP in 369 HD patients using 44 h interdialytic ABPM and found that 82% of patients were hypertensive using an average ambulatory SBP ≥135 mmHg or a DBP ≥85 mmHg, or the use of antihypertensive medications as the definition for hypertension.[14] Despite 88% of these subjects being treated pharmacologically, only 38% of patients had controlled BPs. In this cohort of patients, higher use of hypertension medication and being volume expanded were associated with uncontrolled hypertension.[14] The relationship between hypervolemia and hypertension is strengthened by the finding that end expiration inferior vena cava diameter was independently associated with uncontrolled hypertension.[14]

With respect to patients on peritoneal dialysis (PD), in a cross-sectional analysis of 504 Italian PD patients, 88% had hypertension when defined as SBP > 140 mmHg or DBP > 90 mmHg. Of those who were hypertensive, 81.5% were on antihypertensive therapy.[15]

Comparisons between peritoneal and HD patients are rare and limited to small studies. Rodby *et al.* compared 44 h ABPM among 33 HD and 27 PD patients and reported similar diurnal patterns in both groups.[16] HD patients had significantly higher average systolic BPs and loads (the percentage of systolic BPs > 140 mmHg) compared with those on PD.[16] In a similar study, Tonbul *et al.* compared the results of 44 h ABPM between 22 HD and 24 PD patients and found similar mean systolic and diastolic BPs. HD patients had significantly higher nighttime BPs on the off dialysis day and significantly lower daytime BPs on their dialysis day.[17]

### BP targets

As noted earlier, the KDOQI guidelines of 2005 offered an opinion-based recommendation of a pre-dialysis BP of <140/90 mmHg and post-dialysis target of <130/80 mmHg.[3] The 2015 KDOQI Clinical Practice Guideline for HD Adequacy offers no further guidance, stating "the current paucity of clinical trial data does not allow defining the target pre-dialysis, post-dialysis, or ambulatory BP for HD patients."[18]

In the absence of clinical trial data, observational studies can provide some guidance. The direct relationship between higher BPs and mortality seen in the non-dialysis population is generally absent in the HD population where there appears to be a reverse J- or U-shaped relationship between pre-dialysis BP and death.[19,20] One study found a higher risk of morality with a pre-HD SBP below 140 mmHg.[19] The other showed the lowest risk of mortality with a pre-HD SBP between 130 and 159 mmHg.[20] It is speculated that the increased mortality risk associated with lower pre-HD SBP may be the results of unmeasured confounding with low BPs being a marker of severe cardiovascular disease.[21]

Several studies provide evidence that home BP readings correlate more strongly with mortality and cardiovascular morbidity than do measurements at the dialysis unit. Alborzi *et al.* studied 150 HD patients who had self BP measurements at home, 44 h ABPM during the interdialytic interval, and BP measurements before and after dialysis. Over a median 24 months of follow-up, higher BPs at home and through ABPM measurements predicted all-cause mortality, whereas in-center measurements did not.[22] In a separate analysis, Agarwal also showed that home systolic BPs and ABPM systolic BPs predicted mortality after a median 29-month follow-up period.[23] The lowest mortality was seen for systolic BPs of 120–130 mmHg for values obtained at home and 110–120 mmHg for ABPM values.[23] Increasing quartiles of BP predicted excess mortality for both home measurements and ABPM values.[23]

Although individual trials have not been powered to suggest a BP target, several meta-analyses may provide some information. Agarwal and Sinha performed a meta-analysis of five studies examining different BP medications and found that in 1202 dialysis patients, pharmacologic treatment of BP led to a 38% risk reduction of cardiovascular events compared to those who received placebo.[24] Mortality in this study did

not differ between groups. A separate meta-analysis done of eight trials encompassing 1679 patients by Heerspink *et al.* demonstrated 29% decrease in cardiovascular events, 29% decrease cardiovascular mortality, and 20% decrease in all-cause mortality.[25] Unfortunately, the included trials did not test specific BP targets so the meta-analyses are unable to offer one.

### Non-pharmacological options to treat hypertension in ESRD patients

Volume overload and sodium retention play a central role in hypertension in ESRD patients on dialysis. In healthy individuals, sodium balance is exquisitely regulated, principally through renal sodium loss. In ESRD patients, this natriuresis is typically compromised, and renal replacement therapy is often required for adequate removal of salt and water. Increased dietary sodium in HD patients leads to increased interdialytic weight gain and extracellular volume expansion and is independently associated with higher pre-HD BP and greater mortality.[26] Restoring balance of sodium and volume status is paramount in hypertensive dialysis patients. KDIGO guidelines stress the importance of sodium restriction and recommend salt restriction to <5–6 g/day.[27] In conjunction with reducing salt intake, achieving an appropriate dry weight is also important. A patient's dry weight is defined as the post-dialysis body weight at which extracellular volume (ECV) is in the normal range.[27] Since ECV is difficult to measure, this definition, while accurate, is not of great utility clinically. Nonetheless, based on available evidence, nephrologists should attempt to reduce the dry weight in ESRD patients with high BP. The dry weight reduction in hypertensive HD patients (DRIP) trial reported that a decrease in dry weight by 1 kg at 8 weeks led to a reduction in systolic BP of 6.6 mmHg and diastolic BP of 3.3 mmHg.[6] As most patients in this trial were already being treated for hypertension, this shows that dry weight reduction may work synergistically with medications. While lowering dry weights, practitioners need to keep in mind that intensifying ultrafiltration without increasing dialysis time or frequency may result in intradialytic hypotension, arteriovenous fistula clotting, and cardiovascular morbidity and mortality.[28] It is recommended to limit ultrafiltration rates to <12.4 mL/kg/h as higher rates are associated with increased mortality.[29]

Increasing HD frequency may also help with hypertension management. The Frequent HD Network Trial compared an in-center frequent intensive dialysis regimen to a conventional regimen (3 times a week) and reported improved control of hypertension, although study participants in the frequent HD arm were more likely to require vascular access interventions.[30] Similarly, a randomized crossover trial showed that subjects who underwent short daily HD treatments versus conventional HD required fewer BP medications to maintain a similar BP.[31] Other non-pharmacological interventions include adjusting dialysate sodium and avoiding sodium-containing or sodium exchanging medications.

With respect to PD patients, dietary sodium restriction is also important for the management of volume status and BP. Gunal

*et al.* reported a decrease in systolic BP from 158 to 120 mmHg in hypertensive PD patients by strict attention to a low salt diet and more aggressive ultrafiltration when indicated, without pharmacologic intervention.[32] The International Society for Peritoneal Dialysis has recently designated volume management and BP control as a key aspect of high-quality PD care.[33]

The use of low-sodium PD fluid may also enhance sodium removal and help decrease BP in PD patients. One prospective, non-randomized study compared a low-sodium peritoneal dialysis solution with a conventional solution by substituting one 3–5 h exchange/day for 2 months. The osmolality was kept the same in both groups by increasing glucose concentration in subjects using lower sodium fluid. The use of low-sodium dialysate was associated with improved diffusive peritoneal sodium removal and significant reduction in nighttime SBP.[34] Low-sodium dialysate, however, is not available commercially.

### Pharmacologic management of hypertension in ESRD patients

Antihypertensive regimens in hypertensive ESRD patients should be tailored to individual patients taking in account efficacy, side effects, dialyzability of the medication, pharmacokinetics, and cardioprotective properties of BP-lowering medications along with any associated comorbidities of the patient. All antihypertensive drug classes can be used in this population with the exception of diuretics in oligoanuric patients. Diuretics may help to limit weight gain between dialysis sessions and volume overload in HD patients with preserved residual kidney function[35] and are commonly used in PD patients as adjunct to volume removal by ultrafiltration.[36]

Another consideration is the pattern of BP during the inter- and intradialytic period. Short-acting antihypertensive medications should be avoided just before dialysis sessions, especially in patients prone to intradialytic hypotension. Patients with sustained hypertension during the interdialytic period would benefit by the use of long-acting agents. Much of the time, hypertension in this population is both unpredictable and difficult to control and may require multiple agents with different mechanisms of action. One strategy suggested to reduce pill burden is to administer antihypertensive agents thrice weekly with HD sessions. The hypertension in HD patients treated with atenolol or lisinopril (HDPAL) trial supported this notion and resulted in better interdialytic BP control with thrice weekly dosing.[37] Another strategy in non-dippers includes switching one of the antihypertensive agents to bedtime dosing.[38]

Without randomized control trials comparing the effects of different antihypertensive agents on end-organ damage in ESRD patients, results from studies done in patients without ESRD have been extrapolated to patients on dialysis. The use of beta-blockers is preferred in patients with previous cardiovascular disease based on their cardioprotective properties including improvement in arterial stiffness and improvement in left ventricular hypertrophy.[39] Excessive activation of the sympathetic nervous system in dialysis patients makes them prone to arrhythmias and sudden cardiac death

and beta-blockers may prove to be an attractive antihypertensive agent in this population. Beta-blockers were associated with a lower risk of sudden death in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study, after adjustment for comorbidities.[40] The HDPAL trial also showed superiority of atenolol over lisinopril for the prevention of serious cardiovascular events.[37] Inrig *et al.* demonstrated that carvedilol led to better intradialytic and interdialytic BP, improvement in endothelial dysfunction and reduced incidence of intradialytic hypertension.[41] It is important to consider renal clearance and dialyzability of beta-blockers in this population subset as a recent study suggested that highly dialyzable beta-blockers do not provide a survival benefit or intradialytic protection against arrhythmias.[42]

Trying to extrapolate cardiovascular benefits of renin–angiotensin system (RAS) blockers in dialysis patients from results obtained in general population can be challenging as randomized trials in dialysis patients with hypertension show contradictory results. In the Fosinopril in Dialysis trial, fosinopril led to a significant reduction of pre-dialysis BP; however, no difference was observed in the occurrence of cardiovascular events (fatal or non-fatal) between the fosinopril and placebo arms.[43] In the Olmesartan Clinical Trial in Okinawa patients under dialysis study, the incidence of all-cause mortality, non-fatal stroke, MI, and coronary revascularization was similar in both intervention and control groups.[44] Small randomized studies and a meta-analysis, however, show a beneficial cardioprotective effect of ACEIs and ARBs,[45,46] although this is not consistent in all studies, and it is difficult to say if the cardioprotective effect was mediated by the ACE-I/ARB or by the improved BP control. In PD patients, ACE-I/ARBs may be among the preferred agents due to small clinical trials showing protection of residual kidney function.[47,48]

Mineralocorticoid receptor antagonists (MRAs) are also used for cardioprotective effects, although the initial concern was the risk of life-threatening hyperkalemia in this population subset. The safety of eplerenone was recently studied in 146 HD patients who were followed for 13 weeks. It was found that eplerenone did increase the risk of serious hyperkalemia, however, there was no associated need for discontinuation of the drug.[49] In the Dialysis Outcomes Heart Failure Aldactone Study, 309 HD patients were randomized to receive either spironolactone (25 mg/d) or no add-on therapy and were followed for 3 years. The spironolactone group had significantly lower cardiovascular morbidity and mortality and a low (1.9%) incidence of serious hyperkalemia requiring stopping of the medication.[50] In another randomized trial of 253 non-heart failure, ESRD patients on chronic dialysis (HD and PD) by Lin *et al.*, low-dose spironolactone as add-on therapy was found to reduce the incidence of the composite primary outcome of cardio or cerebrovascular death, observed cardiac arrest, and sudden death by 58%.[51] A recent meta-analysis supports the use of MRAs in low dose in ESRD patients.[52] Potassium levels should be monitored closely if MRAs are used.

Calcium channel blockers (CCBs) may also be used in managing hypertension in dialysis patients. CCBs are often used as combination therapy in dialysis patients and have been shown to work effectively to lower BP, even in the volume overload state.[53] The pharmacokinetics of CCBs is not altered with dialysis and they are generally non-dialyzable.[54]

Other drug classes that can be used as add-on therapy include centrally acting α-agonists, direct acting vasodilators, and α-adrenergic blockers. The centrally acting α-agonist clonidine reduces autonomic activation and is effective in reducing BP in this subset of patients, however, it may lead to significant side effects, such as dizziness, dry mouth, and fatigue. Direct vasodilators such as minoxidil or hydralazine are generally used for resistant hypertension. They usually result in reflex tachycardia, which can be controlled by concomitant use of beta-blockers.[54] Practitioners should be aware that hydralazine may lead to a lupus like syndrome. Minoxidil in rare cases may precipitate a pericardial effusion. Alpha-adrenergic blockers use may be associated with orthostatic hypotension and worsening of intradialytic hypotension.[54]

## Conclusion

There is much uncertainty surrounding hypertension in ESRD patients and many questions remain. Clinicians should be aware of the pitfalls of using peridialysis BP measurements for treatment decisions in HD patients. Home BP monitoring and, if available, ambulatory BP monitoring are better choices in this population given stronger associations with clinical outcomes and mortality and should be employed if possible. The target BP in dialysis patients has not been established. Studies using peridialysis BP show associations between lower BPs and mortality, whereas smaller studies using home or ABPM BPs show that lower BPs are protective. Non-pharmacologic approaches, particularly restoration of sodium and water balance, are of paramount importance. With respect to pharmacologic therapy, evidence to support the use of one agent over another is lacking and the choice of which medication to use should be individualized for each patient. Beta-blockers may be a reasonable first choice given the potential cardio-protection that they offer. In peritoneal dialysis patients, ACE-I/ARBs may be preferentially used to preserve residual kidney function.

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## Review Article

# Obtaining Accurate In-Office Blood Pressure Readings

Brian Ayers[1], Ariana Goodman[1], Sabu Thomas[2]

[1]Department of Surgery, Division of Cardiac Surgery, University of Rochester Medical Center, Rochester, New York, United States, [2]Department of Medicine, Division of Cardiology, Rochester, New York, United States

### Abstract

The ability to consistently obtain accurate blood pressure measurements in the office setting has significant implications for the categorization, risk stratification, and treatment of hypertension at both a societal and individual level. However, obtaining consistently accurate assessments of blood pressure in the outpatient setting is a difficult task. Currently, there is a significant controversy in regard to the optimal method for measuring outpatient blood pressure given the multitude of devices, techniques, and practice guidelines available. In this review, we discuss the pros and cons for different measurement techniques, the most common sources of clinical error, and current guideline recommendations for the optimal timing and method for reliable outpatient blood pressure assessment.

**Key words:** Diagnostic techniques and procedures, blood pressure determination, blood pressure monitoring, ambulatory

## Introduction

Nearly half of adults currently living in the United States have hypertension.[1] Untreated, long-standing hypertension can lead to significant detrimental health effects such as chronic kidney disease, atherosclerosis, heart failure, stroke, retinopathy, and more.[2,3] The American College of Cardiology/American Heart Association 2017 Hypertension guidelines recommend a blood pressure of 140/90 as the cutoff for initiation of hypertension treatment.[4] The ability to consistently obtain accurate BP measurements has significant implications for the categorization, risk stratification, and treatment of hypertension at both a societal and individual level. The gold standard for measuring a patient's true, intraluminal blood pressure is an intra-arterial device. However, this is not practical for an outpatient clinical setting given the invasive nature, practical considerations, and associated risks. Therefore, there are a number of less invasive techniques that have been developed to estimate a BP measurement.

The use of non-invasive techniques is associated with many potential pitfalls that could make BP estimates exceedingly inaccurate, such as the clinical technique, patient setting, or device itself. In this brief review, we describe common sources of error and proper technique for taking non-invasive blood pressure readings, the different types of devices used to estimate BP, and the most recent recommendations highlighting the utility of automated office BP (AOBP) readings.

## Clinical Importance and Sources for Error

There is much controversy in regard to the optimal method for obtaining outpatient BP measurements given the multitude of devices, different techniques, and large discrepancy in adherence to recommended guidelines. Sources of error include patient considerations (recent food intake and movement during measurement), device-related factors (inaccurate calibration), or procedure factors (talking during procedure, inappropriate positioning, or cuff sizing).[5] Studies have found that incorrect technique is common and leads to large discrepancies in single BP readings, thus limiting the clinical utility of a single measurement in the diagnosis and treatment of a hypertensive patient.[5,6]

The difficulty in obtaining accurate and precise BP measurements is demonstrated in studies that have shown the variability in BP measurements acquired in the same setting.

Handler *et al.* analyzed U.S. national data from 22,641 adults and found that 35% of patients diagnosed with hypertension on a single BP measurement during an initial office visit actually had an systolic blood pressure (SBP) less than the hypertensive threshold when averaged over three visits.[7] Similarly, Powers *et al.* found that at least five BP measurements were required to be 80% certain that the true SBP was below the HTN cutoff of 140 mmHg in men taking antihypertensive medications.[8] The 2017 American College of Cardiology/ American Heart Association joint task force on clinical practice guidelines recommend at least two separate measurements per clinic visit given these large discrepancies in BP estimates in the same sitting.[4]

## Proper Cuff Size

Using a blood pressure cuff that is appropriately sized for the patient is essential to obtain an accurate BP estimate. Appropriate cuff size should be determined based on the patient's arm circumference [Table 1].[9] Using a blood pressure cuff that is too small for the respective patient is the most common source of error during BP measurements.[10] Undersized cuffs are not able to appropriately transmit the full pressure generated in the cuff's bladder to the patient's brachial artery. Therefore, the cuff's pressure is higher than the true luminal pressure, leading to a potential significant overestimation of the true BP.

## Auscultation Technique

In terms of how to obtain non-invasive BP estimates, the auscultation method is the traditional technique that has been one of the most commonly used methods since its initial introduction by Dr. Korotkoff in 1905.[11,12] This technique relies on an observer listening for the appearance and disappearance of "Korotkoff sounds" while slowly releasing compression of

**Table 1:** Key points to ensure proper technique during blood pressure measurement[6]

| Key points |
| --- |
| Appropriate environment |
|   Quiet setting without distractions |
|   Patient should refrain from talking |
| Appropriate cuff size |
|   Too small will overestimate, too large WILL underestimate |
|   Cuff length should be 75–100% of patient's arm circumference |
|   Cuff width should be 37–50% of patient's arm circumference |
|   Suggested cuff sizes based on arm circumference:[9] |
|     "Small adult:" 22–36 cm |
|     "Adult:" 27–34 cm |
|     "Large adult:" 35–44 cm |
|     "Adult thigh:" 45–52 cm |
| Appropriate position |
|   Seated is preferred (supine is also acceptable) |
|   BP cuff should be at the level of the right atrium |

BP: Blood pressure

the brachial artery and watching pressure readings through a sphygmomanometer.

The scientific statement from the American Heart Association[6] outlines the recommended technique for measuring blood pressures during outpatient office visits. The key points to patient setup to ensure an accurate BP estimate include a quiet environment, an appropriately sized cuff for the patient, and the correct placement of the BP cuff at the level of the patient's right atrium [Table 1]. The brachial artery should be palpated in the antecubital fossa and the center of the cuff bladder (typically marked by the manufacturer) should be placed over this arterial pulsation on the patient's bare upper arm. The lower end of the cuff should be 2–3 cm above the antecubital fossa to allow for sufficient room for the placement of the stethoscope. The bell of the stethoscope should not be in contact with the BP cuff to avoid artificial noise.[13] Inflate the cuff at least 30 mmHg above the pressure at which the radial pulse disappears and then slowly releases pressure at a rate of 2 mmHg per second (or per heartbeat if patient has very slow heart rate). Listen for the five key phases of Korotkoff sounds: (1) Sudden appearance of sharp tapping sounds (systolic blood pressure), (2) swishing, (3) regular and louder sounds, (4) abrupt muffling of sounds, and (5) loss of sounds (diastolic blood pressure).

Traditional sphygmomanometers rely on a column of mercury to measure pressure, providing simplicity in their design. However, many states are banning the use of such devices due to environmental concerns in regard to the toxicity of mercury.[14] Aneroid designs eliminate the use of mercury by utilizing metal bellows that respond to variations in pressure within the system to rotate gears that turn a calibrated dial. However, these fine-tuned systems are susceptible to error if handled harshly, and it is recommended that they be calibrated every 2–4 weeks for handheld devices or 6 months for wall-mounted units.[15] More recently, there are hybrid designs that are similar to the traditional sphygmomanometer mechanism but replace the mercury column with an electronic pressure gauge. Studies have demonstrated these hybrid models provide a reliable alternative, but the frequency with which they should be calibrated remains unknown.[16,17]

## Oscillometric Technique

An alternative to the auscultation method is the use of an oscillometer. These devices automate the BP measurement by sensing the intraluminal waveforms and evaluating the amplitude of BP oscillations on the arterial wall to calculate estimates for systolic and diastolic BP.[18] These devices all use proprietary algorithms unique to each manufacturer, which can be updated at any time with no obligations to report such changes. Therefore, it is highly recommended to only use a device that has been independently validated.[6] Oscillometric devices may be a cost-effective alternative to auscultation by obviating the costs associated with training staff in manual blood pressure measurement.[14]

## Automated Office Blood Pressure (AOBP) Readings

A potential advantage of utilizing an oscillometer rather than the auscultatory technique is that the devices allow for fully automated BP measurements without the need for an observer to be present. There are numerous studies that have validated the use of automated BP devices with either an observer present or patient alone and in multiple locations throughout an outpatient office.[19-23] AOBP also decreases the reliance on an observer's skills, negates the white coat effect if the patients are left completed unattended,[19] and reduces calibration issues with auscultatory sphygmomanometers.

There is a plethora of studies that have demonstrated AOBP measurements to be more closely correlated to ambulatory BP estimations than auscultatory office BP measurements.[20,24-27] These include the large conventional versus automated measurement of BP in the office (CAMBO) study, which demonstrated a smaller difference between awake ambulatory BP measurements and AOBP estimates than with auscultatory measurements.[27] Moreover, AOBP has also been shown to be closely associated with subclinical potential cardiovascular disease assessed by intima-media thickness of the carotid arteries[28] and LV mass index.[29]

Given this net positive data in favor of unattended AOBP, the Canadian guidelines adopted the AOBP technique as the preferred method for assessing BP in an outpatient setting.[30] Since the recommendation, there is early evidence from a Canadian national survey that AOBP has been widely adopted in primary care offices in Canada with minimal increases to staff time or effort.[31] The potential drawback of AOBP is the reliance on "black box" devices that utilize proprietary algorithms to estimate BP that can be changed without regulation. Therefore, it is important to stress again that it is recommended to only use devices that have been validated against alternative BP estimation techniques in independent testing.[6]

## Alternatives to Measure BP

Despite differences between manual and automated blood pressure methods, both use an inflatable blood pressure cuff to measure pressure. Pain and discomfort caused by the repeated cuff inflation can cause distress for the patient, which can further influence the blood pressure measurement obtained. Alternatively, innovative cuff-less methods have been developed to prevent these inaccuracies. "Checkme," for example, is a cuff-less device that works by measuring the time interval of a pressure wave between two pulse points, which has been found to be indirectly correlated with blood pressure.[32] The handheld device includes other vital measurements as well and allows patients to use it independently in any setting. Further research is needed for these experimental designs.

As new devices and methods become available, regulation and guidelines need to be adjusted to ensure proper calibration and usage. The European Society of Hypertension International Protocol (ESH-IP) 2010 revision provides a methodology to standardize the technical requirements for the testing of any new proposed device.[33] This includes the comparison of the device measurements to observed manual blood pressure measurements using the auscultatory method with a standardized technique that includes multiple repeated measurements, to ensure the accuracy and precision of any new device. The Association for the Advancement of Medical Instrumentation also created standardized protocols for new device testing, including stipulations for non-traditional devices that may use sense or display pulsations, flow, or sound measurements to estimate blood pressure.[34]

## Conclusion

Blood pressure measurements have a significant effect on patients' lives, as a diagnose of hypertension is often accompanied by suggestions for lifestyle changes and prescriptions for life-long medications. The importance of accurate and reliable blood pressure measurements in the clinical setting is imperative in providing comprehensive, patient-centered care. Obtaining consistently accurate assessments of blood pressure in the outpatient setting is a difficult task. There are a variety of factors that affect the accuracy of a patient's baseline blood pressure, including setting, time of day, user error, and device calibration. All of these factors need to be considered when forming a diagnosis of hypertension. Established guidelines for the correct technique should be followed when taking a manual blood pressure measurement. AOBP should be considered as a promising alternative that allows for multiple automated readings, negates any potential white coat effect, and can be implemented in a clinical setting without significant disruption to current workflow.

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# Review Article

# Hypertension in Pregnancy

Erin Armenia, Michael Vornovitsky

Department of Internal Medicine, Division of Cardiology, University of Rochester Medical Center, Rochester, New York, United States

## Abstract

Hypertension in pregnancy is an important cause of maternal morbidity and mortality, and also has a substantial effect on fetal outcomes. In addition, it portends a higher risk of cardiovascular disease for women later in their lives. Thus, it is critical that physicians identify hypertension during the gestational period, and treat it appropriately. First-line agents for treatment typically include beta-blockers and calcium-channel blockers.

**Key words:** Hypertension, pregnancy, women's health

Identification of hypertension in pregnancy is important not only for fetal outcomes but hypertensive disease in pregnancy also portends a higher risk for future cardiovascular events in women.[1] The prevalence of gestational hypertension (hypertension that manifests for the 1st time during pregnancy) is 6%;[2] additionally, up to 3% of childbearing women have chronic hypertension (the prevalence is increasing as obesity rates go up).[3] Hypertension increases the risk of complications during pregnancy, including preeclampsia, fetal growth restriction, and abruptio placentae.[3] In addition, it puts expectant mothers at risk for heart failure (both with reduced and preserved ejection fraction) and right ventricular dysfunction; later in life, women are also at substantially increased risk of coronary artery disease and heart failure.[4] In fact, the treatment of hypertension has been shown to reduce maternal morbidity, but it has not been shown to substantially impact fetal outcomes.[3]

In a normal pregnancy, systemic blood pressure drops due to systemic vasodilation and decreased peripheral vascular resistance. As a result, many women with mild chronic hypertension can stop taking medication during pregnancy. Thus far, no evidence has been found that treatment of mild-to-moderate hypertension improves fetal or maternal outcomes; therefore, guidelines for treatment goals remain controversial.[4] According to the ACC/AHA guidelines, it is reasonable to treat Stage 1 hypertension to prevent future cardiovascular events.

Two of the classic first-line agents for hypertensive control have relative contraindications in pregnancy. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can cause skull hypoplasia in the fetus, as well as anuria and renal failure (particularly in the first trimester).[5] Thiazides can cause neonatal jaundice, volume depletion, or thrombocytopenia (although one study showed no significant difference in adverse pregnancy outcomes with diuretics).[3,6] Calcium channel blockers may be used to treat hypertension in pregnancy, however, and are often considered first-line agents.[4]

The most well-studied agents for hypertension in pregnancy are beta-blockers and methyldopa. Beta-blockers, particularly labetalol, are well-studied and have been shown to be safe in pregnancy. Labetalol also has an enhanced effect on blood pressure because of its concomitant alpha-blockade. In some studies, atenolol has been shown to have an association with fetal growth restriction: Although data are limited, many practitioners avoid using atenolol as a result.[3]

Methyldopa, as mentioned, is one of the drugs that have been used the longest in pregnant women; it acts on a central alpha receptor, decreasing sympathetic tone to the heart, kidneys, and peripheral vasculature.[7] Methyldopa has an extensive safety record in pregnancy; however, its effect on blood pressure is only modest, and many women require a second agent for improved control. Thus, although it is safe, it is no longer frequently used as a first-line agent.

**Address for correspondence:**
Michael Vornovitsky, UR-Cardiology, 600 Red Creek Drive, Suite 100, Rochester - 14623, New York, United States.
E-mail: Michael_Vornovitsky@urmc.rochester.edu

Nifedipine, although less well-studied than methyldopa, has been shown to be a safe an effective agent for treating hypertension in the pregnant population. Nifedipine is a dihydropyridine calcium channel blocker and exerts its effects on the peripheral vasculature. Other calcium channel blockers, such as amlodipine (most commonly used in the treatment of essential hypertension in a non-pregnant population), have limited safety data.[5,8]

Even with proper treatment, women can develop complications from hypertension in pregnancy. Preeclampsia, defined broadly as hypertension during pregnancy with proteinuria or end-organ dysfunction, occurs in 4–5% of pregnancies.[9] Preeclampsia may develop in a woman with pre-existing gestational hypertension, or it may occur de novo. If maternal seizures occur in the setting of preeclampsia, the condition is termed *eclampsia*. The definitive treatment is delivery, but patients with mild disease can be managed expectantly. Blood pressure management is the same as for gestational and chronic hypertension in pregnancy. The pathophysiology of preeclampsia is incompletely understood; however, it has been thought to relate to increased platelet turnover and thromboxane levels.[10] Therefore, low-dose aspirin has been proposed as a preventive therapy. A 2019 meta-analysis demonstrated a modest reduction in rates of preeclampsia and fetal growth restriction in selected populations of women, with a favorable safety profile.[11]

Hypertension in pregnancy remains a significant cause of both maternal and fetal morbidity and mortality. Although the treatment of hypertension may prevent maternal morbidity, positive effects on the fetus are less clear, as described. While novel approaches for the treatment and prevention of preeclampsia are needed, focusing on lifestyle changes to prevent the development of hypertension in young women may reduce the risks for subsequent pregnancies. Short, focused interventions directed at lifestyle counseling at every clinic visit may be helpful to prevent future maternal morbidity.

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# *R*eview *A*rticle

# A Review Article of Hypertension and Cognitive Decline

Zaid Al Jebaje[1], Geoffrey Williams[2]

[1]Fellow of Cardiovascular Medicine, Department of Internal Medicine, Division of Cardiology, University of Rochester Medical Center, Rochester, New York, United States, [2]Professor of Medicine, Psychiatry and Public Health Sciences, Center for Community Health and Prevention, University of Rochester Medical Center, Rochester, New York, United States

## Abstract

**Objectives:** This article will discuss three questions. 1. Is there a link between hypertension and cognitive impairment? 2. Can treatment of hypertension prevent or slow down cognitive decline? 3. Which group of hypertensive patients are at higher risk for developing dementia? The relation between hypertension and cognitive function has been the subject of discussion and research for many years; recently, there has been a trend toward lower blood pressure goals and earlier intervention, this was implemented in the Eighth Joint National Committee (JNC 8) guidelines and adopted by the American Heart Association in 2017 as well as the European Society of Cardiology in 2018, these changes reflect the results of major clinical trials. Although the available data are promising in regard to better cardiovascular and mortality outcomes with lower blood pressure targets, their effect on cognitive decline is still uncertain. In this article, we review recent published literature studying the link between hypertension and cognitive impairment. We review the current understanding of the pathophysiology and identify the challenges facing the scientific community in ongoing and future studies. Identifying high-risk individuals as potential targets for aggressive monitoring and treatment is explored. We also review some of the suggested pharmacological and non-pharmacological intervention strategies to tackle this global epidemic.

**Key words:** Cognitive impairment, dementia, hypertension

## Introduction

Hypertension is a condition with high prevalence that is estimated to affect around eighty million individuals in the United States and one billion persons worldwide.[1] The prevalence of hypertension in India is 29.8%, and is estimated to be responsible for two thirds of stroke deaths and one fourth of coronary deaths.[2] According to the Alzheimer's Association, cognitive dysfunction affected more than 35 million people in 2010, and is projected to double every ten years with about two-thirds of these subjects living in places with limited healthcare resources.[3]

There is adequate evidence in the literature to support an association between high blood pressure and impairment in cognition that is beyond its relationship to frank stroke.[4,5]

Hypertension is thought to be a risk factor for both Alzheimer's dementia and vascular dementia, it is also linked to various degrees of cognitive dysfunction, a spectrum ranging from mild neurocognitive impairment to frank dementia (which is defined as major neurocognitive disorder).[6]

## Mechanism

High blood pressure has been linked to impairment of several aspects of cognitive functions such as decline in abstract thinking (executive dysfunction), delay in mental processing, and deficits in memory.[7]

Among the suggested pathophysiological changes in the brain and its vascular supply are blood vessel remodeling, defects in autonomic regulation, microhemorrhages, lesions of the substantia alba, silent infarcts, amyloid angiopathy, and cerebral atrophy, while this might explain the correlation between hypertension and ischemic strokes or vascular

dementia, this also holds true for other types of dementia, for example, the link between long-term uncontrolled high blood pressure and Alzheimer's dementia has been documented, with hypertension being associated with forming neurofibrillary tangles and senile plaques, the presence of which was observed in brains of hypertensives even when they did not hold a clinical identification of dementia.[8]

## Discussion

While the data may suggest that optimal control of blood pressure may help prevent or at least delay the process of cognitive downturn, especially in those at risk of such impairment, in reality, this question has not been answered fully yet, due to unavailability of randomized clinical trials clearly showing a benefit of such intervention.

In their statement in 2016, the American Heart Association endorsed that chronic hypertension is a well-recognized risk factor for both Alzheimer and vascular dementias. The AHA also deducted that there was lack of enough data to establish evidence-supported recommendations, as information from randomized clinical trials that controlling high blood pressure at any stage of life improves cognition is still inconclusive.[9]

Interestingly, there is well-documented evidence that hypertension earlier in life is associated with changes in cognitive functions that manifest both in mid and late life, but the relation between high BP in later stages of life and cognition is less clear, with evidence of both harmful and beneficial effects of treating high BP on cognition. In other words, the younger the hypertensive individual, the more likely they benefit from lifestyle and/or pharmacological intervention. This enhances the importance of early diagnosis and treatment and the role of preventative medicine in preserving cognitive functions.[10]

Perhaps, the most up-to-date larger scale data come from the SPRINT-MIND trial published in the Journal of American Medical Association, JAMA in 2019 which aimed to investigate whether intensive blood pressure control reduces the occurrence of dementia. The study concluded that intensive blood pressure control (defined as systolic blood pressure of <120 mmHg as opposed to conventional goal of <140 mmHg) did not significantly reduce the risk of probable dementia, but there was statistically significant evidence that it reduces the risk of mild cognitive impairment (MCI). This marks the 1st time an intervention has shown a reduction in MCI in a large group of people. This marks the first time an intervention has shown a reduction in MCI (mild cognitive impairment) in a large group of people. The ongoing SPRINT MIND 2.0 trial seeks to determine whether this intervention can also reduce the risk of progression to dementia.[11]

Another important study furthering our understanding of this complex subject comes from Spain, specifically analysis from the ISSYS cohort (Investigating Silent Strokes in Hypertensives: A Magnetic Resonance Imaging Study), published in Hypertension in January 2019. The study evaluated

incident lacunar infarcts, cerebral microbleeds, changes in the periventricular, and deep white matter hyperintensities (WMHs). The authors concluded that hypertensive patients with progression of periventricular WMH have higher odds of cognitive impairment, even in the early stages of cognitive decline.[12]

In addition to investigating the correlation between hypertension and cognitive decline, other studies have focused on intervention strategies, including lifestyle modification and pharmacological treatments, with some data supporting that adherence to the DASH diet or dietary approach to stop hypertension for long term is crucial to preserve cognitive functions at later stages of life,[13] while another study suggested addressing sleep apnea as an underlying factor for both hypertension and cognitive decline.[14] It is also worth mentioning that some research entertained the idea that certain antihypertensive drugs such as diuretics may have neuroprotective characteristics beyond their role in lowering blood pressure.[15]

## Conclusion

Recent publications and ongoing studies demonstrate efforts to identify at risk populations that are most likely to benefit from intensive treatment. However, the effect of treatment on cognitive function in larger population-based studies has yet to be explored. Challenges in these studies include keeping a standard definition of hypertension, standard method of measurement, controlling for other contributors to cognitive impairment (e.g. diabetes, lipids, alcohol abuse, sleep apnea, diet, physical activity, and tobacco use), as well as having a standard definition and methods of assessing cognitive impairment.

### Recommendations

The current studies suggest that younger hypertensive individuals may particularly benefit from lifestyle and/or pharmacological intervention. Until randomized clinical trials demonstrate that the treatment of hypertension results in less cognitive decline, it is recommended to use standard treatment measures for controlling hypertension and heart healthy lifestyles.

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INDIAN SOCIETY OF HYPERTENSION

# *R*eview *A*rticle

# Hypertension, Left Ventricular Hypertrophy, and Heart Failure

Jeffrey A. Corbett[1], Syed Yaseen Naqvi[2], Farhan A. Bajwa[2]

[1]Department of Medicine, University of Rochester Medical Center, Strong Memorial Hospital, Rochester, New York, United States, [2]Department of Medicine, Division of Cardiology, University of Rochester Medical Center, Strong Memorial Hospital, Rochester, New York, United States

## Abstract

Left ventricular hypertrophy (LVH) is a manifestation of arterial hypertension and is an independent risk factor for cardiovascular disease morbidity and mortality. Both concentric and eccentric LVH independently increase risk of sudden cardiac death, coronary artery disease, arrhythmias, as well as congestive heart failure (CHF). Hypertension precedes the diagnosis of heart failure in the majority of patients with newly diagnosed CHF and remains the most important cause of diastolic heart failure. Treatment aimed at reducing left ventricular (LV) mass improves outcomes in such patients. Treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibior, and aldosterone receptor blockers have been shown to significantly decrease LV mass. SGLT2 Inhibitors are emerging as a new class of medications that have been shown to improve cardiac outcomes likely through their effects on LV remodeling and diastolic function. In this review article we will focus on LVH and cardiovascular outcomes.

**Keywords:** Hypertension, Left Ventricular Hypertrophy, Heart Failure Preserved ejection fraction, Sodium Glucose Co-Transporter 2 Inhibitors

## Introduction

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular disease morbidity and mortality.[1] Both concentric and eccentric LVH independently increase risk of sudden cardiac death (SCD),[2] coronary artery disease (CAD), arrhythmias,[3] as well as heart failure.[4] Recent evidence shows up to 30% increased risk of cardiovascular events in patients with hypertensive target organ damage (TOD).[5] Hypertension-induced TOD encompasses both microvascular injury, namely, nephropathy or retinopathy, and macrovascular injury, namely, coronary or peripheral artery disease causing myocardial infarction or stroke. LVH is another manifestation of TOD from uncontrolled blood pressure and will remain the focus of this article.

Arterial hypertension leads to organ damage on much of the body, with LVH a well-known complication. In fact, LVH is the cardinal manifestation to increased hemodynamic afterload in hypertension.[6] Remodeling of the left ventricle (LV) occurs in response to chronic hemodynamic overload from hypertension. Recently, published data from over 6000 Framingham study patients showed that a one standard deviation increase in mean arterial pressure and central pulse pressure was associated with 37%–45% increased incidence of LVH.[5] Cuspidi *et al.* showed that up to 41% of hypertensive patients and 77% with hypertension and a prior history of diabetes mellitus or cardiovascular disease exhibit echocardiographic evidence of LVH.[7] Insulin resistance is in itself a mediator of LVH, with up to 70% of type two diabetics exhibiting increased LV mass.[8,9]

Increased aortic pulsatile load ultimately leads to increased LV wall stress and LVH.[10] Indeed, the maladaptive mechanisms involved in the developed of LVH are the first step toward overt cardiovascular disease such as congestive heart failure (CHF), ischemic heart disease, arrhythmias, and stroke.[2,11] LVH increases myocardial oxygen consumption while reducing coronary blood flow – predisposing the patient to angina pectoris, myocardial infarction, and sudden cardiac death. Untreated hypertension along with LVH leads to impaired diastolic filling due to LV stiffness.[10] Hypertension precedes the diagnosis of heart failure in up to 91% of patients with newly diagnosed CHF and remains the most important cause of diastolic heart failure.[12,13]

It has been shown that long-standing and untreated hypertension leads to heart failure. Pressure overload caused

by untreated hypertension leads to cardiac remodeling, which can manifest as LV diastolic dysfunction and concentric LVH. With sustained pressure overload, there is progressive diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) ensues. End-stage hypertensive disease presents with both pressure and volume overload and there is eccentric remodeling that leads to dilated cardiomyopathy and heart failure with reduced ejection fraction (HFrEF).[14]

## Regression of LVH and Outcomes

Regression of LVH has been shown to be an effective way to reduce cardiovascular events.[15] This finding has held true independent of blood pressure lowering.[15] Investigators in the HOPE trial showed that reduction of LVH with the ramparil versus placebo significantly lowered the incidence of cardiovascular death and myocardial infarction.[16] Investigators also found that hospitalizations for CHF and unstable angina as well as the risk for the development of CHF were significantly lowered.[16] Investigators in the LIFE trial showed a greater reduction of LVH with losartan at 1 year compared to patients treated with beta-blockers.[17] Reduction in LVH corresponded with a reduction in cardiovascular morbidity, mortality, new-onset atrial fibrillation, and sudden cardiac death.[18-20] More recently, it was shown that sacubitril/valsartan was superior to olmesartan in reduction of LV mass and mass index.[21] Consistent throughout these studies, it has been shown that a reduction in the left ventricular mass reduces cardiac events independent of differences in blood pressure lowering.[16,21] This lends credence to the idea that cardiac myocytes may be affected directly by an inhibitor of the renin angiotensin aldosterone system (RAAS).[22-24]

Despite the positive outcomes in trials showing that reduction in LVH leads to better outcomes, no therapy has been shown to improve mortality in HFpEF, the most common outcome in patients with hypertension and LVH.[25,26] The I-PRESERVE trial and CHARM-PRESERVED failed to show a reduction in death or hospitalization from cardiovascular causes with the use of irbesartan and candesartan, respectively.[25,27] In the I-PRESERVE trial, 30% of patients randomized to the irbesartan arm had LVH at baseline,[25] compared to ~50% of patients in the CHARM-PRESERVED trial.[27,28] Lund *et al.* failed to show a reduction in combined all-cause mortality and CHF hospitalization in patients treated with beta-blockers, of which 43% had cardiomegaly.[26] The TOPCAT trial failed to show that spironolactone significantly reduced death from cardiovascular causes or hospitalization for CHF in patients with HFpEF,[29] of which ~50% had LVH.[28,29]

Interestingly, new data are now available looking at outcomes for HFpEF based on phenotype.[30] From a pathophysiologic standpoint, HFpEF is likely a far more diverse syndrome than HFrEF.[31] Despite this broad heterogeneity, Shah *et al.* were able to show three specific, mutually exclusive, phenotypes of HFpEF.[32] Individuals in phenotype 1 were younger with

moderate diastolic dysfunction and relatively normal brain natriuretic peptide; phenotype 2 were obese, diabetic patients with high prevalence of obstructive sleep apnea and worse LV relaxation; and phenotype 3 were older patients with chronic kidney disease and significant LV remodeling.[32] Overall, individuals in phenotype 2 and 3 were significantly more likely to have diastolic dysfunction, elevated mean left atrial pressures and LVH than those in phenotype 1.[32] Outcomes in the trial were striking – with individuals in phenotypes 2 and 3 being 4–7 times more likely to have heart failure hospitalizations or death.[32]

Certainly, there is some amount of heterogeneity behind that pathophysiology of HFrEF as well. Yet, patients have proven to respond to a "one size fits all" approach. For HFpEF, it may well be necessary to separate patients into clinically relevant phenotypes to tailor a beneficial treatment. In fact, recently published data Cohen *et al.* show that patients in the TOPCAT study with more concentric LVH were more likely to respond to spironolactone and had an improved prognosis.[30]

### Effect of insulin resistance and SGLT2 inhibitors on LVH

In addition to traditional therapy involved angiotensin converting enzyme inhibitors (ACE-inhibitor), angiotensin receptor blockers (ARB), beta-blockers, and aldosterone receptor antagonists, a promising development in recent years has been the substantial evidence that sodium glucose transporter 2 inhibitors (SGLT2) inhibitors reduce LV mass and improve LV diastolic function and overall lower cardiovascular morbidity and mortality and hospitalizations for heart failure.[33-37] Data from the EMPA-REG Outcome Trial showed a significant reduction in LV mass and improvement in diastolic function at 6 months in empagliflozin versus placebo in patients with type 2 DM and coronary artery disease.[35,38] The authors also found that change in 24-hour ambulatory blood pressure did not associate with changes in LV mass, thus similar to inhibition of RAAS, suggesting that there are mechanisms other than blood pressure control to explain reduction in LV mass.[35] Pabel *et al.* showed that empagliflozin causes direct pleotropic effects on myocardium by improving LV stiffness, which, in turn, improves the diastolic LV function.[39] These effects were observed independent of diabetic conditions.[39] Early data from the ongoing DAPA-LVH trial show that dapagliflozin also has a significant reduction of the left ventricular mass.[33] Matsutani *et al.* showed that canagliflozin reduces LV mass and improves LV diastolic function.[40]

Several reasons have been postulated for why SGLT2 inhibitors have had such an impact on cardiac outcomes, including heart failure. Potential mechanisms include significant lowering of systolic and diastolic blood pressure[41] as well as changes to vascular endothelial function, arterial stiffness, vascular resistance, and myocardial fibrosis.[42,43] Through natriuresis, SGLT2 inhibitors can reduce intravascular volume and total body sodium, leading to a reduction in preload and afterload, alleviating cardiac work, and improving LV

function.[44,45] Furthermore, despite its use as a diabetes medication, based on the available evidence, it is less likely that SGLT2 inhibitor's reduction in CVD and HF is mediated by their hemoglobin A1c-lowering effects.[46] A much more likely explanation is that SGLT2 protective effects on LV mass and LV diastolic function as well as possible direct protective effects on cardiomyocytes and anti-inflammatory properties explain their significant cardiac benefits.[35,40,46]

While insulin resistance in itself is a risk factor for LVH,[9] there are significant data indicating that those with LVH and diastolic dysfunction due to hypertension could also benefit from SGLT2 inhibitors. Already there is evidence to suggest that patients without type 2 diabetes mellitus will derive a similar benefit from SGLT2 inhibitors when compared to people with diabetes. Dapagliflozin has been shown to reduce the likelihood of death from cardiovascular causes as well as heart failure admissions in patients with HFrEF with and without diabetes.[47] In non-diabetic rat models, empagliflozin has shown to significantly reduce LV end-diastolic pressure, LV mass, and posterior wall thickness.[48] In humans, empagliflozin has shown to improve diastolic function regardless of diabetes status.[39] Ongoing studies include the EMPEROR-PRESERVED trial, looking at effects of empagliflozin in patients with and without T2DM and HFpEF.[49] Primary outcomes in that study include CV mortality as well as heart failure hospitalizations.[49] The EMPA-TROPISM trial is investigating similar outcomes in non-diabetic patients with LV ejection fraction ≤50%.[50] The ongoing DELIVER trial (NCT03619213) is evaluating Dapagliflozin versus placebo in reducing CV mortality and HF events in patients with HFpEF and evidence of cardiac structural abnormalities (LVH or left atrial enlargement on echocardiogram) with and without diabetes mellitus.

## Conclusion

Left ventricular hypertrophy is a cardinal manifestation of arterial hypertension and significantly increases the risk of heart failure, ischemia, arrhythmia, and cardiac death. It is clear that regression in the left ventricular mass in those with hypertensive heart disease significantly improves outcomes. The recent trend in evidence-based medicine raises the question – do patients with predominately LVH and diastolic dysfunction phenotype of HFpEF derive a significant mortality benefit from a treatment approach that leads to regression of LVH? Indeed, a drugs effect on LV remodeling is the best surrogate to predicate outcomes such as survival and hospitalizations.[51]

Treatment with ACE inhibitors, ARBs, sacubitril/valsartan, and spironolactone has been shown to significantly decrease LV mass. Interestingly, these effects were independent of blood pressure control and they point toward alternative mechanism of improvement in LV remodeling. SGLT2 inhibitors are emerging as a new class of medications that have been shown to improve cardiac outcomes – in both diabetic and non-diabetic patients – likely through their effects on LV remodeling and diastolic function.

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