



# Cardio-Renal Cascade in Hypertensive Patients

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## ABSTRACT

The number of patients with hypertension continues to grow as longevity increases. This is associated with increased risk of premature cardiovascular and chronic kidney disease. The cardiovascular disease manifests in the form of left ventricular hypertrophy, heart failure and atherosclerotic vascular disease. Atherosclerosis develops in the large and medium-sized arteries (carotid, coronary, renal and iliac) manifesting as stroke, ischemic heart disease, ischemic nephropathy and peripheral vascular disease. As a primary etiology, hypertension is an important cause of chronic kidney disease (CKD). Once CKD develops, there is worsening of hypertension which in turn contributes to increased risk of CVD and progression of CKD setting up a cardio-renal cascade. Mortality due to CVD is 10 to 30 times higher in dialysis patients than in the general population. CVD includes disorders of cardiac structure and function (left ventricular hypertrophy, cardiomyopathy and heart failure) and disorders of vascular system (atherosclerosis and arteriosclerosis). These two disorders are frequently associated and exacerbate each other. The increased risk of CVD in CKD results from “traditional” and “nontraditional” risk factors. The traditional risk factors include older age, diabetes mellitus, systolic hypertension, LVH, and low high-density lipoprotein (HDL) cholesterol, which are highly prevalent in CKD. Nontraditional risk factors include hyperhomocysteinemia, oxidant stress, dyslipidemia, malnutrition and elevated inflammatory markers.

## INTRODUCTION

Hypertension is common, readily detectable and usually easily treatable. The number of patients with hypertension continues to grow as longevity increases, since hypertension occurs in one-half of patients older than 65 years. It is estimated that in India, approximately 65.5 million adults are hypertensive. Recent studies using revised criteria (BP  $\geq$  140/90 mmHg) have shown a high prevalence of hypertension among urban adults: men 30%, women 33% in Jaipur (1995), men 44%, women 45% in Mumbai (1999), men 31%, women 36% in Thiruvananthapuram (2000). This is worrisome because hypertension is not only associated with increased risk of cardiovascular disease (CVD) but also chronic kidney disease (CKD). CKD further increases risk of developing CVD. The correlation between the blood pressure level and the risk of adverse outcome (including death) is a continuous variable in which there is an increased incidence of poor outcomes as the blood pressure rises. In this article, I will discuss (1) cardiovascular disease (CVD) associated with hypertension, (2) chronic kidney disease (CKD) associated with hypertension, (3) impact of hypertension on progression of CKD and (4) the risk of CVD in CKD.

## CARDIOVASCULAR DISEASE ASSOCIATED WITH HYPERTENSION

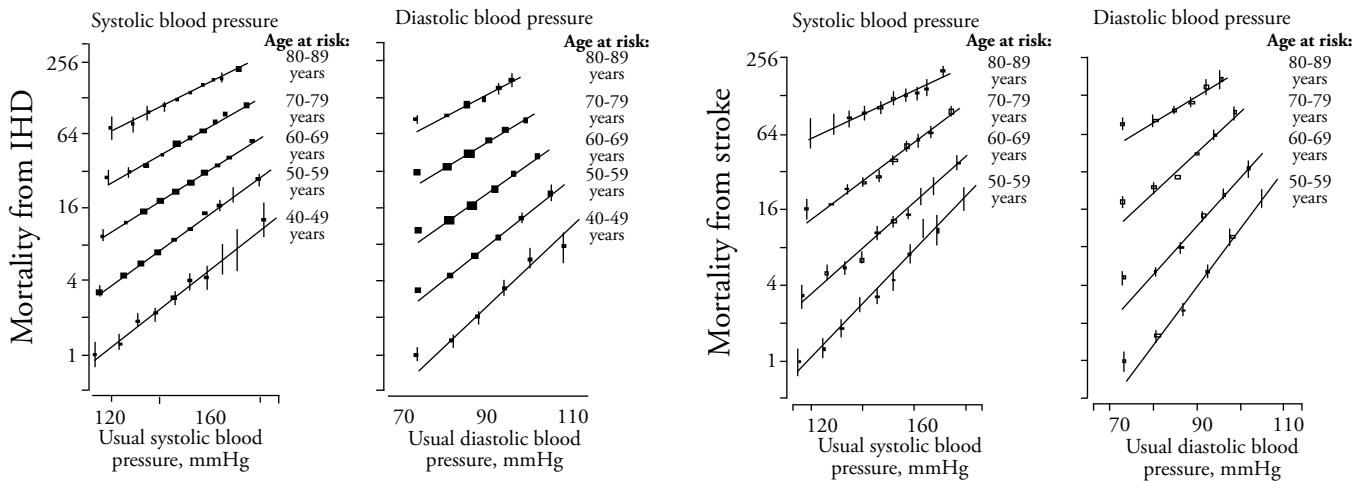
Hypertension is quantitatively the major risk factor for premature cardiovascular disease, being more common than cigarette

smoking, dyslipidemia, and diabetes, the other major risk factors. The increase in risk begins as the blood pressure rises above 110/75 mm Hg (Fig. 1). In older patients, systolic pressure and perhaps pulse pressure are more powerful determinants of risk than diastolic pressure. While systolic pressure and pulse pressure are important risk factors, in our experience they are extremely difficult to treat.

The cardiovascular disease manifests in the form of left ventricular hypertrophy, congestive heart failure, coronary vascular disease, stroke, and peripheral vascular disease.

LVH is characterized by an increase in left ventricular mass. Hypertension may also cause interstitial fibrosis. Both factors result in an increase in left ventricular stiffness resulting in diastolic dysfunction and elevated end-diastolic pressure. Diastolic dysfunction may be further aggravated by ischemia due to coronary artery disease. This in turn is associated with an enhanced incidence of heart failure, ventricular arrhythmias, death following myocardial infarction, and sudden cardiac death.

Atherosclerosis develops in the large and medium size arteries (carotid, coronary, renal and iliac) manifesting as stroke, ischemic heart disease, ischemic nephropathy, and claudicating pain while walking. Atherosclerotic carotid artery disease due to hypertension is the most common and most important stroke risk factor. Both prior and current blood pressure is important risk factors.



**Fig. 1:** Increased mortality from ischemic heart disease (IHD) and stroke with increase in the blood pressure from 110/75 mm Hg. Note that the relation is continuous.

Endothelial dysfunction is the early key event in atherogenesis. Endothelial dysfunction is characterized by the imbalance between endothelium-derived vasodilators and constrictors. Endothelium also plays an important role in maintenance of balance between plasminogen activators (urokinase and tissue-type plasminogen activator) and plasminogen activator inhibitor type 1. This balance is crucial for preventing intravascular thrombosis. A simple marker of endothelial dysfunction is microalbuminuria which is defined as urinary albumin excretion between 30 and 300 mg/day. Essential hypertensive patients with microalbuminuria had higher plasma levels of von Willebrand factor than patients with normal albumin excretion. This too may be responsible for accelerated thrombogenicity. The risk of an adverse cardiovascular event increases progressively with increasing absolute levels of microalbuminuria. Thus, microalbuminuria is a signal via the kidney that warns us about the presence systemic vascular disease.

Severe uncontrolled hypertension is a very strong risk factor for intracranial hemorrhage (ICH). A young person who enters the hospital with the acute onset of a focal neurological deficit and a blood pressure greater than 220/120 mm Hg has a very high likelihood of having an ICH.

The best evidence for a causal role of increasing blood pressure in cardiovascular complications is an improvement in outcome with antihypertensive therapy. An overview of 14 hypertension treatment trials concluded that a long-term (mean five years) 5 to 6 mm Hg decrease in the usual diastolic blood pressure was associated with a 16% reduction in the number of coronary events and 35 to 40 % reduction in stroke.

## CHRONIC KIDNEY DISEASE ASSOCIATED WITH HYPERTENSION

Hypertension is a risk factor for chronic kidney disease (CKD). It can both directly cause kidney disease, called hypertensive nephrosclerosis, and accelerate the progression of a variety of underlying kidney diseases. As a primary etiology, hypertension is the cause in over 25% of patients developing end-stage kidney disease in USA. This has been difficult to prove in our country because most patients present to us with hypertension and CKD.

At this stage it is difficult to say whether hypertension came first and caused CKD or that CKD developed first and caused secondary hypertension.

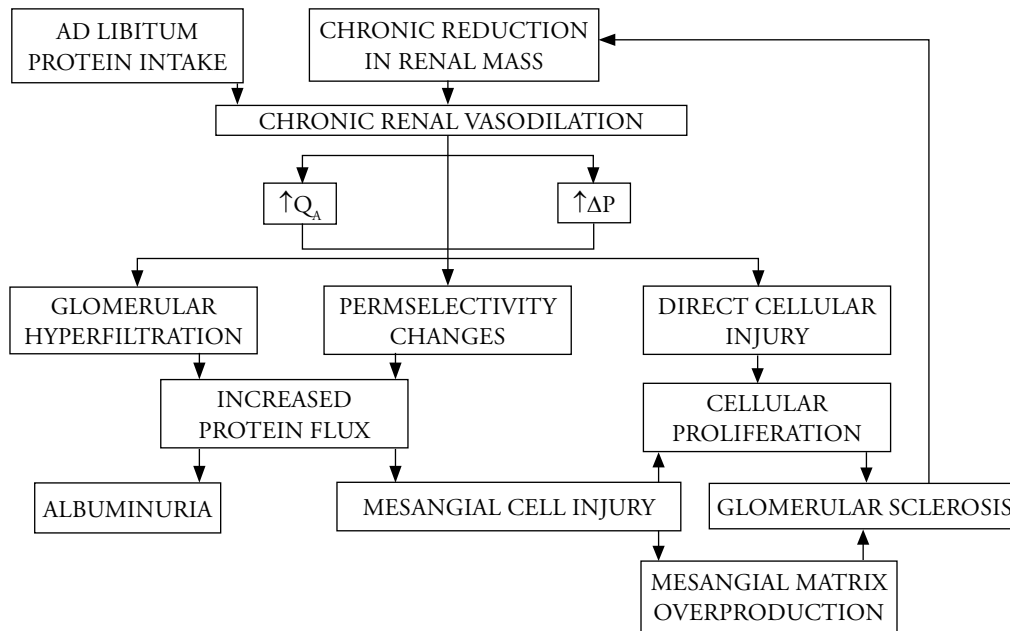
Hypertensive nephrosclerosis can be benign or malignant. Benign nephrosclerosis is seen in patients who are hypertensive for an extended period of time. Such patients, usually in the elder age group are often discovered to be hypertensive on routine examination or as a result of nonspecific symptomatology (headache, weakness, palpitation).

The kidney size is normal to reduced, with loss of cortical mass leading to fine granularity. Although the larger arteries may show atherosclerotic changes, the characteristic pathology is in the afferent arterioles, which have thickened walls due to deposition of homogenous eosinophilic material (hyaline arteriosclerosis). This material is composed of plasma proteins and fats that have been deposited in the arteriolar wall due to injury to the endothelium, probably secondary to elevated intraluminal hydraulic pressure. Narrowing of vascular lumina results, with consequent ischemic injury to glomeruli and tubules.

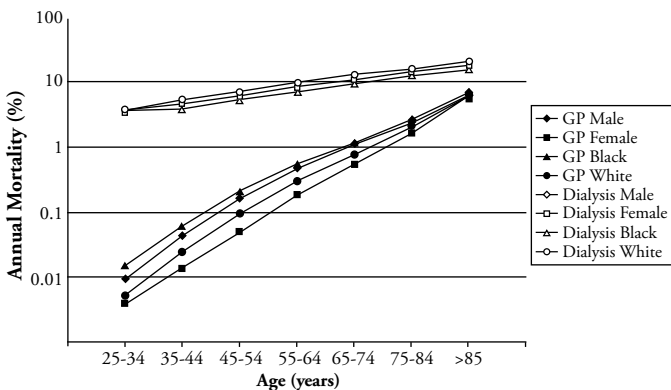
Patients with long standing essential hypertension or patients not known to be hypertensive previously may develop malignant hypertension characterized by sudden (accelerated) elevation of blood pressure (diastolic often above 130 mm Hg) and acute deterioration in renal function. Histologically, two distinct vascular lesions can be seen. The first, in affected arterioles there is fibrinoid necrosis, i.e., infiltration of arteriolar walls with eosinophilic material including fibrin. There is thickening of vessel walls and, occasionally, an inflammatory infiltrate (necrotizing arteriolitis). The second lesion, involving the interlobular arteries, is a concentric hyperplastic proliferation of the cellular elements of the vessel wall with deposition of collagen to form a hyperplastic arteriolitis (onion-skin lesion). Most glomerular and tubular changes are due to ischemia.

## ROLE OF HYPERTENSION IN PROGRESSION OF CKD

Substantial clinical and experimental evidence suggests that hypertension accelerates progression of CKD, whether it results or causes the renal disease. The mechanism by which



**Fig. 2:** Schema describing the mechanism of progressive glomerulosclerosis in chronic kidney disease.  $Q_A$ : Glomerular capillary plasma flow;  $\Delta P$ : glomerular capillary pressure.



**Fig. 3:** Increased mortality from CVD in patients with CKD compared to general population

hypertension accelerates progression of CKD have been studied extensively in animal models. After a partial loss of kidney function, a compensatory decline in the preglomerular resistance allows increased transmission of systemic pressure to glomerular capillaries. Resultant glomerular hypertension damages the capillary wall, releasing cytokines and increasing protein filtration. Activated by these changes, glomerular mesangial cell proliferation and matrix production are stimulated, leading to glomerular sclerosis (Fig. 2).

### What should be the target BP

Blood pressure should be controlled to 130/85 mm Hg. Clinical trials have investigated whether an even lower blood pressure (a target mean arterial pressure of less than 92 mm Hg, which is equivalent to a blood pressure of less than 125/75 mm Hg) is more effective in slowing the progression of nondiabetic kidney disease. The Modification of Diet in Renal Disease (MDRD) Study showed that the target BP of <125/75 mm Hg slows the

progression of CKD in patients with proteinuria greater than 1 g per day.

### Which antihypertensive agents to be preferred?

All hypertensive agents can be used to lower blood pressure in patients with chronic kidney disease. However, dihydropyridine calcium-channel blockers (D-CCBs) such as amlodipine alone are not recommended in patients with renal disease as D-CCBs are not antiproteinuric. They may actually worsen proteinuria, and cause faster progression of CKD, unless strict blood pressure control is achieved.

A number of clinical trials have compared the efficacy of angiotensin converting-enzyme (ACE) inhibitors with that of other classes of antihypertensive agents in slowing the progression of kidney disease. Two large studies – the ACE Inhibition in Progressive Renal Insufficiency Study and the Ramipril Efficacy in Nephropathy Study demonstrated that ACE inhibitors lowered blood pressure, decreased urinary protein excretion, and slowed the progression of kidney disease more than did other types of antihypertensive agents. Short-term studies show that angiotensin-receptor blockers have effects on blood pressure and proteinuria similar to those of ACE inhibitors.

Often combination of two or more drugs is required to achieve the target blood pressure values. Addition of a diuretic is useful, even in the absence of a clinically evident expansion of extracellular volume. Some studies show a synergistic effect of angiotensin-receptor blockers, diuretics, and nondihydropyridine calcium-channel blockers (diltiazem or verapamil) in reducing proteinuria.

### THE RISK OF CARDIOVASCULAR DISEASE IN CKD

In 1998, the National Kidney Foundation (NKF) task force on cardiovascular disease (CVD) in chronic kidney disease issued a

**Table 1: Risk factors for cardiovascular disease in CKD**

Traditional risk factors	Nontraditional risk factors
Older age	Type (diagnosis) of CKD
Male gender	Decreased GFR
Diabetes mellitus	Proteinuria
Hypertension	Renin-angiotensin system activity
Elevated LDL cholesterol	ECF volume overload
Decreased HDL cholesterol	Abnormal Ca-phosphorus metabolism
Family history of CVD	Dyslipidemia
Tobacco use	Anemia
Physical inactivity	Malnutrition
Menopause	Inflammation
Psychological stress	Infection
	Thrombogenic factors
	Oxidative stress
	Elevated homocysteine
	Uremic toxins

report emphasizing the high risk of CVD in CKD. This report showed that there was a high prevalence of CVD in CKD and that mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population (Fig. 3).

CVD is the commonest cause of death (50% of all deaths) in CKD patients. CVD begins early in the course of CKD, and the risk and severity of CVD increases with worsening of CKD. In the Atherosclerosis Risk in Communities (ARIC) study, each 10 ml/min per 1.73m<sup>2</sup> decrease in the GFR had 5% higher cardiovascular risk. The Heart and Soul Study of patients with documented coronary artery disease showed that the presence of concurrent CKD is associated with relatively more severe CVD.

CVD includes disorders of cardiac structure and function (left ventricular hypertrophy, cardiomyopathy and heart failure) and disorders of vascular system (atherosclerosis and arteriosclerosis). These two disorders are frequently associated and exacerbate each other.

Left ventricular hypertrophy (LVH) develops in early stages of CKD and progresses as kidney function decreases. On starting dialysis, 75% of adults have LVH. It is an adaptive response that follows an increase in cardiac work caused by volume and pressure overload. Volume overload results from anemia and sodium and water retention. The creation of arteriovenous fistula for hemodialysis adds to the volume overload. Pressure overload results from increased systolic blood pressure. This structural abnormality may lead to diastolic and systolic dysfunction which may be detectable by echocardiography.

Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions. There is a high prevalence of atherosclerosis in CKD. Atherosclerotic lesions in kidney failure are frequently calcified, as opposed to fibroatheromatous in patients without CKD. Clinical presentations of atherosclerosis

include ischemic heart disease, namely, angina, myocardial infarction, and sudden cardiac death, cerebrovascular disease and peripheral vascular disease.

Arteriosclerosis is characterized by increase in arterial diameter and intima-media thickening. These changes result from nonspecific factors (age, gender, smoking, blood pressure and diabetes) and factors specific to CKD, such as fluid overload, increased endothelin-1, hyperphosphatemia and hyperparathyroidism. In majority of patients with CKD, arteriosclerosis is accompanied by a huge prevalence of highly calcified atherosclerotic plaques.

The risk factors for CVD in CKD can be classified as “traditional” or “nontraditional” (Table 1). Most of the traditional CVD risk factors, such as older age, diabetes mellitus, systolic hypertension, LVH, and low high-density lipoprotein (HDL) cholesterol, are highly prevalent in CKD. Several nontraditional factors such as C-reactive protein, dyslipidemia, hyperhomocysteinemia, malnutrition, elevated inflammatory markers, oxidant stress, and advanced glycosylation end-products are associated with atherosclerosis and may explain the tremendous burden of CVD in CKD. Other factors such as anemia are associated with cardiomyopathy, whereas abnormal calcium and phosphorus metabolism is associated with vascular remodeling and development of noncompliant vessels.

In summary, hypertension significantly increases the risk of cardiovascular disease and chronic kidney disease. Once CKD develops there is further worsening of hypertension with progression of CKD and CVD. Optimal control of blood pressure, preferably with ACE inhibitors or angiotensin receptor blockers can attenuate the cardiorenal cascade.

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