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Is Nocturnal Blood Pressure Reduction the Secret to Reducing the Rate of Progression of Hypertensive Chronic Kidney Disease?

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Abstract

Hypertension is a significant risk factor for cardiovascular and renal disease. Lowering blood pressure (BP) has been shown to reduce the incidence of cardiovascular disease, but randomized trials have not demonstrated a benefit of lowering BP for the progression of renal disease except in secondary analyses in patients with significant proteinuria. Recently, there has been increasing interest in measuring BP outside of the clinic, using both home and ambulatory blood pressure monitoring (ABPM). ABPM has the advantage of measuring BP throughout both the day and night. Elevated nighttime BP and a lack of decline in BP from day to night (nondipping) are more potent risk factors for cardiovascular and renal outcomes than elevated daytime or clinic BP. Studies have shown that it is possible to lower nighttime BP and restore normal dipping with the administration of antihypertensive medications in the evening, known as *chronotherapy*. Evening administration of antihypertensives not only lowers nighttime BP but also is associated with decreased urinary protein excretion, decreased cardiovascular events, and decreased all-cause mortality. Reducing nighttime BP may slow the progression of chronic kidney disease and may be the key to linking the treatment of hypertension with improved renal outcomes.

Keywords

Hypertension; Chronic renal insufficiency; Ambulatory blood pressure monitoring; Drug chronotherapy; Circadian rhythm; Proteinuria; Nighttime BP; Risk factors

Introduction

High blood pressure (BP) has been identified by the World Health Organization as the leading factor contributing to premature mortality in the world; hypertension is responsible for approximately 7.6 million deaths per year, mostly through cardiovascular and cerebrovascular disease [1]. Additionally, elevated BP is known to exacerbate all forms of chronic kidney disease (CKD) and increase risk for progression to end-stage renal disease (ESRD). It is well established that treating high BP reduces the incidence of cardiovascular disease, but reducing BP has not been shown to reduce the rate of decline in renal function,

except in patients with significant proteinuria. Clinical trials that have evaluated different BP targets have utilized clinic BPs, which are also the main focus of current guidelines for the management of hypertension [2]. More attention is now being paid to other forms of BP measurement, including ambulatory blood pressure monitoring (ABPM), which allows for the assessment of BP throughout both the day and night. This paper briefly reviews the data regarding the reduction in cardiovascular disease associated with treatment of hypertension, discusses the association between hypertension and CKD, reviews the data supporting the use of ABPM to assess risk for cardiovascular and renal disease, and discusses the potential to reduce the rate of progression of hypertensive kidney disease by targeting nocturnal BP.

Treating Hypertension Reduces Cardiovascular Disease

A number of seminal studies conducted more than 30 years ago established that treating high BP reduces the risk for cardiovascular disease. The VA Cooperative Study randomized patients with hypertension and diastolic BP between 90 and 129 mm Hg to active treatment or placebo [3]. Among the 143 patients with a diastolic BP greater than 114 mm Hg, there were 27 “morbidity events” in the placebo arm and only 2 in the active-treatment arm [3]. In the UK Prospective Diabetes Study, 1,148 patients with type 2 diabetes and hypertension were randomized to tight BP control (<150/85 mm Hg) or less-tight control (<180/105 mm Hg) [4]. After a median of 8.4 years, randomization to the tight-control arm was associated with a 44% reduced risk of stroke, 32% reduced risk for death related to diabetes, and 56% reduced risk for heart failure [4]. In the Systolic Hypertension in the Elderly Program (SHEP) study, subjects with isolated systolic hypertension were randomized to placebo or active treatment with chlorthalidone [5]. There was a 34% reduction in major cardiovascular disease in the active-treatment arm [5]. Based on these studies and a number of others showing similar benefit, current guidelines recommend treating all patients with hypertension to a target BP of less than 140/90 mm Hg, with lower targets for patients with diabetes or CKD [2].

However, lowering BP has not been shown to reduce adverse renal outcomes. In the UK Prospective Diabetes Study (UKPDS), no differences were observed between the two BP target groups for proteinuria, plasma creatinine concentration, or doubling of serum creatinine [4]. In SHEP, there was no difference between the active-treatment and placebo arms in the number of patients who had a serum creatinine of at least 2 mg/dL. A slight decrease in the rate of ever having 1+ proteinuria on dipstick was observed among patients in the active-treatment arm (32.3% vs 34.6% for patients with diabetes and 17.2% vs 19.8% for those without diabetes) [5]. Similar nonsignificant results (discussed in more detail in the next section) have been observed in trials with renal disease progression as the primary outcome. Although observational data identifying hypertension as a causal risk factor for cardiovascular disease has been corroborated by decreased rates of cardiovascular disease with low BP targets, similar results have not been observed in CKD.

Hypertension and Chronic Kidney Disease

Elevated BP has traditionally been considered to be a cause and a consequence of CKD. Overwhelming observational data reveal a strong association between elevated BP and increased risk for developing ESRD. Among men screened for the Multiple Risk Factor Intervention Trial (MRFIT), the relative risk for ESRD associated with stage 4 hypertension was 22.1 when compared with optimal BP [6]. These findings were independent of baseline creatinine and proteinuria in the subset of men enrolled in the trial [6, 7]. The increased risk for ESRD associated with elevated BP is consistent for both males and females and across multiple different ethnic groups [8-10].

In addition to observational studies linking hypertension with ESRD, certain classes of antihypertensive medications have been shown to effectively treat hypertension in patients with CKD, to reduce proteinuria, to slow progression of renal disease, and to reduce the incidence of ESRD. Angiotensin-converting enzyme (ACE) inhibitors are effective at reducing both the progression of CKD and the incidence of ESRD [11]. In the Angiotensin-converting enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Study, patients with renal insufficiency of various etiologies were randomized to benazepril or placebo [12]. After a median follow-up of 3 years, there was a 53% reduction in risk of doubling of serum creatinine or dialysis in the benazepril arm, even after adjusting for changes in diastolic BP and urine protein excretion, both of which were lower in the benazepril arm [12]. Angiotensin receptor blockers (ARBs) have similar effects on BP and renal function. In both the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study and the Irbesartan Diabetic Nephropathy Trial (IDNT), treatment with an ARB reduced the risk of a composite of doubling of creatinine, ESRD, or death [13, 14]. As with ACE inhibitors, the decrease in renal events seen in the groups treated with an ARB was not explained by differences in BP [13, 14].

However, despite the observational data suggesting that elevated BP is associated with renal disease and evidence from large randomized clinical trials showing that treatment with ACE inhibitors and ARBs reduces progression of renal disease, no trials in adults have been able to demonstrate reduction in the progression of renal disease with lower BP targets (Table 1). In one of the first studies to evaluate different BP targets in patients with CKD, Toto et al. randomized 77 nondiabetic, hypertensive patients with CKD and a normal urine sediment to “strict” control (diastolic BP 65–80 mm Hg) or “conventional” control (diastolic BP 85–95 mm Hg) [15]. There was no difference in the slope of GFR decline or a composite of renal events or death after 3 years of follow-up [15]. Similarly, there was no difference in rate of decline of GFR in a study of 129 patients with type 1 diabetes with nephropathy who were treated with ramipril and randomized to a mean BP of either 92 mm Hg or 100–107 mm Hg [16]. Follow-up 24-hour urinary protein excretion was lower in the low-BP-target arm, but this may be attributable to receipt of higher doses of ramipril [16]. In the Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN-2) study, patients with nondiabetic proteinuria were randomized to a goal diastolic BP of less than 90 mm Hg or an intensified arm with a goal BP of less than 130/80 mm Hg [17]. After a median follow-up of 19 months, there was no difference in the rate of ESRD, decline in GFR, or urinary protein excretion [17]. Although these studies consistently failed to show a benefit of lower BP targets, they are limited by their small size and short follow-up.

The Modification of Diet in Renal Disease (MDRD) study was the first large trial to evaluate whether a low BP target reduces progression of renal disease [18]. Patients with CKD were randomized to a mean arterial pressure target of either 92 or 107 mm Hg [18]. The primary outcome, decline in GFR at 3 years, did not differ between the groups, but the study was limited by a short duration of follow-up (mean 2.2 years) [18]. In patients with proteinuria greater than 1 g/d, however, the low BP target was associated with slower decline in GFR [18, 19]. Additionally, during long-term passive follow-up after the intervention portion of the trial, the adjusted hazard ratio for kidney failure was 0.68 (95% CI, 0.57–0.82) for the low-BP target group compared with the usual-BP target group [20].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study also evaluated whether a low BP target (systolic BP < 120 mm Hg) reduces the incidence of cardiovascular disease more than a standard target (systolic BP < 140 mm Hg) [21••]. After 4.7 years of follow-up in 4,733 subjects, there was no difference in the primary outcome of nonfatal myocardial infarction, nonfatal stroke, or death between the intensive and standard arms [21••]. The intensive BP target was associated with a lower rate of macroalbuminuria.

However, the average GFR was lower in the intensive arm, and more patients in that arm had a GFR less than 30 mL/min/1.73 m² [21••]. Based on ACCORD, a lower BP target does not appear to slow progression of renal disease in diabetics. It is worth noting that ACCORD subjects were at low risk for renal disease, with a median urine albumin-to-creatinine ratio of 14 mg/g and a mean GFR of 92 mL/min/1.73 m² [21••].

The most recent data evaluating whether a low BP target reduces the progression of renal disease come from the African American Study of Kidney Disease and Hypertension (AASK) Collaborative Research Group. In the AASK trial, 1,094 African Americans with hypertensive renal disease were assigned to a usual mean arterial pressure goal of 102–107 mm Hg or to a lower goal of less than 92 mm Hg [22]. Despite an achieved BP difference of 12/7 mm Hg, there was no difference in the primary outcome of GFR slope over 4 years or in the composite outcome of a 50% decline in GFR, ESRD, or death [22]. Results of long-term follow-up in the AASK cohort phase, initiated at the conclusion of the trial, were recently published and again revealed no difference in the primary outcome of doubling of serum creatinine, ESRD, or death between the intensive and standard arms [23]. Prespecified subgroup analyses did reveal that the lower BP target was associated with a reduced risk for the primary composite outcome in subjects with a baseline protein-to-creatinine ratio of more than 0.22 (HR, 0.73; 95% CI, 0.58–0.93) [23].

Although the inability of these trials to demonstrate a reduction in renal outcomes with lower BP targets is in part due to small sample size, short duration of follow-up, and subjects who are at low risk for progressive renal disease, another contributing factor may be the method of BP measurement. That is, where and when BP is measured may be an important factor in reducing renal outcomes with low BP targets [24]. AASK provides the most insight into this issue because data are available from ABPM, albeit obtained at the onset of the cohort phase [25••]. In the AASK cohort, clinic BP and ABPM were concordant in only 54.7% of participants; 42.9% had masked hypertension. Most striking was the finding that of the 61% of patients with controlled clinic BP (<140/90 mm Hg), more than 70% had masked hypertension, with most displaying elevated nighttime BP [25••]. Similar discordance between clinic BP and ABPM was observed in a cohort of Italian hypertensive patients, in whom ambulatory BP was uncontrolled in 70% of patients with controlled clinic BP and 80% of those with uncontrolled clinic BP [26]. These findings raise the possibility that targeting a low clinic BP may not reduce the overall exposure to elevated BP; targeting lower ambulatory BP may be the key to linking treatment of hypertension with reduction in adverse renal outcomes.

Ambulatory BP and Cardiovascular Disease

As with the treatment of hypertension, the initial focus on ambulatory BP related to its ability to predict cardiovascular disease. Multiple studies have shown that ambulatory BP is a more potent predictor than clinic BP for cardiovascular morbidity and mortality [27, 28]. In a cohort of 1,542 Japanese patients, ambulatory systolic BP was associated with cardiovascular mortality, independent of clinic BP [29]. Similarly, in a mostly white cohort from London, ambulatory BPs but not clinic BPs improved prediction of cardiovascular and cerebrovascular morbidity and mortality [30]. A recent meta-analysis confirmed that ambulatory BP predicts cardiovascular events more accurately than clinic BP. Compared with those having controlled clinic BP and ambulatory BP, the risk of cardiovascular events was similar for patients with white-coat hypertension (uncontrolled clinic BP and controlled ambulatory BP) [31]. On the other hand, both masked hypertension (HR, 2.09; 95% CI, 1.55–2.81) and sustained hypertension (HR, 2.59; 95% CI, 2.00–3.35) were associated with increased risk for cardiovascular disease [31].

ABPM not only provides prognostic information above and beyond what is available from BP obtained in the clinic but also allows for an assessment of BP at night and during the sleep state. Nighttime BP may be the best BP for predicting both mortality and cardiovascular disease. A meta-analysis of 23,856 hypertensive patients and 9,641 subjects from population cohorts evaluated the impact of daytime and nighttime BP and the night/day BP ratio on all-cause mortality and cardiovascular events [32••]. Both elevated nighttime and daytime BP were associated with increased risk for total mortality and cardiovascular events after adjustment for traditional risk factors in both hypertensive patients and the general population. However, the risk associated with daytime BP was no longer significant (with the exception of cardiovascular events in the general population) after adjustment for nighttime BP, but nighttime BP remained a significant risk factor for mortality and cardiovascular events in both hypertensive patients and the general population even with adjustment for daytime BP. Additionally, nondipping, defined by a night/day BP ratio greater than 0.9, remained a significant risk factor after controlling for 24-hour BP [32••]. Ambulatory BP, particularly nighttime BP, appears to be the best method for evaluating the increased risk for all-cause mortality and cardiovascular disease attributable to hypertension.

Ambulatory BP and Chronic Kidney Disease

Although the link between ambulatory BP, nocturnal BP, circadian variation, and adverse outcomes (including all-cause mortality and cardiovascular and cerebrovascular events) is well established, whether ambulatory BP is associated with CKD and renal outcomes is not as widely studied. A number of recent investigations have revealed that ambulatory BP and particularly nighttime BP are significant and independent predictors of renal function in both cross-sectional and longitudinal studies.

Lurbe et al. evaluated ambulatory BP at baseline and after 2 years in 75 patients with type 1 diabetes without hypertension or microalbuminuria and followed them prospectively [33]. Patients who developed microalbuminuria after year 2 had elevated daytime and nighttime diastolic BP and elevated nighttime systolic BP. Additionally, the risk for microalbuminuria was 70% lower in dippers (night/day BP ratio ≤ 0.90) compared with nondippers [33]. Recent results confirm this relationship between proteinuria and nighttime BP [34•, 35]. Among 127 subjects with dipping on two consecutive ABPM, those with elevated nighttime BP had higher urine albumin excretion than those with normal nighttime BP [34•]. In a study of 356 patients with resistant hypertension, patients with microalbuminuria had higher daytime diastolic BP, higher nighttime diastolic and systolic BP, and higher 24-hour diastolic BP than patients with normal urinary albumin-to-creatinine ratios [35]. On multivariable analysis, only reduced GFR and elevated nighttime systolic BP (OR, 1.014; 95% CI, 1.001–1.026) were independent predictors of microalbuminuria [35].

Elevated creatinine and low GFR also have been found to be associated with elevated nighttime BP and nondipping. In a retrospective study, the rate of nondipping was lowest among subjects with essential hypertension (30%) and increased from 53% among patients with normal creatinine but underlying renal disease to 75% in patients with a plasma creatinine greater than 600 $\mu\text{mol/L}$ [36]. Agarwal and Light studied the relationship between GFR, proteinuria, and ABPM and found that any proteinuria or decrease in GFR was associated with decreased circadian variation; only subjects with normal GFR and no proteinuria exhibited circadian systolic BP variation [37]. These results demonstrate a strong relationship between nighttime BP and CKD—either low GFR or proteinuria—in cross-sectional analyses.

Whether elevated nighttime BP and nondipping are causally related to the development and progression of CKD has been explored in a few longitudinal studies. A retrospective

analysis evaluated consecutive patients referred for ABPM with at least one follow-up measurement of creatinine 1 year after the ABPM. Patients classified as dipping had no change in GFR (mean change, 1.3%) and only 1.5% had an increase in creatinine greater than 50% [38]. On the other hand, patients classified as nondippers had a decline in GFR (mean change, -15.9%), and a significantly greater percentage (17.3%) had an increase in creatinine greater than 50% [38]. In a small study of nondiabetic patients with CKD, dipping status was not associated with a composite of death or ESRD, but nighttime systolic BP greater than 130 mm Hg (compared with <120 mm Hg) was associated with increased risk of the composite outcome (HR, 2.07; 95% CI, 1.01–4.25) [39•]. Finally, even elevated nighttime BP measured in hospitalized patients is associated with increased risk for renal events [40•]. In a study of 1,085 patients with hypertension, an increase in nighttime BP of 10 mm Hg on the day of or the day before discharge was associated with an increased risk for a 50% decline in GFR (HR, 1.26; 95% CI, 1.08–1.47), a composite of death, ESRD, or a 50% decline in GFR (HR, 1.12; 95% CI, 1.03–1.23), and was marginally associated with ESRD (HR, 1.30; 95% CI, 0.94–1.80) [40•].

However, not all studies have shown a relationship between nighttime BP and renal outcomes. In a cohort of 277 patients with CKD, nondipping was not a significant predictor of ESRD after adjusting for 24-hour BP [41]. In the same study, nighttime BP was predictive of total mortality but not ESRD after adjusting for daytime BP [41]. In a study focused on circadian BP variation, neither nondipping or BP “phase” was associated with ESRD after adjusting for age and 24-hour BP, but nondipping was marginally associated with increased risk for ESRD after adjustment (HR, 1.95; 95% CI, 0.97–3.96; $P=0.063$) [42]. Although these studies did not show nighttime BP or changes in day-to-night BP to be significant independent predictors, the trend towards increased risk of adverse renal outcomes with increased nighttime BP and nondipping was consistent with previous studies.

Nighttime BP Is Modifiable

Elevated nighttime BP and nondipping are not only associated with increased risk for all-cause mortality, cardiovascular disease, and adverse renal outcomes, but evidence is emerging that these risk factors are modifiable. A number of nonspecific measures such as salt restriction and use of diuretics have been shown to lower nighttime BP and convert nondippers to dippers. Among nondippers with essential hypertension, hydrochlorothiazide reduced nighttime BP, resulting in a normal dipping pattern [43]. Similarly, a week of salt restriction converted nondippers to dippers [44]. Finally, a pharmacist–physician collaborative intervention that included lifestyle modification and resulted in increased use of antihypertensive medications was associated with a significant decrease in BP during both the day and night [45, 46]. These studies demonstrate that nighttime BP is modifiable, even with interventions that are not specifically targeted to lower nighttime BP.

The purposeful timing of medications throughout the day, known as *chronotherapy*, has been used effectively to lower nighttime BP. In a number of studies, subjects have been randomized to receive an antihypertensive medication either on awakening or at bedtime. Short-term studies, typically 3–4 months in duration, have demonstrated that evening administration is associated with significantly lower nighttime BP, a greater reduction in BP from day to night, and an increase in the percentage of subjects who are classified as dippers [47–52]. These studies have reported no significant differences between groups with regard to daytime or clinic BP. The effect of evening dosing is consistent for various classes of antihypertensive medications, including ACE inhibitors [47, 48] and ARBs [49–52].

The advantages of evening dosing are also seen among the subset of hypertensive patients at high risk for adverse outcomes. In a study of nondippers, bedtime administration of

valsartan restored 75% of subjects to normal dipping status, compared with only 23.6% with morning dosing [51]. Similarly, among patients with resistant hypertension, those randomized to administration of a new antihypertensive medication in the evening had lower daytime, nighttime, and 24-hour BP than those randomized to receive the new medication on awakening [53]. The benefits of evening dosing of antihypertensives are not limited to lower nighttime BP. Hermida et al. randomized 2,156 hypertensive patients to receive all of their antihypertensive medications in the morning or at least one antihypertensive at bedtime [54••]. After a median follow-up of 5.6 years, patients receiving at least one antihypertensive in the evening had lower nighttime BP, were more likely to be dippers, had a significantly lower rate of cardiovascular disease (HR, 0.39; 95% CI, 0.29–0.51; $P<0.001$), and had a decreased rate of all-cause mortality [54••]. This is the first study to demonstrate decreases in cardiovascular disease and mortality with evening administration of antihypertensive medications. Given that achieved nighttime BP levels differed between the two arms, it is difficult to assess whether the lower rate of cardiovascular disease is due to evening administration of antihypertensive medications or the lower nighttime BPs.

The benefits of evening dosing of antihypertensive medications are likely to apply to patients with CKD. Two small studies have demonstrated that evening dosing of antihypertensive medications effectively lowers nighttime BP in subjects with CKD [55, 56]. The difference in effect of isradipine (5 mg) administered at 08:00 or 20:00 for 4 weeks on ambulatory BP was evaluated in a crossover study of 16 patients with CKD [56]. Although there was no difference in 24-hour mean BP, evening administration was associated with a significantly greater reduction in nighttime BP [56]. Similar results were observed in a noncontrolled study of 32 nondipping patients with CKD, who were evaluated with ABPM at baseline and again 8 weeks after shifting one or more antihypertensive medications to the evening [55]. Evening administration resulted in decreased nighttime systolic BP and conversion to a normal dipping pattern in 87.5% of patients [55]. These small, short-term studies demonstrate that, as in individuals with normal renal function, nighttime BP and dipping status are modifiable in patients with CKD.

Not only is lowering nighttime BP feasible in patients with CKD; data suggest that lowering nighttime BP may be of particular benefit to CKD patients. For instance, a number of studies have demonstrated decreased urinary protein excretion with evening dosing of antihypertensives [51, 52, 56]. Furthermore, there was a significant correlation in these studies between the improvements in nighttime BP and the decrease in urinary protein excretion [51, 52, 56]. Lowering nighttime BP in patients with CKD is possible with chronotherapy and is associated with decreased urinary protein excretion, an accepted surrogate for renal outcomes [57]. Unfortunately, no studies have yet evaluated the long-term effect of lowering nighttime BP on the progression of hypertensive CKD.

Conclusions

Nighttime BP may be the best predictor of adverse cardiovascular and renal events in patients with hypertension. Numerous studies have demonstrated that nighttime BP and nondipping are modifiable risk factors. Recent randomized trial results indicate that chronotherapy lowers nighttime BP and significantly lowers the rate of cardiovascular disease. Small studies have demonstrated that even in patients with CKD, elevated nighttime BP responds to treatment. Additionally, lowering nighttime BP is associated with improvement in urinary protein excretion. Lowering nighttime BP may be the key to slowing the progression of CKD and realizing renal benefits of treating hypertension similar to those that have long been established for cardiovascular disease, but further studies are needed.

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Table 1
Outcomes of trials evaluating the effect of a low blood pressure target on progression of renal disease

Study	Patients	N	Low BP target	Standard BP target	Outcome	Secondary analyses
Toto et al. [15]	Nondiabetic, hypertensive, CKD	77	DBP 65–80	DBP 85–95	GFR slope (mL/min/1.73 m ² /y), -0.31 vs -0.050 (<i>P</i> ≥0.25)	NR
Lewis et al. [16]	Type 1 diabetic nephropathy	129	MAP 92 ^a	MAP 100–107	Change in iGFR (mL/min/1.73 m ²), 62–54 vs 64–58 (<i>P</i> =0.62)	Median proteinuria 535 vs 1723 mg/24 h (<i>P</i> =0.02)
Ruggenenti et al. [17] (REIN-2)	Nondiabetic proteinuria	335	DBP < 90 ^b	< 130/80 ^b	ESRD, HR 1.00 (95% CI, 0.61–1.64; <i>P</i> =0.99)	No difference in urinary protein excretion
Klahr et al. [18] (MDRD, Study 1)	GFR 25–55	585	MAP < 92	MAP 107	GFR slope (mL/min/3 y), 10.7 vs 12.3 (<i>P</i> =0.18)	Benefit of low BP target in patients with significant proteinuria; in long-term follow-up, decreased risk of kidney failure in low BP target arm (HR, 0.68; 95% CI, 0.57–0.82) [20]
Klahr et al. [18] (MDRD, Study 2)	GFR 13–24	255	MAP < 92	MAP 107	GFR slope (mL/min/y), 3.7 vs 4.2 (<i>P</i> =0.28)	
Wright et al. [22] (AASK)	Nondiabetic African Americans with CKD	1,094	MAP < 92	MAP 102–107	GFR slope (mL/min/1.73 m ² /y), -2.21 vs -1.95 (<i>P</i> =0.24)	Long-term follow-up showed no difference in doubling of SCr; ESRD, or death overall; and decreased risk of composite among patients with a UP/C ratio >0.22 (HR, 0.73) [23]

^aPatients assigned to the low BP target group received higher doses of ramipril.

^bThere was no difference in ramipril dose between the groups.

AASK African American Study of Kidney Disease and Hypertension; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESRD end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; iGFR, iothalamate GFR; MAP, mean arterial pressure; MDRD Modification of Diet in Renal Disease; REIN Renoprotection in Patients with Nondiabetic Chronic Renal Disease; SCr serum creatinine; UP/C urinary protein-to-creatinine ratio.