Review Article

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

Paul J. Der Mesropian, DO[a],*, Gulvahid Shaikh, MD[a],
Emmanuelle Cordero Torres, MD[b], Anum Bilal, MD[b], and Roy O. Mathew, MD[c]

[a]*Division of Nephrology, Department of Medicine, Albany Stratton VA Medical Center, Albany, NY, USA;*
[b]*Division of Nephrology, Department of Medicine, Albany Medical Center, Albany, NY, USA; and*
[c]*Division of Nephrology, Department of Medicine, William Jennings Bryan Dorn VA Medical Center, Columbia, SC, USA*

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;12(3):154–181. 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.

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]

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
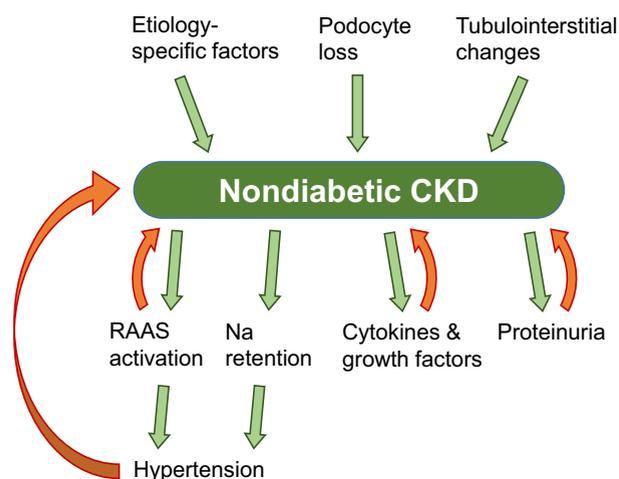

Figure 1. Pathogenesis of the progression of nondiabetic CKD. CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; Na, sodium.

Table 1
Major observational studies evaluating blood pressure control and renal or cardiovascular outcomes in nondiabetic patients

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Design, Follow-up Time	Major Findings
Rosansky et al., 1990[22]	US veterans (average age 53 y old, all male)	100%	0%	None	159	Prospective cohort Mean f/u 9.8 y	Uncontrolled HTN (BP ≥ 180/105 mmHg) was associated with greater rate of SCr increase than "normotension"/mild HTN (BP ≤ 160/95 mmHg) (by 1.5 μmol/L/y). Time-averaged BP, particularly SBP, was better predictor of SCr change than hypertensive category.
Chapman et al., 1994[23]	Subjects (average age 39–48 y) with ADPKD and mostly HTN in >70%	100%	100% (mean eGFR 37–82 mL/min 1.73 m², excluded ESRD)	Mean proteinuria 259 mg/d	270	Cross-sectional study	Proteinuric (>300 mg/d) and microalbuminuric (>45 mg/d) pts had higher mean arterial pressures than nonproteinuric and nonmicroalbuminuric pts (115 vs. 106 mmHg, 113 vs. 107 mmHg, respectively, both $P < .05$).
Perry et al., 1995[24]	US veterans (average age 53 y, all male) with HTN in Hypertension Screening and Treatment Program (HSTP) clinics	92%	N/a	N/a	11,912	Prospective cohort Minimum f/u 13.9 y	High pretreatment SBP > 165 mmHg independently increased risk of ESRD, with risk incrementally rising as BP escalated (compared with SBP ≤ 140 mmHg). Early reduction in SBP >20 mmHg decreased risk of ESRD by factor of ∼2/3 (RR 0.39).
Klag et al., 1996[25]	Middle-aged men (age 35–57 y) who were screened for Multiple Risk Factor Intervention Trial (MRFIT)	98% (82% of developed ESRD had nondiabetic cause)	N/a (39% of MRFIT participants had mild CKD with SCr 1.2–2 mg/dL or dipstick proteinuria ≥1+)	N/a (39% of MRFIT participants had SCr 1.2–2 mg/dL or dipstick proteinuria ≥1+)	332,544	Prospective cohort Mean f/u 16 y	Elevated BP ranges beginning at ≥ 130/85 mmHg were associated with progressively higher risk of ESRD in a stepwise fashion (compared with BP < 120/80 mmHg), independent of use of medications for DM.

							In 12,866 patients who entered MRFIT, relationship was not altered after taking into account baseline SCr and dipstick proteinuria.
Tozawa et al., 2003[26]	Japanese adults (age 20–98 y) who underwent health screening examinations	N/a (76% of developed ESRD had nondiabetic cause)	N/a	5.3% with dipstick proteinuria ≥1+	98,759	Prospective cohort Maximum f/u 17 y	Higher BP starting at ≥ 120/80 mmHg demonstrated a strong graded relationship with higher risk of ESRD (relative to BP < 120/80 mmHg). Associations remained unaltered after adjusting for presence of proteinuria. Risks of ESRD remained significant after excluding diabetic ESRD.
Hsu et al., 2005[27]	Adults (age ≥ 18 years) who participated in Multiphasic Health Checkup (MHC) study	91%	0%	None	316,675	Retrospective analysis Mean f/u 25.9 y	Higher BP beginning at ≥ 120/80 mmHg was observed to have a strong graded association with higher risk of ESRD (relative to BP < 120/80 mmHg). Results similar in subgroup analysis of nondiabetic subjects.
Kovesdy et al., 2006[28]	US veterans (average age 68 years, mostly male) with CKD	47%	100% (eGFR < 60 mL/min/1.73 m^2, excluded ESRD)	Mean proteinuria 0.46–1.37 g/d	860	Retrospective analysis Maximum f/u 15 y	Higher BP ranges ≥ 133/65 mmHg were associated with less mortality than lower BP < 133/65 mmHg. Relationships were consistent in subgroup of pts with ASCVD and eGFR <30 mL/min/1.73 m^2, suggesting low BP may be a surrogate marker (rather than independent risk factor) of ASCVD and low GFR-associated comorbidities.
Agarwal, 2009[29]	Adult US veterans (age ≥ 18 y old, mostly male) with CKD and	68%	100% (eGFR < 60 mL/min/1.73 m^2 or microalbuminuria, excluded ESRD)	Median proteinuria 0.32 g/g	218	Prospective cohort Mean f/u 4.3 y	High SBP ranges starting at ≥ 130 mmHg predicted ESRD (compared to SBP < 130 mmHg), whereas

Table 1 (*continued*)

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Design, Follow-up Time	Major Findings
	mostly HTN in 95%						DBP had no direct ability to predict ESRD. J-shaped curve was seen between SBP or DBP and all-cause mortality and was more pronounced in pts with advanced CKD (stage 4–5), absent clinical proteinuria (<1 g/g), and older age > 65 y. BP was more likely to be controlled if cause of CKD was not diabetes.
Peralta et al., 2012[30]	Adults (age ≥ 18 y old) with CKD who participated in Kidney Early Evaluation Program (KEEP)	57%	100% (eGFR < 60 mL/min/1.73 m^2, excluded ESRD)	22% with microalbuminuria >30 mg/g 4% with macroalbuminuria >300 mg/g	16,129	Prospective cohort Mean f/u 2.9 y	Hypertensive strata beginning at BP ≥ 140/90 mmHg (compared to BP < 130/74 mmHg) and high PP beginning at ≥ 80 mmHg (compared to PP < 50 mmHg) increased risk of progression to ESRD. Results were similar in pts who had macroalbuminuria.
Kovesdy et al., 2013[31]	Adult US veterans (age ≥ 18 y old, mostly male) with CKD	57%	100% (eGFR < 60 mL/min/1.73 m^2 or microalbuminuria, excluded ESRD)	Median microalbuminuria 40 mg/g	651,749	Retrospective analysis Median f/u 5.8 y	Optimal BP range appeared to be 130–159/70–89 mmHg. BP < 120/80 mmHg (low-normal) and BP ≥ 160/100 mmHg (stage 2 HTN) were associated with highest adjusted mortality rates (compared to BP 120–139/80–89 mmHg). Low DBP <70 mmHg was risk factor for mortality even when ideal SBP control was achieved. Results were consistent in subgroup of nondiabetic pts.

Chiang et al., 2014[32]	Taiwanese patients (average age 64 y old) with CKD and HTN in >60%	56%	100% (eGFR 15–60 mL/min/1.73 m^2)	Median proteinuria 0.71 g/g 40% with proteinuria ≥1 g/g	2131	Prospective cohort Median f/u 2.9 y	J-shaped relationship between SBP and CV events, mortality, and renal outcomes (ESRD or rapid renal function decline defined as eGFR slope < −5 mL/min/1.73 m^2) was shown for diabetic CKD pts but not for nondiabetic CKD pts. In subgroup of patients with proteinuria ≥1 g/g, J-shaped curve for diabetic CKD was enhanced.
Anderson et al., 2015[33]	Adults (age 21–74 y old) in Chronic Renal Insufficiency Cohort (CRIC) study with CKD (not due to PKD or primary renal disease requiring immunosuppression) and mostly HTN in >90%	52%	100% (age-specific eGFR 20–70 mL/min/1.73 m^2)	Mean proteinuria 1.0 g/g	3708	Prospective cohort Mean f/u 5.7 y	Elevated SBP and time-averaged SBP (mean of visit SBP and all previous visits) beginning at ≥ 130 mmHg increased risk of CKD progression (ESRD and composite of ESRD or halving of eGFR) (compared to SBP < 120 mmHg). Elevated BP on time-updated measures had stronger association with progression to ESRD than single baseline measures. Findings did not differ in subgroup of pts without DM.
Weiss et al., 2015[34]	Elderly adults (age 65–105 y old) with CKD	70%	100% (eGFR < 60 mL/min/1.73 m^2, excluded ESRD)	9.8%–14.6% with proteinuria	21,015	Retrospective analysis Maximum f/u 11 y	SBP < 120 mmHg was a risk factor for death in all age groups while SBP > 140 mmHg was a risk only in adults aged 65–70 y (compared to SBP 131–140 mmHg). DBP <60 mmHg was a risk factor for death whereas DBP >80 mmHg was not (compared to DBP 61–80 mmHg).

CKD, chronic kidney disease; F/u, follow-up; HTN, hypertension; BP, blood pressure; SCr, serum creatinine; SBP, systolic blood pressure; ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; eGFR, estimated GFR; ESRD, end-stage renal disease; Pts, patients; DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; DBP, diastolic BP; PP, pulse pressure; CV, cardiovascular.

[a] If available, prevalence of nondiabetic CKD reported preferentially over nondiabetic characteristic.

for each 10 mmHg increment in SBP, and 1.56 in men and 1.69 in women for each 10 mmHg increment in DBP, all $P < .0001$). Fundamentally, such results have mimicked investigations that explored connections between prehypertension and cardiovascular disease (CVD) in the general population.[35,36] One example is the meta-analysis of almost one million adults from numerous prospective studies in which it was demonstrated that the risk of CV events and mortality, adjusted for diabetic status, continuously and linearly amplified as BP escalated above 115/75 mmHg, doubling for each 20/10 mmHg increment in BP.[35]

In the aforementioned literature, however, CKD was not specifically analyzed. If observational studies are limited to only those which evaluated CKD of mostly nondiabetic origin, a slightly different trend between BP and outcomes is displayed (Table 1). In general, a J-shaped curve (intensifying hazard rates as BP ventured outside an optimal BP range in either direction) was often perceived. Relative to patients free of renal disease, the optimal BP range tended to be shifted higher and thus more tolerant of high-normal BPs. In 2006, an investigation was undertaken by Kovesdy et al.[28] to determine whether the inverse association between BP and mortality, which had already been observed in patients with ESRD on dialysis, was also noted in patients with predialysis CKD. In the retrospective analysis of 860 US veterans with a nondiabetic rate of 47% and moderately advanced CKD stages 3–5 (mean estimated GFR [eGFR] ∼33 mL/min/1.73 m^2), the authors indeed confirmed the existence of a J-shaped curve, finding that lower BP < 133/65 mmHg was associated with higher mortality than various BP ranges ≥ 133/65 mmHg.[28] Furthermore, significant interactions were seen with prevalent atherosclerotic CVD (ASCVD) and poorer GFR < 30 mL/min/1.73 m^2, suggesting that low BP may not be an independent risk factor for mortality but rather a surrogate marker of ASCVD and low GFR-associated comorbidities. In a subsequent and larger historical cohort study by Kovesdy et al. that analyzed over half a million veterans with a nondiabetic rate of 57% and less severe CKD than previously (mean eGFR approximately 50 mL/min/1.73 m^2), the J-shaped pattern of outcomes once again emerged, with the highest mortality rates occurring at extremes of BP < 120/80 mmHg and ≥160/100 mmHg (adjusted HRs 1.42, 1.05, respectively, relative to prehypertensive category of BP 120–139/80–89 mmHg), and the optimal BP range being 130–159/70–89 mmHg when SBP and DBP combinations were assessed.[31] An upward-shifted lower bound of optimal BP range was also observed in Weiss et al.[34], who found that SBP <120 mmHg was a risk factor for death in elderly individuals aged 65 years old or above with CKD that was principally nondiabetic. Likewise, a relatively high upper demarcation was identified in CKD patients screened in the Kidney Early Evaluation Program, which reported that ESRD risk started at an SBP of 140 mmHg in over 16,000 individuals with CKD

stages 3–5 who were nondiabetic in more than half of cases,[30] as well as in Weiss et al.[34], who found that SBP > 140 mmHg risked death in adults aged 65–70 years old with reduced GFR but not in more elderly adults. Prospectively, the J-curve association between BP and mortality in nondiabetic CKD has also been detected. This was shown in a single-center prospective cohort study of veterans with CKD stage 3 or above stemming from a nondiabetic etiology in 68% and was especially pronounced in subgroups of patients with advanced CKD (Stages 4-5), absent clinical proteinuria (<1 g/g), and older age (>65 yrs).[29] However, it is not always seen—in a prospective cohort analysis of Taiwanese patients with CKD stages 3–4, a J-shaped relationship between SBP and CV events, mortality, and renal outcomes was not observed in nondiabetic patients but seen in diabetic CKD patients, especially those with more significant proteinuria measuring at least 1 g/g.[32]

Taken together, observational studies of individuals with nondiabetic nephropathies have not consistently answered the question of what the optimal BP target should be in practice. Here we ask: what is the extent of BP control that should be achieved with medications to provide the most meaningful clinical benefit with the least adverse effects? In nondiabetic CKD, this trouble seems to be compounded by the observation (but not necessarily causal association) of a higher incidence of major organ events at BPs in the lower ranges of normal. This J-curve phenomenon is commonly believed to be explained by a larger burden of pre-existing CVD or comorbidity rather than actual antihypertensive effect.[37] Potential mechanisms of its occurrence in CKD, a CVD equivalent, include elevation of the BP threshold below which vital organ perfusion is reduced as a consequence of more severe vascular disease or impaired blood flow autoregulation, or increased BP variability.[38] Indeed, CKD has been shown to be linked to alterations in circadian BP profile, manifesting with changes such as greater nocturnal hypertension, nondipping (blunting of nocturnal BP fall), or BP variability.[39,40] High quality, well-designed interventional trials are therefore of utmost importance in elucidating the ideal BP target.

Interventional Evidence

As it became clear from observational data that elevated BP was an independent and continuous predictor of renal and CV disease, a fair number of randomized controlled trials (RCTs) were conducted in nondiabetic CKD to help clarify the ideal BP to target to retard disease progression (Table 2). Whereas almost all studies within this arena have addressed renal outcomes, few have evaluated CV end points; of these, none had sufficient power to detect differences in CV event rates.[55] Evidence from a CV perspective is additionally limited because most clinical trials exploring the interplay between BP lowering and CV

Table 2

Major randomized controlled trials (RCTs) evaluating goal blood pressure and renal or cardiovascular outcomes in nondiabetic chronic kidney disease (CKD) patients

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Intervention, Follow-up Time	Major Outcomes (Intensive BP Control as Compared to Conventional BP Control)
Modification of Diet in Renal Disease (MDRD) Klahr et al., 1994[41]	Adults (age 18–70 y old) with CKD and mostly HTN in >85%	97% (excluded insulin-dependent DM)	100% (eGFR 13–55 mL/min/ 1.73 m^2)	Proteinuria <10 g/d Mean proteinuria 1.09 g/d Median proteinuria 0.35 g/d 54% with proteinuria ≥0.25 g/d 11% with proteinuria ≥3 g/d	840	Aggressive BP control (MAP ≤ 92, ≈125/75 mmHg) vs. usual control (MAP ≤ 107, ≈ 140/90 mmHg) Mean f/u 2.2 y	Aggressive BP target overall did not decrease GFR decline rate or delay occurrence of ESRD or death, particularly in nonproteinuric pts. In subgroup of pts with proteinuric CKD (≥1 g/d for eGFR 25–55 mL/mL/min/ 1.73 m^2, ≥3 g/d for eGFR 13–24 mL/ mL/min/1.73 m^2), low BP target significantly delayed progression of renal disease, with benefits increasing further as amount of proteinuria rose.
Long-term follow-up of MDRD trial Sarnak et al., 2005[42]	–	–	–	–	–	– Mean f/u 10.6 yrs	Low BP target significantly delayed progression to ESRD and combined renal outcome (ESRD or death) (adjusted HRs 0.68, 0.77, respectively, both P < .01). In subgroup of pts with proteinuria ≥1 g/d, these outcomes remained significant (adjusted HRs ∼0.5–0.7), in contrast to less proteinuric pts. Benefits of low BP target did not differ according to cause of CKD.
Long-term follow-up of MDRD trial Ku et al., 2015[43]	–	–	–	–	–	– Median f/u 19.3 y	Strict BP control reduced risk of death after ESRD onset (unadjusted HR 0.72, 95% CI 0.58–0.89) but did not delay progression to ESRD.
Toto et al., 1995[44]	Adults (age 25–73 y old) with presumed hypertensive nephrosclerosis	100%	100% (eGFR ≤ 70 mL/min/ 1.73 m^2, excluded SCr > 7 mg/dL)	Proteinuria ≤2 g/d Mean proteinuria 0.36 g/d	87	Strict BP control (DBP 65–80 mmHg) vs. conventional control (DBP 85–95 mmHg) Mean f/u 3.4 y	Strict BP control did not significantly reduce rate of GFR decline or combined renal end point (doubling of SCr or 50% reduction in GFR, ESRD, or death).

(*continued*)

Table 2 (*continued*)

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Intervention, Follow-up Time	Major Outcomes (Intensive BP Control as Compared to Conventional BP Control)
Hypertension Optimal Treatment (HOT) substudy, CKD subgroup Ruilope et al., 2001[45]	Middle-aged adults (age 50–80 y old) with HTN, CKD subgroup	93%	100% (eGFR ≤ 60 mL/min/ 1.73 m², excluded SCr > 3 mg/dL)	N/a	2821	DBP ≤ 80 vs. ≤ 85 vs. ≤ 90 mmHg Mean f/u 3.8 y	No difference in GFR, mortality, and CV events between various BP target groups, suggesting no benefit of lowering DBP ≤90.
Schrier et al., 2002[46]	Adults (age 20–60 y old) with ADPKD and HTN with LVH	100%	100% (eGFR > 30 mL/min/ 1.73 m²)	Proteinuria ≤3 g/d	79	Rigorous BP control (BP < 120/80 mmHg) vs. standard control (BP 135–140/85–90 mmHg) Maximum f/u 7 y	No statistically significant difference in renal function or time to ESRD between groups. Rigorous BP control was significantly more effective in decreasing LVMI.
African American Study of Kidney Disease and Hypertension (AASK) Wright et al., 2002[47]	African–American adults (age 18–70 y old) with presumed hypertensive nephrosclerosis	100%	100% (eGFR 20–65 mL/min/ 1.73 m²)	Proteinuria ≤2.5 g/g Mean proteinuria 0.30–0.35 g/g (corresponding to 0.38–0.63 g/d) Median proteinuria 0.08 g/g (corresponding to 0.12 g/d) 33% with proteinuria >0.22 g/g (corresponding to 0.30 g/d)	1094	Lower BP goal (MAP ≤ 92, ≈125/75 mmHg) vs. usual goal (MAP 102–107, latter ≈ 140/90 mmHg) Median f/u 4 y	Lower BP goal was not associated with slower GFR decline rate or reduction in composite renal outcome (decrease in GFR by ≥ 50% or ≥ 25 mL/min/ 1.73 m², ESRD, or death). In subgroup of pts with proteinuria >0.22 g/g, outcomes had nonsignificant trend favoring lower BP goal.
Long-term follow-up of AASK trial Appel et al., 2010[48]	–	–	–	–	–	Following initial trial, target BP < 130/80 mmHg in both groups Median f/u 10.5 y	Intensive BP control had no effect on composite renal outcome (doubling of SCr, ESRD, or death). In subgroup of pts with proteinuria >0.22 g/g, lower BP goal reduced the risk of renal progression (adjusted HR 0.73, $P = .01$), in contrast to nonproteinuric pts.

Long-term follow-up of AASK trial Ku et al., 2017[49]	–	–	–	– 16% with proteinuria ≥1 g/d	1067	– Median f/u 14.4 y	Strict BP control did not delay the onset of ESRD but may have reduced risk of death (adjusted HR 0.81, P = .03). In subgroup of pts with proteinuria ≥1 g/d, strict BP goal reduced the risk of ESRD (adjusted HR 0.59, 95% CI 0.41–0.85), in contrast to nonproteinuric pts. No interaction was observed between proteinuria and BP control for mortality outcome.
Ramipril Efficacy In Nephropathy 2 (REIN-2) Ruggenenti et al., 2005[50]	Adults (age 18–70 y old) with proteinuric CKD on ACEI and mostly HTN	100%	100% (eGFR ≤ 70 mL/min/ 1.73 m², excluded ESRD)	Proteinuria ≥1 g/d Mean proteinuria 2.9 g/d 36% with proteinuria ≥3 g/d	338	Intensified BP control (BP < 130/80 mmHg) with additional felodipine vs. conventional control (DBP <90 mmHg) Median f/u 1.6 y	Intensified BP control with CCB did not reduce the rate of GFR decline or progression to ESRD. Outcomes were similar in subgroup of pts with proteinuria 1–3 g/d and ≥3 g/d.
Effect of Strict Blood Pressure Control and angiotensin converting enzyme Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) Trial Wühl et al., 2009[51]	Children (age 3–8 y old) with CKD and HTN on ACEI	100%	100% (eGFR 15–80 mL/min/ 1.73 m²)	Mean proteinuria 1.3 g/g 23% with proteinuria ≥1.5 g/g	385	Intensified BP control (24-hr MAP < 50th percentile) with additional non-RAAS antihypertensives vs. conventional control (MAP 50th–95th percentile) Maximum f/u 5 y	Intensified BP control reduced CKD progression (time to 50% reduction in GFR or ESRD) (adjusted HR 0.65, P = .02). Achievement of BP targets and improvement in proteinuria were independent predictors of delayed progression of renal disease.
Halt Progression of Polycystic Kidney Disease (HALT-PKD) Schrier et al., 2014[52]	Adults (age 15–49) with early ADPKD and HTN	100%	100% (eGFR > 60 mL/min/ 1.73 m²)	Median microalbuminuria 18–19 mg/d	558	Low BP target (95–110/60–75 mm Hg) vs. standard target (120–130/70–80 mmHg) Median f/u 6.5 y	Low BP group had significantly lower annual percentage increase in total kidney volume (5.6% vs. 6.6%, P = .006) and experienced improvement (as opposed to worsening) in microalbuminuria, but overall rate of GFR decline was similar between groups. Low BP group had larger decrease in LVMI. Dizziness and lightheadedness were more common in low BP group.

Table 2 (*continued*)

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Intervention, Follow-up Time	Major Outcomes (Intensive BP Control as Compared to Conventional BP Control)
Systolic Blood Pressure Intervention Trial (SPRINT), CKD subgroup Cheung et al., 2017[53]	Older adults (age ≥ 50 y old) with HTN (SBP ≥ 130 mmHg) and increased CV risk, CKD subgroup	100%	100% (eGFR 20–59 mL/min/ 1.73 m^2)	Minimal proteinuria ≤1 g/d or albuminuria ≤600 mg/d Mean microalbuminuria 80.6 mg/g Median microalbuminuria 13.3 mg/g	2646	Intensive BP treatment (SBP < 120 mmHg) vs. standard treatment (SBP < 140 mmHg) Median f/u 3.3 y	Intensive BP control significantly lowered all-cause mortality (adjusted HR 0.72, $P = .04$) and nonsignificantly improved primary CV outcome (ACS, stroke, HF, or CV death; adjusted HR 0.81, $P = .12$) perhaps because of loss of statistical power (results significant for all trial participants with lack of evidence of effect modification by CKD status). Intensive BP control had no effect on composite renal outcome (≥50% reduction in GFR or ESRD) or development of incident albuminuria. Intensive group had higher rate of eGFR decline in initial 6 months (−0.47 vs. −0.32 mL/min/1.73 m^2/y, $P = .03$) likely related to an acute hemodynamic effect, but thereafter rate was very similar although statistically still slightly faster than standard group.
Systolic Blood Pressure Intervention Trial (SPRINT), moderately advanced CKD subgroup Obi et al., 2017[54]	Older adults (age ≥ 50 y old) with HTN (SBP ≥ 130 mmHg) and increased CV risk, moderately advanced CKD subgroup	100%	100% (eGFR 20–44 mL/min/ 1.73 m^2)	Minimal proteinuria ≤1 g/d or albuminuria ≤600 mg/d Median microalbuminuria 25 mg/g	891	Intensive BP treatment (SBP < 120 mmHg) vs. standard treatment (SBP < 140 mmHg) Median f/u 3.3 y	Intensive BP treatment did not reduce primary CV outcome (ACS, stroke, HF, or CV death); CV benefit significantly attenuated with lower eGFR ($P_{interaction} = .019$). Intensive treatment increased the risk of AKI compared to standard treatment (13.9% vs. 8.5%); effect was not significantly modified by eGFR ($P_{interaction} = .179$).

CKD, chronic kidney disease; BP, blood pressure; DM, diabetes mellitus; HTN, hypertension; GFR, glomerular filtration rate; eGFR, estimated GFR; MAP, mean arterial pressure; F/u, follow-up; ESRD, end-stage renal disease; Pts, patients; HR, hazard ratio; SCr, serum creatinine; DBP, diastolic BP; CV, cardiovascular; ADPKD, autosomal dominant polycystic kidney disease; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; ACEI, Angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; SBP, systolic blood pressure; ACS, acute coronary syndrome; HF, heart failure; AKI, acute kidney injury.

[a] If available, prevalence of nondiabetic CKD reported preferentially over nondiabetic characteristic.

outcomes have excluded CKD patients. Furthermore, goal BP trials are especially hindered by smaller sample sizes or shorter follow-up periods, as such shortcomings may result in failure to detect the effects of subtle hemodynamic interventions on clinically important outcomes. The most impactful trials that examined target BP in adult nondiabetic CKD are widely considered to be Modification of Diet in Renal Disease (MDRD), African American Study of the Kidney Disease and Hypertension (AASK) trial, Ramipril Efficacy In Nephropathy 2 (REIN-2), and recently the CKD portion of the Systolic Blood Pressure Intervention Trial (SPRINT).

Evidence Against a Strict BP Target

The landmark MDRD trial completed in 1994 enrolled 840 primarily Caucasian patients (about 85%) with a reduced GFR from nondiabetic causes in nearly all, and followed them for a mean of 2.2 years.[41,56] PKDs and glomerular diseases accounted for almost half of cases. It showed that aggressive BP control (mean arterial pressure [MAP] $\leq$ 92, $\approx$125/75 mmHg) offered no benefit over usual control (MAP $\leq$ 107, $\approx$140/90 mmHg) in limiting the rate of GFR decline or preventing the development of ESRD or death. Interestingly, an interaction was noted with proteinuria such that study participants with higher levels of urinary protein excretion ($\geq$1 g/d for moderately reduced GFR, or $\geq$ 3 g/d for severely reduced GFR), but not those with lesser amounts of proteinuria, appeared to derive benefit from the low BP intervention. Moreover, the margin of benefit seemed to augment with successively higher levels of proteinuria. It should be pointed out, however, that a major criticism of this trial was that 51% of patients in the low BP group received Angiotensin-converting enzyme inhibitor (ACEI) therapy versus 32% in the usual BP group.[57] When follow-up of MDRD was extended to a mean of 10.6 years, a statistically significant difference favoring the low BP target was able to be detected in all patients for the ESRD and combined ESRD/death outcome (adjusted HRs 0.68, 0.77, respectively, both P < .01).[42] Furthermore, the benefit of the low BP target did not depend on the cause of kidney disease and, as previously, extended only to participants with proteinuria $\geq$1 g/d. Unfortunately, it was not possible to ascertain the mechanism underlying this benefit because of lack of follow-up BP measurements after the original trial. At an even more protracted median follow-up time of 19.3 years achieved by linking MDRD enrollees to dialysis and mortality databases, a reduction in ESRD progression with strict BP control was not confirmed, but mortality after ESRD onset was lowered.[43]

Since the pivotal MDRD trial, a number of interventional trials in the nondiabetic CKD population similarly failed to show an improvement in renal prognosis with a strict BP target, yet often raised the possibility of benefit in

proteinuric patients. For example, in the smaller trials by Toto et al.[44] of 87 adults with hypertensive nephrosclerosis and by Schrier et al.[46] of 79 adults with autosomal dominant PKD (ADPKD), strict BP control did not affect progression of CKD. In addition, when a subgroup analysis of CKD patients in the massive Hypertension Optimal Treatment trial was undertaken (2821 subjects with CKD stages 3–4, 93% nondiabetic), assignment to tighter BP targets was not found to significantly improve serum creatinine, mortality, and CV events at the end of the 3.8-year treatment period.[45] It is plausible, although, that loss of statistical power accounted for this result as it contrasted with data from the entire Hypertension Optimal Treatment cohort showing less frequent CV events at lower BP targets.[58]

Perhaps, the most compelling body of direct evidence denying support from a renal standpoint for an aggressive BP target in nondiabetic CKD arose from the AASK trial in 2002.[47] This RCT looked at 1094 African American adults with presumed hypertensive renal disease associated with relatively modest proteinuria $\leq$2.5 g/g (mean proteinuria 0.30–0.35 g/g, corresponding to 0.38–0.63 g/d) and randomized them in a multifactorial fashion to ACEI, calcium channel blocker (CCB), or beta blocker therapy and to two different BP targets (MAP $\leq$ 92, $\approx$125/75 mmHg or MAP 102–107, latter $\approx$ 140/90 mmHg), adding other antihypertensives as necessary to achieve BP goals. The hypothesis was that tighter BP control may be more suited for black patients with CKD given their known faster renal function decline compared with white patients with similar BPs. The distribution of antihypertensive agents at baseline, most notably ACEIs, was similar between the BP target groups. Over 3.8 years of median follow-up, the lower BP goal was not preferred over usual BP control in slowing GFR loss (the primary outcome) or reducing renal events (the secondary outcome, a composite of decrease in GFR by $\geq$ 50% or $\geq$ 25 mL/min/1.73 m^2, ESRD, or death). However, the subgroup of patients with proteinuria equivalent to >0.30 g/d (357 patients representing about a third of the entire cohort) had a nonsignificant trend toward improved clinical outcomes favoring the lower BP goal. Adverse events including mortality, CV events, and hypoperfusion episodes (dizziness, lightheadedness, or syncope) did not differ significantly between the groups. In a subsequent phase of the trial in which follow-up was extended to a median of 10.5 years by targeting a BP < 130/80 mmHg in both groups with ACEI/angiotensin receptor blocker (ARB) therapy, intensive BP control still did not reduce progression of renal disease (instead defined as doubling of serum creatinine, ESRD, or death) overall, yet in proteinuric patients, a significant reduction in CKD progression was observed (adjusted HR 0.73, P = .01).[48] When endstage outcomes were examined at an even longer median follow-up of 14.4 years by linking AASK participants to dialysis and mortality databases, ESRD events were again

not discovered to occur less frequently with the low BP goal except in proteinuric individuals (n = 175 with proteinuria ≥1 g/d; adjusted HR 0.59, 95% CI 0.41–0.85), while mortality may have decreased (adjusted HR 0.81, P = .03).[49] Combining AASK trial data with MDRD data yielded similar results in terms of ESRD and mortality.[49]

Given the prospect of an advantage of tight BP control in proteinuric nondiabetic CKD, the REIN-2 trial was designed to evaluate whether intensified BP control offered additional benefit on top of ACEI therapy in proteinuric individuals.[50] In the 338 patients studied required to have proteinuria ≥1 g/d, mean proteinuria was 2.9 g/d. After background treatment with ramipril, the patients were randomly assigned to intensified BP control achieved with additional felodipine therapy (BP < 130/80 mmHg) or conventional control with placebo (DBP <90 mmHg) and followed for the primary outcome of ESRD over a median of 1.6 years. Throughout the study, a good mean BP separation of 4.1/2.8 mmHg was maintained. The trial was stopped early as the conclusion was that further BP reduction with felodipine offered no additional protection against renal disease progression, even in patients with higher levels of proteinuria ≥3 g/d. Although mortality was similar between the groups, nonfatal serious adverse events such as stroke or myocardial infarction appeared to occur more often in the intensified control group compared with conventional BP control group (22.2% vs. 14.9%; significance data not available). The results of REIN-2, therefore, conflicted with the prior MDRD and AASK reports, which had suggested potential benefit of a stricter BP target in proteinuric CKD. As a matter of fact, REIN-2 was better designed to assess the effect of proteinuria as an interaction variable.[57] The REIN-2 authors additionally performed a pooled analysis that included other nondiabetic nephropathy trials AASK and MDRD as well as the Irbesartan Diabetic Nephropathy Trial, taking into account whether ACEI therapy was intensified in the intensified BP group or comparable between the BP arms.[50] The determination was that the key component of intensified BP control in providing renoprotection was more effective inhibition of RAAS, rather than more effective BP reduction.

Strictly speaking, the largest body of data on clinical outcomes actually emanates from subgroup analyses of SPRINT trial participants with CKD. SPRINT evaluated nondiabetic older adults (age ≥ 50 years old) with hypertension and increased CV risk.[59] Although severe CKD was excluded, milder CKD was permitted (eGFR 20–59 mL/min/1.73 m^2, minimal proteinuria ≤1 g/d, or albuminuria ≤600 mg/d), allowing for the extraction of a formidable 2646 patients with nondiabetic CKD stages 3–4 associated with a mean microalbuminuria of 80.6 mg/g (28.3% of the original 9361 enrollees).[53] The etiologies of CKD, unfortunately, were not documented. Races other than Caucasians were well represented in roughly one-third of the cases. Over a median follow-up of 3.3 years,

intensive BP control targeting SBP <120 mmHg significantly lowered the secondary outcome of all-cause mortality (adjusted HR 0.72, P = .04), in line with the main cohort results, but nonsignificantly improved the primary CV outcome (acute coronary syndrome, stroke, acute decompensated heart failure, or death from CV causes; adjusted HR 0.81, 95% CI 0.63–1.05, P = .12) compared with standard treatment aiming for SBP < 140 mmHg.[53] Underpowering clearly limited interpretation here. In agreement with prior studies, intensive treatment did not slow progression of CKD, as denoted by the composite renal outcome (≥50% reduction in GFR or ESRD; adjusted HR 0.90, 95% CI 0.44–1.83) or development of incident albuminuria, although it was also not viewed to exert a substantial deleterious effect on kidney outcomes. Although the intensive group initially had a slightly higher rate of eGFR decline (−0.47 vs. −0.32 mL/min/1.73 m^2/yr, P = .03) and an increased risk of a 30% decline in eGFR at 6 months after randomization, the subsequent eGFR decline rate was very similar between the groups. This faster GFR decline rate within the first 6 months of the trial was believed to be related to hemodynamic changes in the renal microcirculation after acute BP lowering. Most serious adverse events were comparable between BP groups (eg, hypotension, syncope, bradycardia, injurious falls), but potassium abnormalities (hypokalemia, hyperkalemia) and acute kidney injury (AKI, defined by documentation of this diagnosis at a hospitalization or emergency visit) were more common with intensive treatment, findings which should not be dismissed. Some have contended that adverse events stemming from hypotension might be even higher if an SBP <120 mmHg was applied in clinical practice given the fact that SBP recorded in SPRINT, and other randomized trials was likely ∼5–10 mmHg lower than that measured in routine clinical practice (ascribed to a difference in measurement technique).[60] The value of intensive BP lowering in CKD was evaluated further in a subsequent post hoc analysis of 891 SPRINT participants with more advanced renal dysfunction characterized by eGFR ≥20 to <45 mL/mL/min/1.73 m^2 (median microalbuminuria 25 mg/g).[54] Here, a nonsignificant reduction in the CV outcome was again discovered (HR 0.92, 95% CI 0.62–1.38). However, CV events appeared to display a significant interaction with GFR such that the CV benefit from intensive treatment attenuated with lower eGFR ($P_{interaction}$ = .019). The risk AKI was also greater. It should be stressed that results from this subgroup analysis (an even smaller subset of the less than one-third of study participants with CKD) must be interpreted with great caution.

Evidence for a Strict BP Target

A handful of RCTs have displayed favorable effects of strict BP control in nondiabetic CKD. The benefits that have been noted are primarily CV in nature. In the earlier

mentioned trial of ADPKD patients by Schrier et al.[46], a greater extent of left ventricular hypertrophy (LVH) reversal indicative of a cardioprotective effect was suggested with rigorous BP control. In the subsequent and larger Halt Progression of PKD (HALT-PKD) trial which examined 558 ADPKD patients, a low BP target was associated with a significantly lower annual percentage increase in total kidney volume relative to a standard target (5.6% vs. 6.6%, $P = .006$).[52] Although the low BP target did not preserve overall GFR better than standard BP control and led to an increased incidence of dizziness and light-headedness, there was a nonsignificant inclination toward improvement in eGFR (eGFR decline rate improved in long term but worsened in short term), a reduction in urinary albumin excretion by 3.8% compared with an increase with the standard target ($P < .001$), and a decrease in left ventricular mass index. The Cardio-Sis trial corroborated such cardiac effects, finding that strict BP control reduced the rate of LVH along with CV events within 1111 nondiabetic patients with systolic hypertension but no renal dysfunction.[61] In pediatric patients, intensified BP control was shown in The Effect of Strict Blood Pressure Control and angiotensin converting enzyme Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial to alleviate CKD progression (time to 50% reduction in GFR or ESRD)[51]; although it is unlikely these data can be applied to adults who have very different BP profiles than children as well as causes and risk factors for CKD. Finally, in SPRINT participants who had an eGFR $\geq$20 to <60 mL/mL/min/1.73 m^2, intensive BP control significantly lowered the secondary outcome of all-cause mortality by 28% (adjusted HR 0.72, $P = .04$) and conceivably also improved the primary CV outcome by a nonsignificant margin (adjusted HR 0.81, $P = .12$).[53] The argument was that statistical significance would have been reached, as in the entire cohort, if adequate power were present because CKD status (as a dichotomous variable) did not exhibit effect modification. It has been suggested here that the ''hard'' outcome of mortality may more aptly reflect overall clinical status in CKD because it balances the competing effects of multiple clinical outcomes (eg, GFR decline or CV events) on all-cause death.[62] In addition, a prior meta-analysis examining more versus less intensive BP-lowering regimens similarly found that CKD status (eGFR < 60 mL/min/1.73 m^2) and eGFR (as a continuous variable) did not significantly interact with treatment effect on major CV events.[63] Although the smaller analysis of SPRINT participants with eGFR $\geq$20 to <45 mL/mL/min/1.73 m^2 also found a nonsignificant decrease in CV events (HR 0.92, 95% CI 0.62–1.38), it was instead reported that eGFR (as a continuous variable) modified the effects of intensive BP control on CV events.[54] Certainly, further investigation is warranted since inferences drawn from CKD subgroups are impaired by loss of statistical power.

Meta-Analyses and Systematic Reviews

Various meta-analyses and systematic reviews have been published within the realm of nondiabetic renal disease. In 2003, Jafar et al.[64] pooled data on 1860 nondiabetic patients (not including MDRD, AASK, or REIN-2). The mean duration of follow-up was 2.2 years. By themselves, SBP <110 mmHg, rising SBP >140 mmHg (with a nonsignificant trend beginning at > 130 mmHg), and proteinuria $\geq$2.0 g/d represented risks for kidney disease progression (defined as doubling of serum creatinine or ESRD). On testing for interactions between BP and urine protein excretion, the optimal SBP was determined to be 110–129 mmHg. Strikingly, only patients with urinary protein excretion $\geq$1 g/d ($P < .006$) but not those with lower proteinuria, experienced a progressively higher RR for renal disease progression above an SBP of 130 mmHg.[64]

Following the completion of MDRD, AASK, and REIN-2, a systematic review of these trials totaling 2272 nondiabetic CKD participants reached the conclusion that a BP target of <125–130/75–80 mmHg was not more beneficial than <140/90 mmHg in the improvement of renal and CV outcomes but could be considered in patients with proteinuria >300–1000 mg/d based on lower quality evidence (subgroup analyses of MDRD and AASK but not REIN-2).[57] Of note, participants in the low target groups were noted to require more antihypertensive medications and have a slightly higher rate of adverse events. A later meta-analysis that coalesced 11 trials (including MDRD, AASK, and REIN-2) to comprise over 9000 CKD participants who were mostly nondiabetic at a rate of 55% came to essentially the same conclusion—an intensive BP-lowering strategy reduced the risk of renal progression (defined as a composite of doubling of serum creatinine level and 50% decline in GFR, or ESRD) by 27% compared with a standard regimen in patients with proteinuria (>300 mg/d) but had no effect in those without proteinuria (Figure 2).[65] Baseline proteinuria here was verified to exert significant effect modification ($P_{interaction} = .006$). There was also no effect on the risk of CV events or death. It has been suggested that greater benefits from aggressive BP control may be seen in proteinuric rather than nonproteinuric CKD patients because proteinuria may reflect increased glomerular pressure transmission or may be a biologic marker of enhanced intrinsic glomerular susceptibility to hypertensive renal damage.[66]

In a meta-analysis of 26 RCTs examining the CV effects of different BP-lowering regimens, active treatment with various antihypertensives consistently reduced the risk of major CV events compared with placebo in the 30,295 individuals with CKD (defined as eGFR < 60 mL/mL/min/1.73 m^2; HR 0.83, 95% CI 0.76–0.90), without evidence for heterogeneity according to eGFR.[63] However, in the smaller analysis of trials comparing more versus less intensive BP lowering to comprise 5073 individuals with CKD
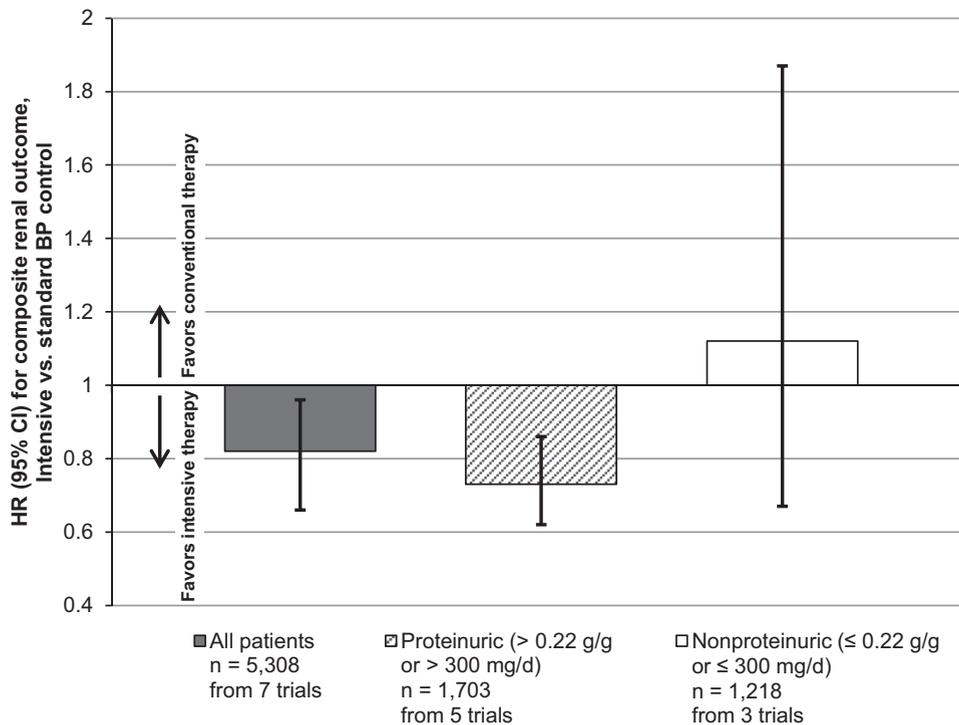
Figure 2. Effect of intensive vs. standard BP control on CKD progression (composite of 50% decline in GFR and doubling of SCr, or ESRD) according to proteinuric classification (data from meta-analysis of reference 60). HR, hazard ratio; CI, confidence interval; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; SCr, serum creatinine; ESRD, end-stage renal disease.

(over 90% nondiabetic), significant improvement in the CV event rate was not shown.[63] Most recently, a meta-analysis was performed that included close to 16,000 patients from 18 RCTs in CKD Stages 3–5, among them the SPRINT trial.[62] Half of the trials excluded diabetes in some form (six excluded type 1 diabetes; three excluded all diabetes). Consistent with SPRINT's discovery in the CKD subset, more intensive BP control resulted in 14.0% lower risk of mortality (OR, 0.86; 95% CI 0.76–0.97; $P = .01$) compared with less intensive control—a revelation that was without significant heterogeneity and appeared consistent across multiple subgroups. It should be pointed out, however, that the overall intensity of BP reduction achieved was less than that attained in SPRINT (mean achieved SBP 132 mmHg and 140 mmHg in intensive and standard treatment arms, respectively, versus 121.5 mmHg and 134.6 mmHg in SPRINT).[59,62]

Given the alarmingly high CVD-related mortality in CKD and the fact that intensive BP management seemed to offer the same mortality and CVD benefit seen in the full SPRINT cohort, the 2017 practice guidelines from American College of Cardiology/American Heart Association Task Force recently recommended a BP target of <130/80 mmHg in CKD patients, particularly those with a 10-year ASCVD risk ≥ 10%.[67] It was recognized, however, that such patients may be at greater risk of complications from intensive BP treatment. Therefore, incremental

BP reduction with careful monitoring of physical and kidney function may be a more reasonable approach in this population.

24-Hour BP Control

In any discussion about goal BP, control of BP over a 24-hour period is an important treatment consideration. Almost all studies which have made inferences between BP levels and clinical outcomes have assumed that BP readings (often the average of multiple readings) obtained at limited points in time reflect overall, or longitudinal, BP control. In interventional studies, this assumption may not present a major issue because BPs were often followed at interval periods of time. However, in most observational studies, BPs were only available at baseline. Reliance upon a single measure of BP may be especially problematic because associations may attenuate with extended follow-up. This was illustrated, for example, by Rosansky et al.[22] in nondiabetics and by Anderson et al.[33] in a majority-nondiabetic CKD cohort, who both found that time-averaged BP was more strongly correlated with renal outcomes than single baseline measures. Dependence on a relatively limited number of BP measurements in clinical settings may result in the misclassification of hypertensive persons as nonhypertensive (ie, masked hypertension) or normotensive individuals as hypertensive (ie, white-coat hypertension), or

even in failure to detect BP variability (within-visit or visit-to-visit) or nondipping in nighttime BP. This may lead to an underestimation or overestimation of the impact of BP on outcomes. In CKD particularly, the matter is further complicated by the higher prevalence of masked and white-coat hypertension as well as the higher probability of BP variability and nondipping.[68–70] This problem can be well illustrated by a cross-sectional analysis of the AASK cohort in which, for example, 70% of the patients believed to have controlled clinical BP actually had masked hypertension according to Ambulatory Blood Pressure Monitoring data, and in another cross-sectional analysis of hypertensive CKD patients, where BP misclassification was found to be present in one of every three hypertensive patients.[71,72] BP variability (ie, large BP deviations from the mean) may also influence outcomes, as visit-to-visit variability has been linked with poorer renal and CV outcomes in nondiabetic CKD.[69,73,74] Ideally, 24-hour Ambulatory Blood Pressure Monitoring is required to reliably assess BP levels and fully comprehend its relationship to intended targets. However, widespread adoption of this method is understandably impractical and does not translate to everyday clinical practice. Some of the remedies that have been proposed to improve 24-hour BP control include nighttime dosing of medications particularly in nondippers and the use of beta blockers in high BP variability, although the ultimate clinical effects of such interventions are presently unclear.[69,75–77]

Choice of Antihypertensive Drug Therapy

Renin-Angiotensin-Aldosterone System (RAAS) Antagonists

RAAS antagonists have been well documented to delay the progression of CKD in diabetic and proteinuric nephropathies as well as lessen the risk of CV morbidity and mortality attached to chronic renal disease.[78,79] Apart from a BP-lowering effect, RAAS blockers preserve kidney function through several nonhemodynamic actions.[5,80–82] First, they decrease intraglomerular pressure by preferentially dilating the efferent arteriole, mediated by AT2 inhibition as well as potentiation of bradykinin in the case of ACEIs. Second, they reduce proteinuria by normalizing intrarenal hemodynamics and directly affecting glomerular basement membrane permeability. Finally, they downregulate profibrotic mediators of RAAS, among which include AT2 and aldosterone. As in diabetic nephropathy, ACEI/ARB use in nondiabetic nephropathy has also been proven to provide benefit (Table 3). However, the preponderance of evidence supporting their use is based on cohorts containing proteinuric patients or a mixture of proteinuric and nonproteinuric patients. As a result, there is a severe dearth of studies that have directly (by trial design) examined the role

of ACEI/ARBs in nonproteinuric (<0.5–1 g/d), nondiabetic CKD.

The utility of ACEI in nondiabetic nephropathy was first established by Maschio et al.[83] in 1996, who demonstrated that benazepril reduced the progression of renal disease (defined as doubling of serum creatinine and dialysis need) compared with placebo in 583 nondiabetic CKD patients from a variety of etiologies, most commonly glomerulopathies (RR reduction 53%, $P < .001$). Notably, benazepril was not effective in subgroups of polycystic disease and proteinuria <1 g/d. A major limitation of this trial, however, was that attained BP was significantly lower in the ACEI group (mean BP 135/84 vs. 144/88 mmHg). Soon afterward, the REIN trial was published which confirmed that the benefit of ACEIs extended to both sub-nephrotic (1–2.9 g/d) and nephrotic (≥3 g/d) proteinuric nondiabetic CKD.[84,85] Importantly, the renoprotective effect of this drug appeared to be independent of the BP-lowering effect (since treatment groups achieved similar BP control and results remained significant after adjustment for changes in BP), a discovery that since been duplicated in several other trials.[47,87,98] Moreover, the REIN trial provided support for ACEI use in advanced renal disease because patients with non-nephrotic proteinuria and a baseline eGFR ≤45 mL/min/1.73 m^2 and subjects with the lowest eGFR tertile 11–33 mL/min/1.73 m^2 in a post hoc analysis gained from ramipril treatment.[50,99] The safety and efficacy of ACEIs in advanced nondiabetic renal insufficiency has also been substantiated by Hou et al.[87], where benazepril conferred renal benefits down to an eGFR of 20 mL/min/1.73 m^2 without significantly increasing major adverse effects or hyperkalemia. Following the REIN trial, AASK in 2002 attempted to answer the question of whether ACEIs should be initiated over other types of antihypertensive agents in African–Americans with hypertensive nephrosclerosis, as up until that point they had been used less often in this demographic.[47] Indeed, the hypothesis that ACEIs would be renoprotective in African–Americans was proven—ramipril reduced the risk of composite renal outcome (defined as decrease in GFR by ≥ 50% or ≥ 25 mL/min/1.73 m^2, ESRD, or death) compared with metoprolol and amlodipine. Although GFR decline rate was unaffected by ramipril, in the subgroup of patients with proteinuria >0.22 g/g (corresponding to approximately > 300 mg/d), it both reduced the risk of the composite end point by 48% and slowed GFR decline by 36% relative to amlodipine.[86]

With respect to other RAAS blockers, ARBs have been shown to be as beneficial as ACEIs on kidney disease outcomes.[100,101] Evidence supporting equivalent efficacy in nondiabetic nephropathies was lent, for instance, by the Renoprotection of Optimal Antiproteinuric Doses (ROAD) trial and CKD subgroup of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) trial, in which ARBs

Table 3

Select randomized controlled trials (RCTs) evaluating antihypertensive agent choice and renal or cardiovascular outcomes in nondiabetic chronic kidney disease (CKD) patients

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Comparison, Follow-up Time	Major Findings
Renin-Angiotensin-Aldosterone system (RAAS) Antagonists							
Maschio et al., 1996[83]	Adults (age 18–70 y old) with CKD and mostly HTN >80%	96% (excluded insulin-dependent DM)	100% (eGFR 30–60 mL/min/ 1.73 m²)	Mean proteinuria 1.8 g/d	583	Benazepril vs. placebo Maximum F/u 3 y	Benazepril reduced risk of combined CKD outcome (doubling of SCr and dialysis need) by 53% but was also associated with lower mean attained BP (135/84 vs. 144/88 mmHg). In subgroup of pts with proteinuria >1 g/d, reduction in CKD progression was greater than less proteinuric pts. Benazepril was not effective in pts with polycystic disease.
Ramipril Efficacy In Nephropathy (REIN) Remuzzi et al., 1997[84]	Adults (age 18–70 y old) with CKD, nephrotic-range proteinuria, and mostly HTN in >85%	100%	100% (eGFR 20-70 mL/min/ 1.73 m²)	Proteinuria ≥3 g/d Mean proteinuria 5.3 g/d	166	Ramipril vs. placebo Mean f/u 1.3 y	In pts with nephrotic proteinuria, ramipril reduced rate of GFR decline, proteinuria, and combined end point for CKD progression (doubling of SCr or ESRD), but did not decrease CV events. Renoprotective effect appeared to exceed that expected by BP lowering alone (BP control similar between groups; results remained significant after adjustment for changes in BP).
Ramipril Efficacy In Nephropathy (REIN) Ruggenenti et al., 1999[85]	Adults (age 18–70 y old) with CKD, non-nephrotic proteinuria, and mostly HTN in >80%	100%	100% (eGFR 20–70 mL/min/ 1.73 m²)	Proteinuria ≥1 and <3 g/d Mean proteinuria 1.7 g/d	186	Ramipril vs. placebo Median f/u 2.6 y	In pts with non-nephrotic proteinuria, ramipril significantly reduced progression to ESRD and progression to nephrotic proteinuria but did not reduce the rate of GFR decline or CV events.
African American Study of Kidney Disease and Hypertension (AASK) Wright et al., 2002[47,86]	African–American adults (age 18–70 y old) with presumed hypertensive nephrosclerosis	100%	100% (eGFR 20–65 mL/min/ 1.73 m²)	Proteinuria ≤2.5 g/g Mean proteinuria 0.30-0.35 g/g (corresponding to 0.38-0.63 g/d) Median proteinuria	1094	Metoprolol vs. ramipril vs. amlodipine Median f/u 4 y	In entire cohort, ACEI reduced the risk of composite renal outcome (decrease in GFR by ≥ 50% or ≥ 25 mL/min/1.73 m², ESRD, or death) compared to β-blocker and CCB but not GFR decline rate. Similar BP measurements between groups.

Table 3 (*continued*)

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Comparison, Follow-up Time	Major Findings
(TRANSCEND), CKD subgroup Tobe et al., 2010[89]							
Other antihypertensives							
Nephros Study Herlitz et al., 2001[90]	Adults (age 18–74 y old) with CKD and HTN on diuretic and β-blocker	100%	100% (GFR below age-adjusted normal, excluded GFR < 10 mL/min/1.73 m²)	Mean microalbuminuria 365–530 mg/d	158	Ramipril vs. felodipine vs. ramipril + felodipine Mean f/u 1.5–1.8 y	Groups containing ramipril had slower GFR decline rate than felodipine. Combination of felodipine and ramipril did not slow GFR loss more than ramipril alone. Felodipine was associated with rise in albuminuria.
PROCOPA Study group Ruilope et al., 2001[91]	Subjects (average age 43) with proteinuric primary renal disease and HTN	100%	100% (eGFR ≥ 50 mL/min/1.73 m²)	Proteinuria ≥1 g/d Mean proteinuria 4.2-–5.3 g/d	119	Atenolol vs. trandolapril vs. verapamil vs. verapamil + trandolapril Maximum f/u 0.5 y	Verapamil nonsignificantly reduced proteinuria mildly (by 6.2% when used alone and by 8.3% when combined with trandolapril). Only trandolapril significantly reduced proteinuria. No difference in GFR between arms.
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), nondiabetic CKD subgroup Rahman et al., 2005[92]	Older adults (age ≥ 55 y old) with HTN and increased CV risk, nondiabetic CKD subgroup	100%	100% (eGFR < 60 mL/min/1.73 m², excluded SCr > 2 mg/dL)	N/a	3774	Chlorthalidone vs. amlodipine vs. lisinopril Mean f/u 4.9 y	No significant difference between ACEI, CCB, and diuretic in risk of ESRD or composite renal end point (ESRD or ≥ 50% decline in GFR).
Long-term follow-up of ALLHAT, nondiabetic CKD subgroup Rahman et al., 2012[93]	–	–	–	–	3515	– Mean f/u 8.8 y	No significant difference between ACEI, CCB, and diuretic in CV outcomes (CAD, CVD, stroke, HF), mortality, or ESRD.

Combination therapy							
Bianchi et al., 2006[94]	Subjects (average age 55) with chronic proteinuric glomerulonephritis on ACEI/ARB and mostly HTN in >85%	100%	100% (eGFR 34–116 mL/min/1.73 m²)	Proteinuria ≥1 g/g Mean proteinuria 2.1 g/g	165	Spironolactone vs. conventional therapy (no placebo control) Maximum f/u 1 y	Spironolactone added to conventional ACEI/ARB therapy decreased mean proteinuria by 58% and reduced GFR decline rate after 1 mo. Spironolactone was associated with increased risk of hyperkalemia.
Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), CKD subgroup Tobe et al., 2010[89]	Older adults (age ≥ 55 y old) with increased CV risk and mostly HTN in >75%, CKD subgroup	56%	100% (eGFR < 60 mL/min/1.73 m², excluded SCr > 3 mg/dL)	Mean microalbuminuria 52 mg/g 21% with microalbuminuria 11% with macroalbuminuria	5623	Telmisartan vs. ramipril vs. telmisartan + ramipril Median f/u 4.7 y	Dual therapy with ACEI and ARB increased risk of renal progression (doubling of SCr or ESRD) compared to monotherapy, especially in albuminuric pts. Combination therapy led to more dialysis-requiring AKI and hyperkalemia. No benefit of dual therapy on CV outcomes (composite of CV death, MI, stroke, or hospitalization for HF).
Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, CKD subgroup Bakris et al., 2010[95]	Older adults (age ≥ 55 y old) with increased CV risk and HTN, CKD subgroup	41%	100% (eGFR ≤ 55 mL/min/1.73 m²)	Mean microalbuminuria 29 mg/g 53% with microalbuminuria ≥30 mg/g	1093	Benazepril + amlodipine vs. benazepril + HCTZ Mean f/u 2.9 y	Benazepril/amlodipine group had lower CKD progression (doubling of SCr or ESRD) and lower combined end point of CKD progression and mortality than benazepril/HCTZ group.
Woo et al., 2014[96]	Subjects (average age 55) with CKD and many HTN in >45%	100%	100% (eGFR 30–60 mL/min/1.73 m² or proteinuria ≥1 g/d)	Proteinuria ≥1 g/d if GFR not reduced Mean proteinuria 1.3 g/d	155	Aliskiren vs. losartan vs. aliskiren + losartan Maximum f/u 3 y	Combination therapy with DRI and ARB was not more effective than DRI or ARB alone in reducing primary renal end point (CKD stage 5 or ESRD), GFR decline rate, or proteinuria. Hyperkalemia was a major problem in combination group.

Table 3 (*continued*)

Study, Year	Patient Population	Nondiabetic[a], %	CKD, %	Proteinuria	No. of Patients	Comparison, Follow-up Time	Major Findings
Halt Progression of Polycystic Kidney Disease (HALT-PKD) Torres et al., 2014[97]	Adults (age 18–64 y old) with late ADPKD and HTN	100%	100% (eGFR 25–60 mL/min/ 1.73 m²)	Median microalbuminuria 29 mg/d	486	Lisinopril + telmisartan vs. lisinopril + placebo Mean f/u 5.2 y	ARB addition to ACEI did not improve primary composite outcome (50% reduction in GFR, ESRD, or death), rate of GFR decline, urinary albumin excretion, or BP control. AKI and hyperkalemia occurred with similar frequency in each group.

CKD, chronic kidney disease; HTN, hypertension; DM, diabetes mellitus; GFR, glomerular filtration rate; eGFR, estimated GFR; F/u, follow-up; SCr, serum creatinine; BP, blood pressure; Pts, patients; ESRD, end-stage renal disease; CV, cardiovascular; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; MI, myocardial infarction; HF, heart failure; CAD, coronary artery disease; CVD, cardiovascular disease; ARB, angiotensin II receptor blocker; AKI, acute kidney injury; HCTZ, hydrochlorothiazide; DRI, direct renin inhibitor; ADPKD, autosomal dominant polycystic kidney disease.

[a] If available, prevalence of nondiabetic CKD reported preferentially over nondiabetic characteristic.

displayed similar improvement in the combined renal end point (doubling of creatinine, ESRD, or death) compared with ACEIs but had no effect on CV outcomes.[88,89] The role of mineralocorticoid antagonists (MRAs) and direct renin inhibitors as add-on therapy to ACEI/ARBs is discussed in the combination section below.

Meta-Analyses and Systematic Reviews

A multitude of meta-analyses has validated the utility of ACEIs in nondiabetic renal disease. In a meta-analysis of trials that compared ACEIs to other antihypertensives and comprised 1124 patients among whom 50% had nondiabetic renal disease, it was concluded that ACEIs conferred the most potent antiproteinuric effect.[102] Furthermore, their antiproteinuric response was above and beyond that attributable to their BP-lowering effect. In a meta-analysis of 10 RCTs amounting to 1594 patients, it was revealed that ACEIs were more effective than other antihypertensive agents in reducing the progression of nondiabetic CKD to ESRD (RR 0.7, 95% CI 0.51–0.97) and did not increase the mortality.[103] In another meta-analysis of 1389 subjects with overt proteinuria and renal insufficiency from a variety of causes (70% nondiabetic), ACEI treatment decreased the risk of doubling of serum creatinine concentration or ESRD development by 40% compared with placebo (RR 0.60, 95% CI 0.49–0.73).[104] In a systematic review of people with albuminuria, both ACEIs and ARBs reduced several measures of renal disease progression (doubling of serum creatinine, development of ESRD, and progression of microalbuminuria to macroalbuminuria) compared with placebo.[105]

Although it might have appeared before the year 2000 that all nondiabetic CKD gained from ACEI therapy, it was not until 2001 when Jafar et al.[106] pooled data on 1860 nondiabetic renal disease patients that substantial evidence came forth suggesting an interaction between ACEI efficacy and proteinuria. Unsurprisingly, antihypertensive regimens that included ACEIs, compared to those that did not, significantly slowed kidney disease progression (defined as doubling of serum creatinine or ESRD) over a mean follow-up duration of 2.2 years (13.2% vs. 20.5%, RR 0.70, 95% CI 0.55–0.88). However, a significant interaction was detected between baseline urinary protein excretion and ACEI therapy such that patients with greater proteinuria benefited more from ACEI therapy ($P = .001$). Although the effect appeared robust above proteinuria levels of approximately 0.5 g/d, it was inconclusive at lesser values. A separate analysis of the 142 patients with PKD came to the same conclusion, that is, ACEI effectiveness on CKD progression which enhanced as proteinuria ascended. The findings prompted a later analysis in 2007 in which patients were stratified according to their baseline urinary protein excretion.[107] Sure enough, only patients with proteinuria ≥500 mg/d (61% of subjects) were found

to benefit from treatment. Conversely, ACEI treatment did not offer an advantage to patients with proteinuria <500 mg/d, even when the risk for kidney disease progression was relatively high. Thus, in PKD, the presence of proteinuria rather than PKD status may have been the determinant of benefit in this population since the condition is typically characterized by low-grade proteinuria and has not been previously noted to respond to ACEIs significantly.[23,83,108]

Calcium Channel Blockers

CCBs are among the other antihypertensives that have indicated potential in improving renal outcomes in nondiabetic CKD (Table 3). CCBs are known to have differential effects depending on their classification and thus antihypertensive mechanism—dihydropyridines act by vasodilation along with chronotropic effect, whereas nondihydropyridine CCBs have less of a vasodilatory effect but slow contractility and conduction.[109] Despite similar efficacy between subclasses of calcium antagonists in lowering BP, dihydropyridine CCBs have had variable effects on proteinuria, whereas nondihydropyridine CCBs have consistently exhibited a reduction in proteinuria, by about 30% on average when used as monotherapy or 39% when combined with RAAS antagonists.[102,110–112] Despite the potential for an antiproteinuric effect, preservation of renal function has not been validated in the short term and has yet to be revealed in the long term, where data are profoundly lacking. For instance, lack of efficacy in slowing GFR loss more than ACEI was illustrated for felodipine in the Nephros and REIN-2 studies, for amlodipine in the AASK trial, and for verapamil in the PROCOPA study even when there was a mild reduction in proteinuria.[47,50,90,91] In conflict with these data, a post hoc analysis of over 3000 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial with nondiabetic CKD (eGFR < 60 mL/min/1.73 m^2) found that dihydropyridine CCBs performed equivalently to ACEI and thiazide-like diuretics in the prevention of ESRD over 4.9 years of mean follow-up and CV end points over 8.8 years of mean follow-up.[92,93] However, data from this subgroup analysis should be interpreted with caution. For instance, proteinuria was not available in these patients to assess whether an interaction existed. On the whole, current evidence favors the use of nondihydropyridine CCBs, preferably in combination with ACEI/ARBs, in nondiabetic CKD on the basis of antiproteinuric effects and the absence of demonstrable harm.[111]

Combination Therapy

It is possible that the advantageous effects of the dihydropyridine CCB/ACEI combination, discovered after the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, also extend to the CKD population.[113] In the subgroup of 1093 CKD patients from ACCOMPLISH, 41% of whom were nondiabetic, the benazepril/amlodipine group experienced a significantly lower rate of CKD progression and mortality than the benazepril/hydrochlorothiazide group.[95] However, a meta-analysis of 628 patients with hypertension and CKD (roughly half nondiabetic) came to the alternative conclusion that combining CCBs (both dihydropyridine and nondihydropyridine types) with ACEI/ARB provided no additional renoprotective or CV mortality benefit beyond that which could be achieved with ACEI/ARB monotherapy.[114]

MRAs have shown promise in preserving nondiabetic renal function, as in diabetic CKD. Most studies have only investigated their role as add-on therapy to ACEI/ARB and are deficient in long-term data on renal end points or other hard outcomes such as mortality or CV events. In a meta-analysis of 19 trials in CKD encompassing 1646 patients (six trials with nondiabetic CKD), MRA on top of RAAS inhibition resulted in a significant reduction in mean BP by 5.7/1.7 mmHg and urinary protein excretion by 39%.[115] However, renal end points were not reported in sufficient numbers to analyze, and there was a 3-fold risk of hyperkalemia. Another systematic review and meta-analysis of 11 trials in adult CKD patients found a similar reduction in BP and proteinuria, but this did not translate into an improvement in GFR over the short term (<1 year), and the incidence of hyperkalemia was also 3-fold.[116] In nondiabetic CKD specifically, the effects of the MRA and ACEI/ARB combination can be well exemplified by Bianchi et al.[94]'s study of 165 subjects with proteinuric glomerulonephritis, where spironolactone added to conventional ACEI/ARB therapy decreased mean proteinuria by 58% and reduced GFR decline rate over a maximum of 1 year of follow-up but led to an increased risk of hyperkalemia.

Regarding the combination of ACEIs and ARBs in nondiabetic CKD, the general consensus is that dual therapy is not more efficacious than either agent alone in conserving renal function and has a higher risk of adverse events. The CKD cohort of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, the majority of which enlisted nondiabetic subjects, most convincingly exemplified this point after it found an increased risk of renal disease progression, dialysis-requiring AKI, and hyperkalemic events, as well as a lack of CV benefit.[89] Lack of renal improvement was additionally shown in ADPKD patients in the HALT-PKD trial.[97] The combination of direct renin inhibitors and ACEI/ARB appears to have similar consequences. In one study in nondiabetic renal disease, aliskiren addition to losartan did not retard progression of renal disease at 3 years of follow-up and significantly increased the incidence of hyperkalemia.[96]

Conclusion

From a CV perspective, present evidence seems to favor targeting a more aggressive BP target (BP < 125–130/80 mmHg) in persons with nondiabetic CKD on the basis of mortality benefit and potential CV benefit (SPRINT CKD), including LVH improvement. Although randomized data in this specific circumstance is limited and the risk of adverse events may be higher with intensive treatment, currently available data appear to suggest that net benefit outweighs net harm, especially in view of the fact that CV disease represents the major cause of death in people with CKD. It is possible, although, that CV benefit gained by strict BP control diminishes as GFR deteriorates or that the risk-benefit ratio alters in more advanced CKD (SPRINT CKD). Further study is necessary to fully comprehend the implications of intensive treatment from both a CV and safety standpoint.

From a renal perspective, most data have not supported the maintenance of a strict BP target (<125–130/75–80 mmHg) over a more relaxed target (<140/90 mmHg) in the preservation of nondiabetic renal dysfunction (MDRD, AASK, REIN-2, SPRINT CKD subgroups). Lower quality evidence may advocate for intensive BP lowering in patients with higher grade proteinuria >300–1000 mg/d (AASK and MDRD proteinuric subgroups but not REIN-2), in whom rising benefit commensurate with level of proteinuria has been perceived, and possibly individuals with PKD (HALT-PKD). However, there is no clear-cut proof to date that intensive treatment slows CKD progression, and the risk of AKI may be greater (SPRINT CKD).

Because achieving a lower BP target is more likely to be accompanied by manifestations of hypoperfusion (eg, dizziness/lightheadedness or AKI), goals should still be individualized, and the risks of adverse events versus disease progression weighed accordingly. Further high quality trials in nondiabetic CKD, particularly those designed specifically to assess renal outcomes in the context of proteinuria as a modifier and those intended to evaluate CV outcomes, are necessary to more solidly inform recommendations.

Regarding the choice of antihypertensive therapy, ACEIs and ARBs have revealed strong and consistent benefits in slowing the progression of proteinuric, nondiabetic CKD, but do not appear to offer an advantage in nonproteinuric (<500 mg/d) kidney disease, in which scenario direct evidence is severely lacking. Addition of MRAs to ACEI/ARB therapy can be employed to reduce proteinuria further by about 40% on average, but to date has not been evidenced to result in additional GFR improvement in the short term (<1 year) and carries a higher risk of hyperkalemia. The use of nondihydropyridine CCBs in concert with ACEI/ARBs is an alternative option to potentiate antiproteinuric effect, but further preservation of GFR has also not been demonstrated by this practice. In addition, whether the CV benefit of the dihydropyridine CCB and ACEI/ARB combination (ACCOMPLISH) applies to patients with nondiabetic CKD is unclear as results have been conflicting. Further validation with well-powered, long-term RCTs is required to better understand the implications of combination therapy in nondiabetic renal disease.

References

1. Rao MV, Qiu Y, Wang C, Bakris G. Hypertension and CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES), 1999-2004. Am J Kidney Dis 2008;51(suppl 2):S30–7.
2. United States Renal Data System. 2015 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2015.
3. Atkins RC. The epidemiology of chronic kidney disease. Kidney Int Suppl 2005;(94):S14–8.
4. Ghaderian SB, Hayati F, Shayanpour S, Beladi Mousavi SS. Diabetes and end-stage renal disease; a review article on new concepts. J Renal Inj Prev 2015;4:28–33.
5. Fogo AB. Mechanisms of progression of chronic kidney disease. Pediatr Nephrol 2007;22(12):2011–22.
6. Shankland SJ. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int 2006;69(12):2131–47.
7. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis 1992;20(1):1–17.
8. Hodgkins KS, Schnaper HW. Tubulointerstitial injury and the progression of chronic kidney disease. Pediatr Nephrol 2012;27(6):901–9.
9. Tedla FM, Brar A, Browne R, Brown C. Hypertension in chronic kidney disease: navigating the evidence. Int J Hypertens 2011;2011:132405.
10. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl 2013;3(4):368–71.
11. Drawz PE, Rosenberg ME. Slowing progression of chronic kidney disease. Kidney Int Suppl 2013;3(4):372–6.
12. Thomas MC. Preventing progression of chronic kidney disease: renin–angiotensin–aldosterone system blockade beyond blood pressure. In: Arici M, editor. Management of Chronic Kidney Disease. Berlin, Heidelberg: Springer; 2014.
13. Rüster C, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol 2006;17(11):2985–91.
14. D'Amico G, Bazzi C. Pathophysiology of proteinuria. Kidney Int 2003;63(3):809–25.

15. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol 2006;17(11):2974–84.

16. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med 1998;339(20):1448–56.

17. Williams JD, Coles GA. Proteinuria–a direct cause of renal morbidity? Kidney Int 1994;45(2):443–50.

18. Silverstein DM. Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. Pediatr Nephrol 2009;24(8):1445–52.

19. Saklayen MG, Deshpande NV. Timeline of history of hypertension treatment. Front Cardiovasc Med 2016;3:3.

20. Veterans Administration Cooperative Study Group on Anti-hypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 115 through 129 mmHg. JAMA 1967;202:1028–34.

21. Veterans Administration Cooperative Study Group on Anti-hypertensive Agents. Effects of treatment on morbidity in hypertension: II–results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA 1970;213:1143–52.

22. Rosansky SJ, Hoover DR, King L, Gibson J. The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. Arch Intern Med 1990;150(10):2073–6.

23. Chapman AB, Johnson AM, Gabow PA, Schrier RW. Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1994;5(6):1349–54.

24. Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 1995;25(4 Pt 1):587–94.

25. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996;334(1):13–8.

26. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S. Blood pressure predicts risk of developing end-stage renal disease in men and women. Hypertension 2003;41(6):1341–5.

27. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med 2005;165(8):923–8.

28. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. Nephrol Dial Transplant 2006;21(5):1257–62.

29. Agarwal R. Blood pressure components and the risk for end-stage renal disease and death in chronic kidney disease. Clin J Am Soc Nephrol 2009;4(4):830–7.

30. Peralta CA, Norris KC, Li S, Chang TI, Tamura MK, Jolly SE, et al; KEEP Investigators. Blood pressure components and end-stage renal disease in persons with chronic kidney disease: the Kidney Early Evaluation Program (KEEP). Arch Intern Med 2012;172(1):41–7.

31. Kovesdy CP, Bleyer AJ, Molnar MZ, Ma JZ, Sim JJ, Cushman WC, et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. Ann Intern Med 2013;159(4):233–42.

32. Chiang HP, Lee JJ, Chiu YW, Tsai JC, Hung CC, Hwang SJ, et al. Systolic blood pressure and outcomes in stage 3-4 chronic kidney disease patients: evidence from a Taiwanese cohort. Am J Hypertens 2014;27(11):1396–407.

33. Anderson AH, Yang W, Townsend RR, Pan Q, Chertow GM, Kusek JW, et al; Chronic Renal Insufficiency Cohort Study Investigators. Time-updated systolic blood pressure and the progression of chronic kidney disease: a cohort study. Ann Intern Med 2015;162(4):258–65.

34. Weiss JW, Peters D, Yang X, Petrik A, Smith DH, Johnson ES, et al. Systolic BP and mortality in older adults with CKD. Clin J Am Soc Nephrol 2015;10(9):1553–9.

35. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360(9349):1903–13.

36. Shen L, Ma H, Xiang MX, Wang JA. Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease. Am J Cardiol 2013;112(2):266–71.

37. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP; INDANA Project Steering Committee. INdividual Data ANalysis of Antihypertensive intervention. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. Ann Intern Med 2002;136(6):438–48.

38. Kang YY, Wang JG. The J-curve phenomenon in hypertension. Pulse (Basel) 2016;4(1):49–60.

39. Velasquez MT, Beddhu S, Nobakht E, Rahman M, Raj DS. Ambulatory blood pressure in chronic kidney disease: ready for prime time? Kidney Int Rep 2016;1(2):94–104.

40. Mallamaci F, Tripepi G. Blood pressure variability in chronic kidney disease patients. Blood Purif 2013;36(1):58–62.

41. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary

protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of diet in Renal Disease Study Group. N Engl J Med 1994;330(13):877–84.

42. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 2005;142(5):342–51.

43. Ku E, Glidden DV, Johansen KL, Sarnak M, Tighiouart H, Grimes B, et al. Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease. Kidney Int 2015;87(5):1055–60.

44. Toto RD, Mitchell HC, Smith RD, Lee HC, McIntire D, Pettinger WA. "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. Kidney Int 1995;48(3):851–9.

45. Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. J Am Soc Nephrol 2001;12(2):218–25.

46. Schrier R, McFann K, Johnson A, Chapman A, Edelstein C, Brosnahan G, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. J Am Soc Nephrol 2002;13(7):1733–9.

47. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002; 288(19):2421–31.

48. Appel LJ, Wright JT Jr, Greene T, Agodoa LY, Astor BC, Bakris GL, et al; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363(10):918–29.

49. Ku E, Gassman J, Appel LJ, Smogorzewski M, Sarnak MJ, Glidden DV, et al. BP control and long-term risk of ESRD and mortality. J Am Soc Nephrol 2017;28(2):671–7.

50. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, et al; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet 2005;365(9463):939–46.

51. ESCAPE Trial Group, Wühl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med 2009;361(17):1639–50.

52. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al; HALT-PKD Trial Investigators. Blood pressure in early autosomal dominant polycystic kidney disease. N Engl J Med 2014; 371(24):2255–66.

53. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al; SPRINT Research Group. Effects of intensive BP control in CKD. J Am Soc Nephrol 2017;28(9):2812–23.

54. Obi Y, Kalantar-Zadeh K, Shintani A, Kovesdy CP, Hamano T. Estimated glomerular filtration rate and the risk-benefit profile of intensive blood pressure control among non-diabetic patients: a post hoc analysis of a randomized clinical trial. J Intern Med 2017. https://doi.org/10.1111/joim.12701. [Epub ahead of print].

55. Taler SJ. How does SPRINT (systolic blood pressure intervention trial) direct hypertension treatment targets for CKD? Am J Kidney Dis 2016;68(1): 15–8.

56. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 1995;123(10):754–62.

57. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med 2011;154(8):541–8.

58. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351(9118): 1755–62.

59. Research Group SPRINT, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373(22): 2103–16.

60. Bakris GL. The implications of blood pressure measurement methods on treatment targets for blood pressure. Circulation 2016;134(13):904–5.

61. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, et al; Cardio-Sis investigators. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet 2009; 374(9689):525–33.

62. Malhotra R, Nguyen HA, Benavente O, Mete M, Howard BV, Mant J, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and

meta-analysis. JAMA Intern Med 2017;177(10): 1498–505.

63. Blood Pressure Lowering Treatment Trialists' Collaboration, Ninomiya T, Perkovic V, Turnbull F, Neal B, Barzi F, Cass A, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ 2013;347:f5680.

64. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al; AIPRD Study Group. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med 2003;139(4):244–52.

65. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 2013; 185(11):949–57.

66. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension 2004;44(5):595–601.

67. ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/AS PC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American heart association Task Force on clinical practice guidelines. J Am Coll Cardiol 2017. https://doi.org/10.1161/HYP.00000000000000 65. [Epub ahead of print].

68. Bangash F, Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. Clin J Am Soc Nephrol 2009;4(3): 656–64.

69. Mallamaci F, Minutolo R, Leonardis D, D'Arrigo G, Tripepi G, Rapisarda F, et al. Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease. Kidney Int 2013;84(2):381–9.

70. Agarwal R, Pappas MK, Sinha AD. Masked uncontrolled hypertension in CKD. J Am Soc Nephrol 2016;27(3):924–32.

71. Pogue V, Rahman M, Lipkowitz M, Toto R, Miller E, Faulkner M, et al; African American Study of Kidney Disease and Hypertension Collaborative Research Group. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension 2009;53(1):20–7.

72. Gorostidi M, Sarafidis PA, de la Sierra A, Segura J, de la Cruz JJ, Banegas JR, et al; Spanish ABPM Registry Investigators. Differences between office and 24-hour blood pressure control in hypertensive patients with CKD: a 5,693-patient cross-sectional analysis from Spain. Am J Kidney Dis 2013;62(2): 285–94.

73. Kawai T, Ohishi M, Kamide K, Onishi M, Takeya Y, Tatara Y, et al. The impact of visit-to-visit variability in blood pressure on renal function. Hypertens Res 2012;35(2):239–43.

74. Yokota K, Fukuda M, Matsui Y, Hoshide S, Shimada K, Kario K. Impact of visit-to-visit variability of blood pressure on deterioration of renal function in patients with non-diabetic chronic kidney disease. Hypertens Res 2013;36(2):151–7.

75. Schneider MP, Hilgers KF. What should be the goal blood pressure in nondiabetic chronic kidney disease? Curr Opin Nephrol Hypertens 2014;23(2): 180–5.

76. Carter BL, Chrischilles EA, Rosenthal G, Gryzlak BM, Eisenstein EL, Vander Weg MW. Efficacy and safety of nighttime dosing of antihypertensives: review of the literature and design of a pragmatic clinical trial. J Clin Hypertens (Greenwich) 2014;16(2):115–21.

77. Rahman M, Greene T, Phillips RA, Agodoa LY, Bakris GL, Charleston J, et al. A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. Hypertension 2013;61(1): 82–8.

78. Devonald MAJ, Karet FE. Targeting the renin-angiotensin system in patients with renal disease. J R Soc Med 2002;95(8):391–7.

79. Chiurchiu C, Remuzzi G, Ruggenenti P. Angiotensin-converting enzyme inhibition and renal protection in nondiabetic patients: the data of the meta-analyses. J Am Soc Nephrol 2005;16(Suppl 1):S58–63.

80. Ram CV, Vergne-Marini P. Role of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in the prevention of progression of renal disease. Curr Hypertens Rep 1999;1(5):431–5.

81. Wühl E, Schaefer F. Therapeutic strategies to slow chronic kidney disease progression. Pediatr Nephrol 2008;23(5):705–16.

82. Hasslacher C, Bostedt-Kiesel A, Kempe HP. [ACE inhibitor effects on structure and function of the glomerular basement membrane]. Klin Wochenschr 1992; 69(Suppl 29):39–44 [Article in German].

83. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in progressive renal insufficiency study group. N Engl J Med 1996;334(15):939–45.

84. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal

failure in proteinuric, non-diabetic nephropathy. Lancet 1997;349(9069):1857–63.

85. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999;354(9176):359–64.

86. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al; African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001;285(21):2719–28.

87. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006;354(2):131–40.

88. Hou FF, Xie D, Zhang X, Chen PY, Zhang WR, Liang M, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol 2007;18(6):1889–98.

89. Tobe SW, Clase CM, Gao P, McQueen M, Grosshennig A, Wang X, et al; ONTARGET and TRANSCEND Investigators. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: results from the ONTARGET and TRANSCEND studies. Circulation 2011;123(10):1098–107.

90. Herlitz H, Harris K, Risler T, Boner G, Bernheim J, Chanard J, et al. The effects of an ACE inhibitor and a calcium antagonist on the progression of renal disease: the Nephros Study. Nephrol Dial Transplant 2001;16(11):2158–65.

91. PROCOPA Study Group. Dissociation between blood pressure reduction and fall in proteinuria in primary renal disease: a randomized double-blind trial. J Hypertens 2002;20(4):729–37.

92. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT Jr, Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165(8):936–46.

93. Rahman M, Ford CE, Cutler JA, Davis BR, Piller LB, Whelton PK, et al; ALLHAT Collaborative Research Group. Long-term renal and cardiovascular outcomes in antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) participants by baseline estimated GFR. Clin J Am Soc Nephrol 2012;7(6):989–1002.

94. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int 2006;70(12):2116–23.

95. Bakris GL, Sarafidis PA, Weir MR, Dahlöf B, Pitt B, Jamerson K, et al; ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet 2010;375(9721):1173–81.

96. Woo KT, Choong HL, Wong KS, Tan HK, Foo M, Fook-Chong S, et al. Aliskiren and losartan trial in non-diabetic chronic kidney disease. J Renin Angiotensin Aldosterone Syst 2014;15(4):515–22.

97. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, et al; HALT-PKD Trial Investigators. Angiotensin blockade in late autosomal dominant polycystic kidney disease. N Engl J Med 2014;371(24):2267–76.

98. Ishimitsu T, Akashiba A, Kameda T, Takahashi T, Ohta S, Yoshii M, et al. Benazepril slows progression of renal dysfunction in patients with non-diabetic renal disease. Nephrology (Carlton) 2007;12(3):294–8.

99. Ruggenenti P, Perna A, Remuzzi G; Gruppo Italiano di Studi Epidemiologici in Nefrologia. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results. Ramipril Efficacy in Nephropathy. J Am Soc Nephrol 2001;12(12):2832–7.

100. Laverman GD, Remuzzi G, Ruggenenti P. ACE inhibition versus angiotensin receptor blockade: which is better for renal and cardiovascular protection? J Am Soc Nephrol 2004;15(Suppl 1):S64–70.

101. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med 2008;148(1):30–48.

102. Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, de Jong PE. Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials. Nephrol Dial Transplant 1995;10(11):1963.

103. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. Ann Intern Med 1997;127(5):337–45.

104. Kshirsagar AV, Joy MS, Hogan SL, Falk RJ, Colindres RE. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. Am J Kidney Dis 2000;35(4):695–707.

105. Maione A, Navaneethan SD, Graziano G, Mitchell R, Johnson D, Mann JF, et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macro-albuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrol Dial Transplant 2011;26(9):2827–47.

106. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 2001;135(2):73–87.

107. Kent DM, Jafar TH, Hayward RA, Tighiouart H, Landa M, de Jong P, et al. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. J Am Soc Nephrol 2007;18(6):1959–65.

108. Sharp C, Johnson A, Gabow P. Factors relating to urinary protein excretion in children with autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1998;9(10):1908–14.

109. Triggle DJ. Drug targets in the voltage-gated calcium channel family: why some are and some are not. Assay Drug Dev Technol 2003;1(5):719–33.

110. Derwa A, Peeters P, Vanholder R. Calcium channel blockers in the prevention of end stage renal disease: a review. Acta Clin Belg 2004;59(1):44–56.

111. Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney Int 2004;65(6):1991–2002.

112. Ruggenenti P, Perna A, Benini R, Remuzzi G. Effects of dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). J Am Soc Nephrol 1998;9(11):2096–101.

113. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008; 359(23):2417–28.

114. Huang RS, Cheng YM, Zeng XX, Kim S, Fu P. Renoprotective effect of the combination of renin-angiotensin system inhibitor and calcium channel blocker in patients with hypertension and chronic kidney disease. Chin Med J (Engl) 2016;129(5): 562–9.

115. Currie G, Taylor AH, Fujita T, Ohtsu H, Lindhardt M, Rossing P, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol 2016;17(1):127.

116. Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2009;4(3):542–51.