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Review Article

# Antihypertensive therapy in nondiabetic chronic kidney disease: a review and update

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## Abstract

Hypertension is an important contributor to progression of nondiabetic chronic kidney disease (CKD). Compelling observational evidence indicates that the divergence of blood pressure (BP) away from an ideal range in either direction is associated with a progressive rise in the risk of mortality and cardiovascular and renal disease progression. To date, various clinical trials and meta-analyses examining strict versus less intensive BP control in nondiabetic CKD have not conclusively demonstrated a renal advantage of one BP-lowering approach over another, except in certain subgroups such as proteinuric patients where evidence is circumstantial. As recent data have come to light suggesting that intensive BP control yields superior survival and cardiovascular outcomes in patients at high risk for cardiovascular disease, interest in the prospect of whether such benefit extends to individuals with CKD has surged. This review is a comprehensive analysis of antihypertensive literature in nondiabetic renal disease, with a particular emphasis on BP target. J Am Soc Hypertens 2018; ■(■):1–28. Published by Elsevier Inc. on behalf of American Society of Hypertension.

*Keywords:* Nondiabetic; kidney; antihypertensive; target; goal.

## Introduction

Hypertension is a common place in predialysis chronic kidney disease (CKD), complicating at least 85% of CKD Stage 3 or above.[1] As diabetes has become the single leading cause of CKD worldwide, accounting for approximately 45% of incident end-stage renal disease (ESRD) in the US after overtaking other causes in the late 1980s,[2,3] management of hypertension in the presence of CKD has been based mainly on studies that included patients with diabetic nephropathy. However, the majority of CKD is collectively comprised of various nondiabetic etiologies in which hypertension, glomerulonephritis, and cystic kidney disease predominate as causes.[2] Moreover, nondiabetic renal disease tends to be more prevalent in developing countries, such as Egypt or other African nations.[4] Nondiabetic CKD also has a different pattern of kidney function decline than its diabetic counterpart, depending on the specific disease process present. The fact that proteinuria, a feature that is implicated in disease progression, is typically associated with renal disease of diabetic origin but not with certain nondiabetic nephropathies supports this notion. It therefore behooves us to deepen our comprehension of antihypertensive management in this area. This manuscript serves to provide a comprehensive review and update of antihypertensive therapy in the setting of CKD not attributable to diabetes, focusing primarily on evidence regarding blood pressure (BP) target.

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## Mechanisms for Progression of Nondiabetic Chronic Kidney Disease (CKD)

The mechanisms for progression of nondiabetic CKD are multifactorial (Figure 1). First and foremost, the pathogenesis of loss of nephron function is directly related to the specific nondiabetic disease process at hand (eg, cyst growth in polycystic kidney disease [PKD] or tubulointerstitial inflammation in interstitial nephritis). In glomerular diseases, podocyte injury and subsequent loss is often a contributor.[5] Podocyte damage typically results in effacement and proteinuria but may eventually lead to glomerulosclerosis if injury persists.[6] Tubulointerstitial injury is also a major determinant in the progression of renal damage, irrespective of the type of disease or compartment in which it originates.[5,7,8] Thereafter, many of the factors that promote advancement of CKD are created by CKD itself. Systemic hypertension, which commonly arises secondarily in CKD, is a major contributor to progression of CKD. The pathophysiology of hypertension in CKDs involves not only volume expansion related to sodium retention but also increased peripheral vascular resistance secondary to an enhancement of vasoconstriction systems (eg, activation of renin-angiotensin-aldosterone system [RAAS], stimulation of sympathetic nervous system) and a reduction of vasodilatory agents (eg, nitric oxide or prostaglandins).[9] As autoregulation of glomerular pressure is disturbed, increments in systemic BP lead to a rise in glomerular pressure (intraglomerular hypertension), glomerulosclerosis, and ultimately further loss of glomerular filtration rate (GFR), setting off a vicious cycle if BP remains uncontrolled.[10] Hence, control of BP is paramount in preventing acceleration of CKD progression. In addition, RAAS upregulation, independent of its hemodynamic effects, also plays a pathophysiologic role in CKD progression. Mediators of this system (eg, angiotensin II [AT2]) may promote inflammation and fibrosis.[11] Indeed, evidence that RAAS inhibitors provide renoprotection beyond their BP-lowering effects offers support for this notion.[12,13] Proteinuria, which may accompany nondiabetic kidney diseases as a consequence of damage to the glomerular permeability barrier and increased intraglomerular pressure, may itself be nephrotoxic.[14] This concept is a departure from the past belief of proteinuria as merely a marker of the severity of dysfunction of the glomerular filtration barrier. The mechanism of detriment to kidney function involves protein overload of tubular and mesangial cells leading to induction of tubulointerstitial inflammation (through complement activation and chemokine expression) and later fibrosis and glomerulosclerosis.[15–17] Finally, CKD instigates a proinflammatory state in which there is a release of various cytokines and growth factors that modulate progression of glomerular and tubulointerstitial scarring.[5,18]

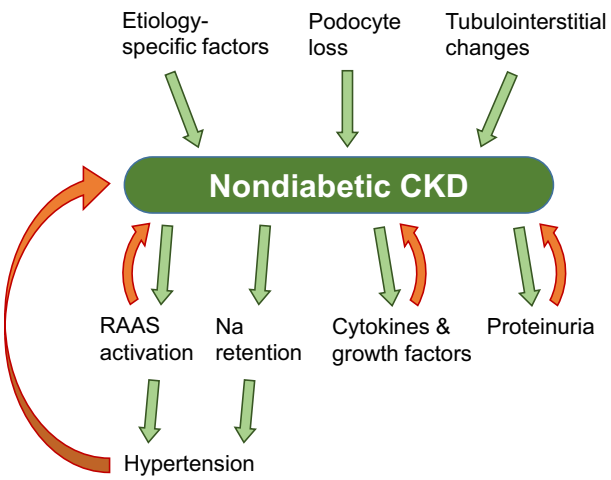


**Figure 1.** Pathogenesis of the progression of nondiabetic CKD. CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; Na, sodium.

## Goal Blood Pressure (BP)

### *Observational Evidence*

Ever since the 1950's, it has been clear that elevated BP is associated with increased cardiovascular (CV) risk.[19] By the early 1970's, it was indisputably demonstrated that active treatment of hypertension with medical therapy dramatically reduced CV events and progressive kidney damage.[20,21] Later on, the benefits of BP control afforded by antihypertensive therapy were proven in various subpopulations, which have certainly extended to both patients with renal insufficiency and patients without diabetes (Table 1). As epidemiological studies examining the relationship between BP and end-organ damage continued, the focus naturally narrowed toward defining precisely the levels of BP at which there is CV and renal risk. As in the general population, risk in nondiabetic or CKD patients has been consistently found to begin in the low-normal or normal BP range and then mount as BP rose. However, heterogeneous results have been yielded with respect to the exact threshold of BP elevation required for major organ impairment. These discrepancies are conceivably more attributable to differences among studies in power and follow-up duration than variations in population characteristics or outcome definitions. In large prospective cohorts of mostly nondiabetic individuals with minimal percentage of CKD, the risk of ESRD was discovered to begin at relatively modest BP elevations no higher than 130/85 mmHg, thereafter exhibiting a stepwise relationship with various strata of systolic BP (SBP) and diastolic BP (DBP) elevations.[25–27] For instance, Tozawa et al.[26] showed that the relative risk (RR) of ESRD in largely nondiabetic subjects successively increased as BP scaled above 120/80 mmHg and was also positively correlated with SBP and DBP increases (RR 1.29 in men and 1.34 in women