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Rajiv Karnik
Senior Consultant Cardiology,
Fortis Hospital, Marathon
Chambers, 306, Purushottam
Kheraj Rd, Mulund West,
Mumbai, Maharashtra, India

Referral Pathway for Hypertension with High Cardiovascular Risk: A Review

Rajiv Karnik

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Abstract

Hypertension is considered as a common and powerful contributor to all the major cardiovascular diseases (CVDs), including coronary disease, stroke, peripheral artery disease, renal disease, and heart failure. Results from the Framingham study indicated that high blood pressure (BP), even within what is regarded as the non-hypertensive range, imposes an increased risk of CVD. The median BP at which cardiovascular sequelae appeared in the Framingham study was 130/80 mmHg. Epidemiological data have shown that the risk of CVD rises with increasing BP levels, starting at $\geq 115/75$ mmHg in a strong, independent, graded, and continuous manner. Early and aggressive BP lowering is mandatory as it can contribute to long-term CV risk reduction. According to the Framingham study data, 31% of strokes occur in patients with normal or high normal hypertension. Clinical trial data suggest that antihypertensive therapies, particularly those that block the renin-angiotensin-aldosterone system (RAAS), can reduce CVD risks at least partly independently of BP lowering, although a major controversy involves this question. An optimal strategy to reduce CV risk may include lifestyle modifications, promoting adherence to early and aggressive target level achievement, appropriate drug choice, and especially global risk reduction.

Keywords: Cardiovascular risk; risk reduction; RAAS blockers; Framingham study

Introduction

Hypertension, the leading risk factor for cardiovascular disease (CVD), originates from combined genetic, environmental, and social determinants. Environmental factors include obesity, unhealthy diet, excessive dietary sodium, inadequate dietary potassium, insufficient physical activity, and consumption of alcohol ^[1].

Epidemiologic research has established that blood pressure (BP) elevation is a common and powerful contributor to all of the major CVDs, including coronary disease, stroke, peripheral artery disease, renal disease, and heart failure ^[2]. Approximately 54% of strokes and 47% of coronary heart diseases (CHDs), worldwide, are attributable to high BP ^[3].

Six national level consensus meetings were held in 2021, wherein 60 eminent experts (cardiologists) from different regions of the country attended panel meetings and discussed the importance of creating a referral pathway for patients with high cardiovascular risk. This article reviews the discussion held during these meetings and provides a consensus roadmap and a composite model for the treatment of hypertension.

Risk stratification in hypertension: insights from the framingham study

Results from the landmark Framingham study clearly indicated that higher levels of BP, even within what is regarded as the non-hypertensive range, impose an increased risk of CVD. The median BP at which cardiovascular sequelae appeared in the Framingham Study was only 130/80 mmHg. In this stage 1 and stage 2 hypertension, the total burden of risk factors must be assessed to efficiently target candidates for treatment to prevent CVD. High risk of cardiovascular sequelae of hypertension is concentrated in patients with dyslipidemia, glucose intolerance, cigarette smoking, or left ventricular hypertrophy (LVH). Among persons with hypertension, about 40% of coronary events in men and 68% in women are attributable to the presence of two or more additional risk factors. Only 14% of coronary events in hypertensive men and 5% of those in hypertensive women occurred in the absence of additional risk factors ^[2].

Corresponding Author:
Rajiv Karnik
Senior Consultant Cardiology,
Fortis Hospital, Marathon
Chambers, 306, Purushottam
Kheraj Rd, Mulund West,
Mumbai, Maharashtra, India

Risk factor clustering

The Framingham study data indicated that elevated BP tends to cluster with other major risk factors such as obesity, dyslipidemia, glucose intolerance, and LVH. Less than 20% of hypertension cases occur in the absence of one or more of the following risk factors: high triglyceride and low-density lipoprotein cholesterol (LDL-C) levels, reduced high-density lipoprotein cholesterol (HDL-C) levels, glucose intolerance, hyperinsulinemia, obesity, and LVH. A cluster of two or more additional risk factors occurs in about half of the hypertensive individuals, a frequency twice that expected by chance. Clusters of three or more occur at four times the expected rate [2].

Strategies for prevention and control of hypertension

Abundant epidemiological data have shown that the risk of CVD rises with increasing BP levels, starting at $\geq 115/75$ mmHg in a strong, independent, graded, and continuous manner. Numerous clinical trials have shown that lowering BP reduces CV risk by 20% to 25% for myocardial infarction (MI), by 35% to 40% for stroke, and by 50% for heart failure. Today, a target of 65% risk reduction in hypertensive patients and 80% risk reduction in the general population seems feasible; yet, the precise physiologic mechanisms by which hypertension increases CV risk and antihypertensive therapy lowers the risk, remain unclear [4].

In adults with hypertension, controlling BP to non-hypertensive levels via non-pharmacological and pharmacological treatment reduces the risk for CVD events and all-cause mortality by 20% to 40% [1].

Clinical trial data suggest that antihypertensive therapies, particularly those that block the renin-angiotensin-aldosterone system (RAAS), can reduce CVD risks at least partly independently of BP lowering, although a major controversy involves this question. An optimal strategy to reduce CV risk may include lifestyle modifications, promoting adherence to early and aggressive achievement of target levels, appropriate drug choice, and especially global risk reduction [4].

Lifestyle modifications

All guidelines recommend weight control, reduced salt intake, reduced alcohol consumption, and regular exercise. Mortality risk was found to be almost halved in hypertensive patients who exercise and achieve a good physical performance (exercise tolerance >8 metabolic equivalents) [4].

Early and aggressive BP lowering

Early and aggressive BP lowering is mandatory as it leads to long-term CV risk reduction. According to the Framingham study data, 31% of strokes occur in patients with normal or high normal hypertension [4].

Treatment to target levels

It is well accepted that only 30% of hypertensives are treated at target level although almost all patients can achieve the target with the appropriate combination of drugs [4].

Choice of drugs

Kidney disease trials provide strong evidence and a lot of important lessons. Modulation of RAAS along with BP lowering is probably the best root for an optimal CV risk

reduction. A significant CV death reduction was observed in studies HOPE, LIFE, ASCOT (22%, 13%, and 24%, respectively) where the BP advantage was gained by a RAAS regimen [4].

Global cardiovascular risk reduction: an important therapeutic target

Hypertension from the beginning to all stages is associated with other CV risk factors, and this global risk profile is essential for CVD prevention. The nine important risk factors that account for 90% of CVD case include Hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, dyslipidemia, microalbuminuria or estimated glomerular filtration rate (GFR) <60 mL/min, age (>55 for men, >65 for women), and family history of premature CVD [4].

Clinical Case Discussions

Profile 1: Hypertension with acute coronary syndrome

A 65-year-old man with hypertension and CAD was on lisinopril 20 mg/day and hydrochlorothiazide 25 mg/day. Blood pressure measured at office was 138/88 mmHg; the patient had a history of MI 5 years back. He reported angina on exertion. Metoprolol 50 mg once daily (OD) and aspirin were added to his regimen, with which his anginal episodes were controlled and BP remained within 130/80 mmHg. In follow-up after 2 months, he presented with acute chest pain. Echocardiogram (ECG) revealed an anteroseptal non-ST-segment elevation MI (NSTEMI). His vital signs were stable, but his BP was 172/94 mmHg. There was some pulmonary venous congestion on a chest radiograph, but he did not have any other signs of heart failure. His serum creatinine concentration was 1.0 mg/dL.

Hypertension and patients with acute coronary syndrome (ACS): Placing BP levels into perspective

Epidemiological data with respect to hypertension history and associated prognosis in patients with ACS are rather scarce. Prevalence of hypertension is reportedly 30% to 40% among patients with an ST-elevation MI (STEMI) and rises up to 70% in patients with NSTEMI [5].

Key practice points:

A BP target of $<140/90$ mmHg is recommended in most patients with CAD and hypertension. A target of 130/80 mmHg is reasonable in selected patients with CAD, including those with previous MI, stroke, or CAD risk equivalents. Recommended medications for patients with hypertension and chronic stable angina include beta-blockers (in those with a history of MI), angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), and thiazide-like diuretics [6].

Management of hypertension in patients with ACS

Medications with evidence that they reduce risks in patients with ACS include beta-blockers, ACEis or ARBs, and possibly aldosterone antagonists. Nitrates are also useful. Caution should be taken to avoid hypotension [6].

An intravenous beta-blocker (esmolol) can be considered if the patient has severe hypertension or ongoing ischemia. Beta-blocker therapy should be delayed in patients who are hemodynamically unstable or who have decompensated heart failure. A non-dihydropyridine calcium channel blocker (CCB) like diltiazem or verapamil may be

substituted for the beta-blocker in patients with ongoing ischemia and no left Ventricular dysfunction (LVD), and a long-acting dihydropyridine CCB can be added if hypertension and angina are not controlled with initial treatment [6].

Nitrates (sublingual or intravenous nitroglycerin) should be considered to lower BP or relieve ongoing ischemia or pulmonary congestion [6].

An ACEi or ARB should be added if the patient has an anterior MI or diabetes, if hypertension persists, or there is evidence of LVD or heart failure. An ACEi is the first-line therapy for low-risk patients [6].

Aldosterone antagonists are indicated in patients already taking a beta-blocker and ACEi after an MI, and have LVD and heart failure or diabetes. Serum potassium levels should be monitored, and the medications should be avoided in patients with elevated serum creatinine levels [6].

Loop diuretics are preferred over thiazide-like diuretics in patients with ACS and heart failure, or in patients with chronic kidney disease (CKD) and an estimated GFR <30 mL/min. If persistent hypertension is not controlled with a beta-blocker, ACEi and aldosterone antagonist, a thiazide or thiazide-like diuretic may be selectively added [6].

A BP target of 140/90 mmHg is reasonable in hemodynamically stable patients with ACS, and a target of 130/80 mmHg is appropriate at the time of hospital discharge [6].

Management of hypertension in patients with heart failure of ischemic origin

In patients with hypertension and heart failure with preserved ejection fraction (HFpEF), the goal is to control systolic and diastolic hypertension [6].

The aldosterone receptor antagonists spironolactone and eplerenone should be added in patients with heart failure and reduced ejection fraction (HFrEF) <40%. They may be substituted for a thiazide diuretic in patients requiring a potassium-sparing agent. Serum potassium should be monitored if an aldosterone receptor antagonist is used with an ACEi or an ARB, or if the patient has renal insufficiency. Aldosterone receptor antagonists should be avoided in men with a serum creatinine level of 2.5 mg/dL (221 µmol/L) or more, in women with a serum creatinine level of 2 mg/dL (177 µmol/L) or more, and in patients with a serum potassium level of 5 mEq/L (5 mmol/L) or more. Spironolactone or eplerenone may be used with a thiazide or thiazide-like diuretic, particularly if the patient has resistant hypertension. Hydralazine and isosorbide dinitrate should be added to the diuretic, ACEi or ARB, and beta-blocker regimen in black patients with New York Heart Association class III or IV HFrEF [6].

Key practice points

In hypertension with ACS, the target of BP is <140/90 mmHg in general and <130/80 mmHg in individuals with diabetes mellitus or CKD. Complete investigation with lipid, renal, and cardiovascular (echocardiography) profile should be done. CV risk assessment would definitely help this patient group. The patient should be started on high-intensity statins for vascular and endothelial function. Metoprolol and ramipril can be initiated in these patients with ACS and must be referred to cardiologist for angiography.

Profile 2: Hypertension with cerebrovascular stroke

Hypertension is the most prevalent risk factor for stroke, based on data from 30 studies and has been reported in about 64% of patients with stroke [7].

A 70-year-old woman with type 2 diabetes, dyslipidemia, and untreated hypertension was under treatment by her family physician. Her current medications were metformin 500 mg twice daily (BD) and atorvastatin 40 mg BD. Her office BP was 140/92 mmHg. Her glycated hemoglobin (HbA1c) was 8%, and lipid profile was as follows: total cholesterol = 227 mg/dL, HDL-C = 40 mg/dL, LDL = 125 mg/dL, and TG = 140 mg/dL.

On evaluation

It was found that the patient was having blood glucose of 175 mg/dL. Her ECG revealed a normal sinus rhythm, with evidence for LVH by voltage criteria and nonspecific ST changes. Brain computed tomography (CT) scan revealed age-appropriate atrophy and several small, old, deep white matter infarcts but no acute changes or bleeds.

American Heart Association (AHA)/American Stroke Association (ASA) recommendations for BP management in acute ischemic stroke

Patients eligible for treatment with intravenous thrombolytics or other acute reperfusion intervention and systolic BP (SBP) >185 mmHg or diastolic BP (DBP) >110 mmHg should have BP lowered before the intervention. A persistent SBP of >185 mmHg or a DBP >110 mmHg is a contraindication to intravenous thrombolytic therapy. After reperfusion therapy, keep SBP <180 mmHg and DBP <105 mmHg for at least 24 hours. Patients who have other medical indications for aggressive treatment of BP should be treated. For those not receiving thrombolytic therapy, BP may be lowered if it is markedly elevated (SBP >220 mmHg or DBP >120 mmHg). A reasonable goal would be to lower BP by approximately 15% during the first 24 hours after onset of stroke. In hypotensive patients, hypovolemia and cardiac arrhythmias should be treated and in exceptional circumstances, vasopressors may be prescribed in an attempt to improve cerebral blood flow [8].

Recommendations for BP management for prevention of recurrent stroke

The absolute target BP level is uncertain and benefit may be noted with an average BP drop of 10/5 mmHg. Lifestyle modifications are included as part of a comprehensive approach. A diuretic or diuretic plus an ACEi is a reasonable choice; however, compelling indications may exist for a specific class of antihypertensive, and use of the 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure is recommended [8].

Reducing BP appears to be more important than the choice of agents, and the effectiveness of the BP reduction diminishes as initial baseline BP declines. Angiotensin inhibitors, CCBs, and diuretics are reasonable options for initial antihypertensive monotherapy and may be used in such patients [7].

Key practice points

Target BP should be 130/80 mmHg. Most guidelines on hypertension in diabetes suggest to bring the BP down to 140/90 mmHg; if the patient tolerates the therapy well, it

should further be brought down to 130/80 mmHg. Lipid, thyroid, renal, echocardiography, and coronary calcium score should be assessed prior to treatment. Antihypertensive agents like ACEis or ARBs are more preferred. CCBs can also be considered. Drug of choice should be a combination of CCB plus ACEis/ARBs.

Profile 3: Hypertension with advanced diabetes

Hypertension and type 2 diabetes are common comorbidities. Hypertension is twice as frequent in patients with diabetes compared with those who do not have diabetes [9].

A 55-year-old woman was referred by her primary physician for poorly controlled diabetes and hypertension. She was diagnosed with diabetes 5 years ago and had been taking sulfonylurea 10 mg OD. Hypertension was diagnosed 7 years back, and she was receiving amlodipine 10 mg and hydrochlorothiazide 25 mg daily. Her last HbA1c, 3 months back, was 8.8%.

An ECG a year back showed LVH. Lipid profile was as follows: total cholesterol = 230 mg/dL and LD-C = 145 mg/dL.

On examination

The patient's pulse rate was 88 bpm, BP was 154/94 mmHg, and body mass index (BMI) was 35 kg/m².

Funduscopy revealed exudative retinopathy. Examination of the heart showed that the point of maximum impulse (PMI) was shifted to the anterior auxiliary line and sustained, with an S4 gallop present. Examination of the lower extremities showed that the dorsalis pedis and posterior tibial pulses were noticeably decreased in amplitude, and pretibial pitting edema was present.

Laboratory investigations showed fasting glucose of 140 mg/dL, HbA1c of 8.5%, creatinine of 2.0 mg/dL, urinary albumin of 0.8 mg/dL, total cholesterol of 250 mg/dL (HDL-C = 35 mg/dL, LDL-C = 165 mg/dL, triglycerides = 250 mg/dL), and serum potassium of 4.7 mmol/L.

Recommendations

Blood pressure targets

It is recommended that most patients with diabetes and hypertension should be treated to a SBP goal of <140 mmHg and a DBP goal of <90 mmHg. Lower SBP/DBP targets, such as <130/80 mmHg, may be appropriate for individuals at high risk of CVD if they can be achieved without undue treatment burden [10].

Definitions, screening, and diagnosis

BP should be measured at every routine clinical care visit. Patients found to have an elevated BP ($\geq 140/90$ mmHg) should have BP confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. All hypertensive patients with diabetes should have home BP monitored to identify white-coat hypertension. Orthostatic measurement of BP should be performed during initial evaluation of hypertension and periodically at follow-up, or when symptoms of orthostatic hypotension are present, and regularly if orthostatic hypotension has been diagnosed [10].

Pharmacologic antihypertensive treatment

Patients with confirmed office-based BP $\geq 140/90$ mmHg should, in addition to lifestyle therapy, have timely titration

of pharmacologic therapy to achieve BP goals. Patients with confirmed office-based BP $\geq 160/100$ mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with diabetes. Treatment for hypertension should include drug classes demonstrated to reduce CV events in patients with diabetes: ACEis, ARBs, thiazide-like diuretics, or dihydropyridine CCBs. Multiple-drug therapy is generally required to achieve BP targets (but not a combination of ACEis and ARBs). An ACEi or ARB at the maximum tolerated dose indicated for BP treatment is the recommended first-line treatment for hypertension in patients with diabetes and urine albumin-to-creatinine ratio ≥ 300 mg/g creatinine or 30–299 mg/g creatinine. If one class is not tolerated, the other should be substituted. For patients treated with an ACEi, ARB, or diuretic, serum creatinine/estimated GFR and serum potassium levels should be monitored [10].

Lifestyle management

For patients with SBP >120 mmHg or DBP >80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a dietary approach to stop hypertension (DASH)-style dietary pattern including reduced sodium and increased potassium intake; increased fruit and vegetable consumption; moderation of alcohol intake; and increased physical activity [10].

Key practice points

Target BP should be 130/80 mmHg, but acceptable level is $<140/90$ mmHg. Single drug therapy should be started in presence of albuminuria with ACEis or ARBs. If the patient is in stage 2 hypertension, combination therapy should be started. Lifestyle management is a must in this case. In this patient group without complications or contraindication, ARB or CCB or their combination can be used. Sodium glucose cotransporter (SGLT2) inhibitors along with metformin can be given to the patients with hypertension and diabetes.

Profile 4: Hypertension with CKD

The prevalence of hypertension in CKD patients ranges from 60% to 90% depending on the stage of CKD and its cause [11].

Case scenario

A 44-year-old teacher, mother of two children, presented to her family physician complaining of knee pain. She smoked 10 cigarettes per day and was overweight. She was prescribed ibuprofen and advised to lose weight. Ibuprofen helped, so she continued it for long-term. Later that year, she met her family physician again for generalized pruritus. She mentioned that it could be because of a change in washing powder. She was prescribed an antihistaminic and advised some tests. Her creatinine level was 1.55 mg/dL and estimated GFR was 38 mL/min.

Her BP was measured as 136/84 mmHg, and she was prescribed amlodipine 5 mg OD. She was asked to repeat her tests and follow up after 3 months. However, she failed to repeat her tests.

Follow-up

She met a different general practitioner complaining of anxiety and palpitations due to work-related stress. Her BP

was found to be 216/107 mmHg. She was prescribed propranolol and diazepam. An ECG was performed on the same day which showed LVH. Her creatinine was 2.4, and eGFR was 21 mL/min. A family history of CVD was confirmed on enquiry.

Goals of BP reduction and BP targets

The American College of Cardiology (ACC) 2017 guidelines recommended that all adults with hypertension and CKD should be treated to a target BP of <130/80 mmHg regardless of proteinuria. The National Institute for Health and Care Excellence (NICE) and UK Renal Association suggest a more conservative target of <140/90 mmHg, provided proteinuria is <1 g/day. In the presence of greater degrees of urinary protein leak, this target is revised to <130/80 mmHg. Kidney Disease: Improving Global Outcomes (KDIGO) guidance also suggests a lower BP target for those with significant proteinuria, although it deploys a cut-off of >300 mg/day. The 2018 European Society of Cardiology and the European Society of Hypertension (ESC/ESH) guidelines suggest a target SBP of <140 mmHg regardless of proteinuria^[12].

Achieving BP targets is challenging. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that despite intensive input including monthly medication reviews, >50% of those in the intensive treatment group failed to achieve the target SBP. Results in those with CKD suggest that it may be even more challenging to achieve BP goals than in the general hypertension population. Despite treatment with non-pharmacological interventions and multiple antihypertensive agents, the majority of CKD patients fail to reach target BP^[12].

Non-pharmacological treatment

Slagman, *et al.* found that in patients already established on RAAS inhibitors, reducing dietary sodium intake to a target of <50 mmol/day (~3 g/day of salt) decreased SBP by a further ~10 mmHg. A restriction to a target <100 mmol/day (~6 g/day of salt) has also demonstrated a reduction in proteinuria by ~25%, an effect that is unlikely to be explained by BP reduction alone. Weight loss is effective in reducing BP, and proteinuria and may slow CKD progression. In overweight patients (BMI >27 kg/m²) with CKD and proteinuria (>1 g/24 h), a mean weight loss of ~4% can reduce proteinuria by ~30%. The benefits of a multidisciplinary approach have also been demonstrated in CKD^[12].

Key practice points

Regular monitoring of the patient's creatinine would be useful. The desired target BP in this patient is 130/80 mmHg. Creatinine clearance divided by 10 is the frequency of follow-up for patients. Ambulatory BP monitoring or home BP monitoring is suggested. Morning surge patients are more susceptible for CKD. ACEis and ARBs are considered first-line antihypertensive agents, SGLT2 inhibitors are also in use for these patient groups.

Conclusion

Hypertension is the powerful contributor to all the major cardiovascular diseases, including coronary disease, stroke, peripheral artery disease, renal disease, and heart failure. Abundant epidemiological data have shown that the risk of CV disease rises with increasing blood pressure levels,

starting at ≥115/75 mmHg, in a strong, independent, graded, and continuous manner. Early, aggressive, and optimal BP control is necessary in some patient groups such as patients with diabetes, CKD, or CAD for better cardiovascular outcomes.

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Declarations

The expert group discussion was conducted in association with Abbott Healthcare Pvt. Ltd. This article is based on the views expressed during the expert group discussion. The views expressed and discussed in the meetings and stated in this article are the independent views of the author and not of Abbott Healthcare Pvt. Ltd.

Conflict of interest: The author is a member of American College of Cardiology, American Heart Association, European Society of Cardiology, and Cardiology Society of India and has received speakers' honoraria from Abbott for participating in the advisory board meetings.

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