Treatment of hypertension in patients with nondiabetic chronic kidney disease

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M Ruzicka, KD Burns, B Culleton, S Tobe; for the Canadian Hypertension Education Program. Treatment of hypertension in patients with nondiabetic chronic kidney disease. Can J Cardiol 2007;23(7):595-601.

Hypertension is highly prevalent in patients with chronic kidney disease (CKD). As either the cause or the consequence of CKD, hypertension is an important independent factor determining the rate of loss of renal function. Hypertension is also a significant independent risk factor for cardiovascular events in patients with CKD, the leading cause of their morbidity and mortality.

Based on evidence from observational cohort studies and randomized clinical trials, the Canadian Hypertension Education Program (CHEP) recommends a target blood pressure (BP) of lower than 130/80 mmHg in hypertensive patients with nondiabetic CKD. The CHEP also endorses the use of renin-angiotensin system blockers for the BP-lowering regimen in nondiabetic patients with CKD and significant proteinuria. It is recognized that the majority of nondiabetic patients with CKD will require two or more BP-lowering drugs to attain target BP. Furthermore, extracellular fluid volume expansion is a major contributor to hypertension in patients with CKD, and diuretics should be part of the BP-lowering regimen in the majority of patients.

Patients with CKD are recognized to be at high risk for cardiovascular events, and studies testing new emerging treatments of hypertension to reduce the burden of CKD on renal and cardiovascular outcomes are underway. In this regard, the CHEP will continue to review and update all its recommendations annually.

Key Words: *Blood pressure target; Chronic kidney disease; Hypertension; Proteinuria*

Le traitement de l'hypertension chez les patients atteints d'une maladie rénale chronique non diabétique

L'hypertension est très prévalente chez les patients atteints d'une maladie rénale chronique (MRC). Qu'elle soit la cause ou la conséquence de la MRC, l'hypertension est un facteur de risque indépendant important pour déterminer le taux de perte de la fonction rénale. L'hypertension est également un facteur de risque indépendant important des événements cardiovasculaires chez les patients atteints de MRC, la principale cause de leur morbidité et de leur mortalité.

D'après les données tirées d'études de cohortes par observation et d'études cliniques aléatoires, le Programme éducatif canadien sur l'hypertension (PÉCH) recommande une TA cible inférieure à 130/80 mmHg chez les hypertendus atteints d'une MRC non diabétique. Le PÉCH appuie également le recours aux inhibiteurs du système rénine-angiotensine comme posologie visant à abaisser la TA chez les patients non diabétiques atteints d'une MRC et d'une protéinurie marquée. Il est reconnu que la majorité des patients non diabétiques atteints d'une MRC devront prendre au moins deux médicaments pour abaisser la TA afin d'obtenir la TA cible. De plus, l'expansion du volume de liquide extracellulaire est un important élément contributif de l'hypertension chez les patients atteints de MRC, et les diurétiques devraient faire partie de la posologie pour abaisser la TA chez la majorité des patients.

Les patients atteints de MRC sont reconnus comme très vulnérables aux événements cardiovasculaires, et des études évaluant des traitements émergents de l'hypertension afin de réduire le fardeau de la MRC sur les issues rénales et cardiovasculaires sont en cours. À cet égard, le PÉCH continuera d'évaluer et de mettre à jour toutes ses recommandations chaque année.

Hypertension is highly prevalent in patients with chronic kidney disease (CKD), as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (1,2). As either the cause or the consequence of CKD, hypertension is an important independent factor determining the rate of loss of renal function (3-9). Hypertension is also a significant independent risk factor for cardiovascular events in patients with CKD, the leading cause of their morbidity and mortality (10). Thus, two major objectives of the treatment of hypertension in patients with CKD include slowing the rate of renal function loss, and decreasing cardiovascular morbidity and mortality.

Independent of blood pressure (BP), it has become apparent that the rates of decline in renal function loss vary based on the etiology of renal disease per se (11-13). In addition, the degree of urinary protein excretion is a significant predictor of the rate of renal function loss (11,13). These rates may further vary based on the presence of comorbidities such as dyslipidemia and ischemic heart disease (14-17).

In patients with nondiabetic nonproteinuric CKD (ie, proteinuria less than 0.5 g/day), the development of renal 'outcomes' (such as end-stage renal disease [ESRD] or a greater than 50% decline in glomerular filtration rate [GFR]) is relatively infrequent, resulting in the requirement to study large patient populations for prolonged periods to acquire a sufficient number of events to detect differences in BP targets or antihypertensive strategies (6,7,9-13). In this context, the evidence for strict BP targets and initial therapy with blockers of the renin-angiotensin system (RAS) is primarily based on the results of clinical trials that included patients with both diabetic and nondiabetic proteinuric CKD (18-20).

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Received for publication March 26, 2007. Accepted April 15, 2007

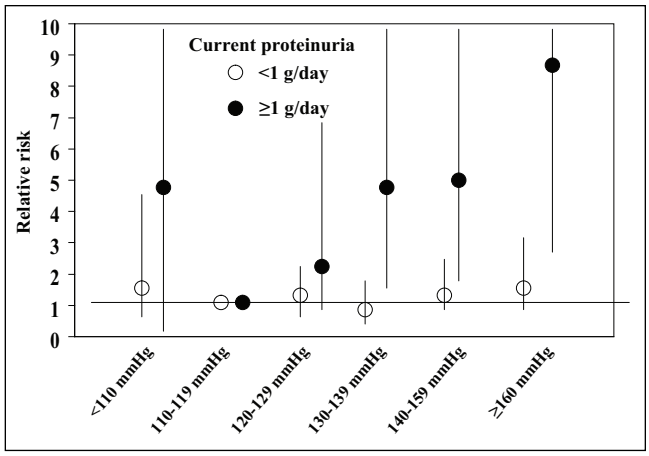

Figure 1) *The relative risk for kidney disease progression based on current systolic blood pressure and urine protein excretion. The relative risk for patients with a current protein excretion of 1.0 g/day or more represents 9336 patients (223 events), and the relative risk for patients with a current urine protein excretion of less than 1.0 g/day represents 13,274 patients (88 events). Modified from reference 9*

With regard to cardiovascular outcomes, patients with CKD were, to a major extent, excluded from most hypertension clinical trials that addressed cardiovascular outcomes in relation to BP targets and/or BP-lowering regimens. Thus, in patients with CKD, the evidence for strict BP control and initial therapy with blockers of the RAS for cardiovascular outcomes remains limited.

In the present manuscript, we review the evidence for BP targets and choice of initial BP-lowering drugs in hypertensive, nondiabetic CKD patients with or without proteinuria. Nonpharmacological interventions, namely, lifestyle modifications as specified by the Canadian Hypertension Education Program (CHEP) (pages 539-550 of the current issue of the *Journal*), are indeed an important component of BP-lowering regimens, but are not discussed in the present manuscript.

Pathophysiology of hypertensive nephropathy

Chronic hypertension has been proposed to cause CKD via at least two pathways (21,22). First, chronic hypertension induces glomerular ischemia secondary to damage to preglomerular arteries and arterioles, leading to progressive luminal narrowing and a fall in glomerular blood flow. Postglomerular renal ischemia also ensues, contributing to progressive nephron loss (21). The alternative view is that chronic hypertension leads to loss of afferent arteriolar autoregulation, such that high systemic BP is transmitted to the glomeruli, inducing hyperperfusion and hyperfiltration, which in turn cause structural damage to the glomeruli (ie, glomerulosclerosis) and progressive renal function loss (22). The following evidence from both prospective cohort studies and antihypertensive interventional trials has defined the relationship between hypertension and CKD.

BP targets for patients with nondiabetic CKD: Renal outcomes

Prospective cohort studies: Klag et al (23) assessed the development of ESRD in a cohort of 332,544 men (35 to 57 years of age) screened for the Multiple Risk Factor Intervention Trial (MRFIT) over an average follow-up of 16 years. Compared with men with an optimal BP (lower than 120/80 mmHg), the RR of ESRD independent of multiple cofactors, including age, race, use of medications for diabetes mellitus and history of myocardial infarction, increased gradually to 22.1 (95% CI 14.2 to 34.3) in those with BPs greater than 210/120 mmHg (23). However, there were several limitations to this strong, graded relationship between both systolic and diastolic BP and the development of ESRD (23). First, only 4% of the screened cohort (ie, those who actually entered the MRFIT) had serum creatinine or dipstick proteinuria measured at baseline (23). Thus, the strong association between BP and the incidence of ESRD might have been due to the initiation of renal disease by hypertension per se and/or to the accelerated progression of pre-existing renal disease. Second, BP was only measured on one occasion (ie, during the screening phase for the MRFIT), which might have underestimated the strength of the association of ESRD with BP (23). With the above limitations in mind, the authors' conclusion that BP is a strong independent risk factor for ESRD is quite reasonable (23).

In a pooled analysis of 11 randomized clinical trials (RCTs) that included patients with nondiabetic CKD (n=1860) and antihypertensive regimens either with or without angiotensin-converting enzyme (ACE) inhibitors, Jafar et al (9) reported the lowest risk for CKD progression at the achieved follow-up systolic BP of 110 mmHg to 129 mmHg, and an increase in the RR for CKD progression at BPs starting above 130 mmHg (9). There was a graded relationship between higher levels of urinary protein excretion (more than 2 g/day) and the progression of renal disease (9). After adjustment for urinary protein excretion, the relationship between BP and risk for CKD progression was clear for patients with proteinuria 1 g/day or greater, but not for those with proteinuria less than 1 g/day (Figure 1). These data were limited, however, by the small number of events in both groups with proteinuria (ie, 223 events in 9336 patients with proteinuria of 1 g/day or more, and 88 events in 13,274 patients with proteinuria of less than 1 g/day), as well as by further stratification of these patients to six different BP categories (9). Thus, while systolic BP lower than 130 mmHg may be beneficial for patients with nondiabetic CKD and proteinuria of 1 g/day or more, as concluded by the authors, the results of this meta-analysis would not support such a conclusion for patients with urinary protein excretion less than 1 g/day (9).

Hsu et al (6) reported a graded relationship for hypertension and risk of development of ESRD in a historical cohort study of 316,675 adult patients within the Kaiser Permanente health management organization of northern California (USA). Patients in this cohort had at least one measurement of BP, a baseline serum creatinine level with an estimated GFR of greater than 60 mL/min/1.73 m^2, and a dipstick urinalysis negative for blood and protein (6). Patients were followed for an average of 25.9 years. Compared with subjects with a BP of lower than 120/80 mmHg, the risk of ESRD increased gradually with higher BPs to a factor of 4.25 (95% CI 2.63 to 6.86) in those with BP of 210/120 mmHg or higher (Figure 2). In African-American nondiabetic patients, the incidence of ESRD was significantly higher, even at BPs of lower than 120/80 mmHg, and showed an earlier and steeper increase at BPs of 120-159/80-99 mmHg than Caucasian nondiabetic patients (Figure 2). This study provided the strongest data to date, indicating that even a mild increase in BP is an independent risk factor for the development of ESRD. However,

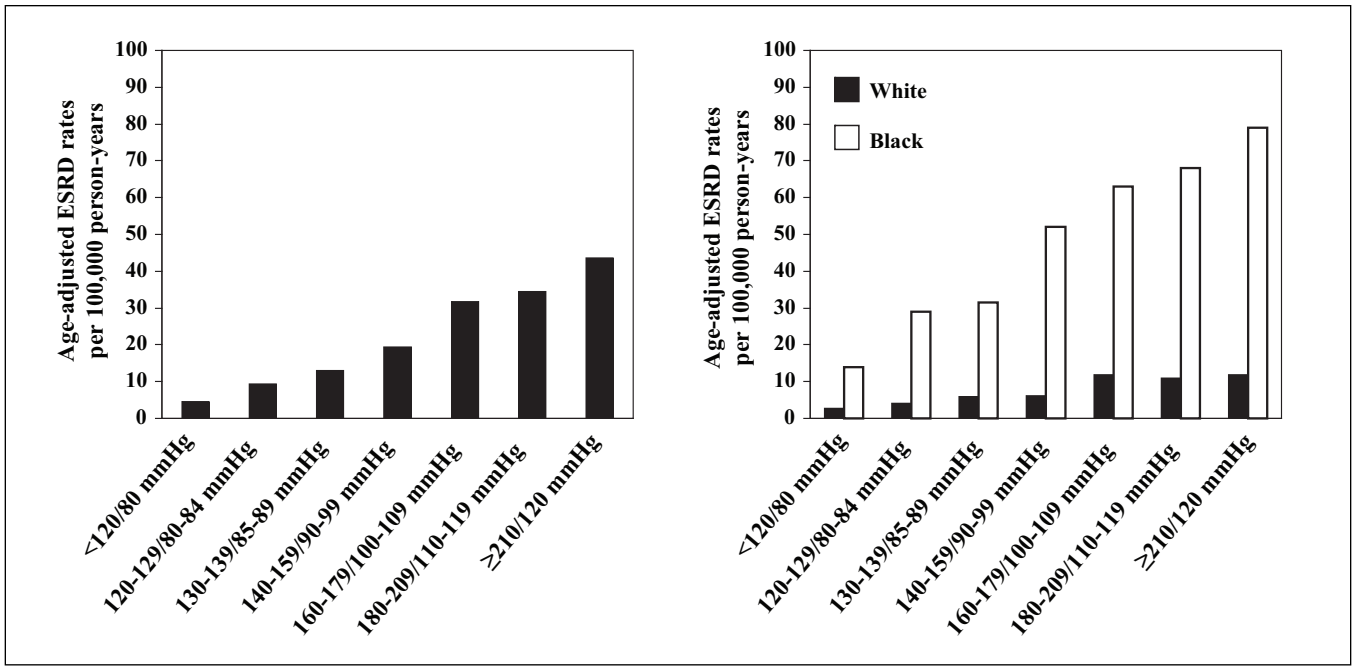

Figure 2) *Age-adjusted risk for end-stage renal disease (ESRD) in the whole cohort and in subgroups stratified by race (black [n= 57,085], white [n=218,261]. The number of patients in different blood pressure strata were as follows: ≤120/80 mmHg (n=89,774), 120-129/80-84 mmHg (n=72,192), 130-139/85-89 mmHg (n=56,078), 140-159/90-99 mmHg (n=69,083), 160-179/100-109 mmHg (n=21,340), 180-209/110-119 mmHg (n=6626) and ≥210/120 mmHg (n=1582). Modified from reference 6*

the study did not assess the effect of urinary protein excretion on CKD progression in relation to BP level.

RCTs: The Modification of Diet in Renal Disease (MDRD) study (20) was a multicentre, randomized study that determined the effect of dietary protein restriction and strict BP control on the progression of CKD. In this study, 585 patients 18 to 70 years of age with CKD (serum creatinine 124 µmol/L to 619 µmol/L in men and 106 µmol/L to 619 µmol/L in women) were enrolled (20). A variety of renal diseases were represented, the most common of which were polycystic kidney disease (25%) and primary glomerular disease (24%). Only 3% of enrolled patients had diabetes (20). Patients were randomly assigned to 'low' BP (mean arterial pressure [MAP] 92 mmHg [lower than 125/75 mmHg] in participants 60 years of age and younger, and MAP lower than 98 mmHg in those 61 years of age and older) and the 'usual' BP (MAP lower than 107 mmHg [lower than 140/90 mmHg] in participants 60 years of age and younger, and MAP lower than 113 mmHg in participants 61 years of age and older). After a follow-up period of as long as 48 months, the decline in GFR did not differ between the two BP groups, despite differences in BP: BP decreased from 130/80 mmHg to 126/77 mmHg in the low BP group and remained unchanged (131/80 mmHg versus 134/81 mmHg) in the usual BP group (20). Post hoc analysis demonstrated a benefit of the low BP target in slowing the rate of GFR loss in a subgroup of patients with GFR of 25 mL/min/1.73 m^2 to 55 mL/min/1.73 m^2 and baseline proteinuria more than 1 g/day (20).

The long-term follow-up of patients enrolled in the MDRD study was published in 2005 (7). Outcomes included kidney failure (initiation of dialysis or kidney transplantation) and the composite outcome of kidney failure or all-cause mortality (7). Long-term follow-up demonstrated a hazard ratio for kidney failure of 0.66 (95% CI 0.53 to 0.81) and for the composite outcome of 0.76 (95% CI 0.63 to 0.91) in the low target BP

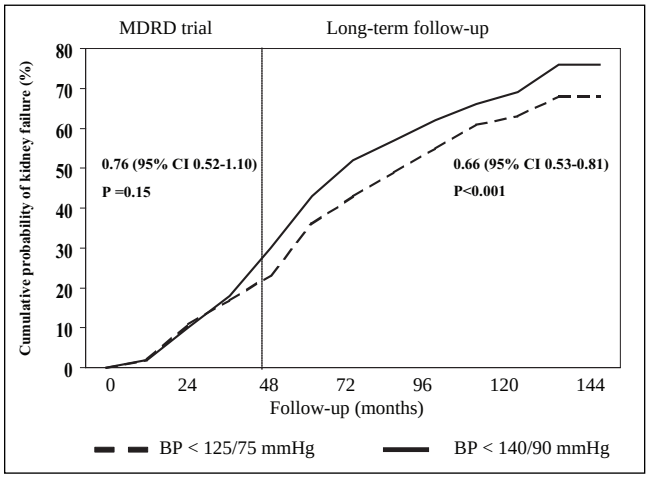

Figure 3) *Cumulative probability of end-stage renal disease in patients randomly assigned to usual blood pressure (BP) (mean arterial pressure lower than 107 mmHg) or low BP (mean arterial pressure lower than 92 mmHg in patients 60 years old or younger, or lower than 98 mmHg in those 61 years old or older) during the long-term follow-up of the Modification of Diet in Renal Disease (MDRD) trial. Modified from reference 7*

group compared with the usual target BP group (Figure 3). Most of this benefit was already present after four years, with little further benefit seen over the next six to eight years (Figure 3). There were no BP measurements taken during the follow-up period, and the differences in BP control over time likely became minimal, perhaps explaining the parallel curves after four to six years. With regard to baseline proteinuria, the risk reductions in the low target BP group tended to be larger for patients with baseline proteinuria more than 1 g/day, but the interaction between the BP group and baseline proteinuria

did not reach statistical significance (7). Significance of this interaction (present in the original study) may not have been detected in the long-term follow-up because of limited power, and because of the long interval between the baseline measurement and the occurrence of most outcomes (7). Finally, it is worth noting that in the original study, only 32% of patients randomly assigned to the usual BP target received an ACE inhibitor, compared with 51% assigned to the low target BP group. Possible broader use of blockers of the RAS in both groups during the follow-up might also have contributed to the loss of interaction between baseline proteinuria and BP group during follow-up. In conclusion, it appears that a lower target for BP in nondiabetic patients with CKD delays the progression of CKD. Although this effect is more robust in those with proteinuria of 1 g/day or more, the evidence from this study is insufficient to address the impact of baseline proteinuria on outcomes.

The African American Study of Kidney disease and hypertension (AASK [13]) followed 1094 African-Americans with hypertension-induced CKD and no other identifiable cause of renal insufficiency. The objective of the study was to compare the effects of two levels of BP control and three antihypertensive drug classes on GFR decline (13). Patients 18 to 70 years of age with a GFR of between 20 mL/min/1.73 m^2 and 65 mL/min/1.73 m^2 were randomly assigned to the usual MAP target (102 mmHg to 107 mmHg) or the lower MAP target (92 mmHg or lower), as well as to treatment with one of three antihypertensive drugs (ie, metoprolol, ramipril or amlodipine); they were followed for up to four years (13). Compared with the usual BP group (average achieved BP 141/85 mmHg), the lower BP group (average achieved BP 128/78 mmHg) did not experience a reduction in either GFR decline or the composite outcome (reduction of GFR by 50% or more, ESRD or death) (13). Baseline proteinuria was a strong predictor of GFR loss in this study: for each twofold higher proteinuria level, GFR declined faster at a rate of approximately 0.5 mL/min/year ($P<0.001$) (24). Although there were trends favouring the lower BP target for patients with baseline proteinuria (more than 300 mg/day), differences in renal outcomes did not reach statistical significance. Thus, the only demonstrated benefit of lower BP in this study was a decrease in proteinuria by 17% during the first six months, whereas urinary protein excretion increased by 7% in the usual BP group (both effects persisting throughout the study) (13). In conclusion, this trial showed that even in African-Americans (patients generally considered to have difficult-to-control BP), the target BP of 130/80 mmHg or lower could be achieved and maintained (with an average of 3.1 antihypertensive drugs) (13). Second, in this population, which is considered to be at high risk for target organ involvement from hypertension, the decline in GFR at 2.0 mL/min/1.73 m^2/year was relatively low (compared with patients with diabetic nephropathy), and a 10 mmHg lower BP per se over the period of up to six years was not enough to translate into a significantly slower rate of GFR loss (see below) (13). On the other hand, given the impact of proteinuria on GFR loss, lower BP targets may be justified, considering the decrease in proteinuria (a surrogate end point) in the lower BP group.

Finally, in the REnoprotection In patients with Non-diabetic chronic renal disease (REIN-2) study (25), 335 patients 18 to 70 years of age with nondiabetic CKD and proteinuria (more than 1 g/day) were randomly assigned to one of two BP target groups: conventional BP control, with diastolic BP lower than 90 mmHg irrespective of systolic BP, or intensified BP control, with BP lower than 130/80 mmHg. All patients were receiving an ACE inhibitor (ramipril up to 5 mg/day), and a dihydropyridine calcium channel blocker (felodipine up to 10 mg/day) was permitted as add-on therapy in the intensified BP group (25). The primary objective of the study was to assess the effect of intensified versus conventional BP control on progression to ESRD over a period of 36 months (25). Despite the difference in BP between the groups (BP fell from 137/84 mmHg and 136/84 mmHg before random assignment to 130/80 mmHg and 134/82 mmHg throughout the study in the intensified BP control and the conventional BP control groups, respectively), there was no difference in the development of ESRD between the groups (25). Thus, in conclusion, data from the REIN-2 study suggest that further decreasing BP by dihydropyridine calcium channel blockade in nondiabetic patients with proteinuric nephropathy treated with ACE inhibitors does not improve renal outcomes.

BP targets for patients with nondiabetic CKD: Cardiovascular outcomes

Prospective cohort studies: Based on the abundance of evidence from observational studies in the general population, high BP is recognized as a risk factor for cardiovascular disease. CKD itself (in hypertensive and nonhypertensive patients) is also a well-recognized risk factor for cardiovascular mortality (26). The impact of having a systolic BP of 140 mmHg or higher on cardiovascular death in community-based subjects (65 years of age or older) with and without CKD (defined as a GFR of less than 60 mL/min/1.73 m^2) was recently reported by Shlipak et al (27). During an average follow-up time of 8.6 years, the cardiovascular mortality risk rate was twice as high in those with CKD (342 events in 1249 patients) than in those without (750 events in 4559 patients). Systolic BP of 140 mmHg or higher was a significant risk factor for cardiovascular death in both groups, but was not more significant in patients with CKD (average [± SD] of GFR 50±10 mL/min/1.73 m^2) than in patients without (27). These data suggest that the cardiovascular risk associated with a BP of 140 mmHg or higher does not differ by the presence or absence of mild, (mostly) nondiabetic CKD.

RCTs: The Hypertension Optimal Treatment (HOT) trial (28) randomly assigned 18,790 hypertensive patients (fewer than 10% were diabetic) to one of three diastolic BP target groups (90 mmHg or lower, 85 mmHg or lower and 80 mmHg or lower) to determine the impact of these BP targets on incident cardiovascular events. The subjects were followed for an average of 3.8 years. Proteinuria was not measured at baseline. In a nonprespecified, post hoc analysis, the incidence of major cardiovascular events in patients with a serum creatinine level higher than 133 µmol/L (n=470) did not differ between the three different BP target groups (29). In an analysis in which CKD was defined as a creatinine clearance of less than 60 mL/min (calculated by the Cockroft-Gault formula based on parameters at the time of enrolment; n=2821), cardiovascular events tended to be less frequent in patients with lower BP targets, but this trend was not statistically significant (29).

In conclusion, the recommendation for a strict BP target (lower than 130/80 mmHg) in patients with nonproteinuric, nondiabetic CKD is largely based on renal outcomes from historical cohort observations (6,23). In hypertensive, nondiabetic

TABLE 1
Changes in glomerular filtration rate (GFR) from baseline in the three drug groups in the African American Study of Kidney disease and hypertension (AASK) trial

	Acute phase (mL/min/1.73 m^2/3 months)	Chronic phase (mL/min/1.73 m^2/year)	Total (mL/min/1.73 m^2/year)
Ramipril	–0.23±0.44*	–1.87±0.17*	–1.81±0.17
Metoprolol	–1.73±0.40*†	–2.12±0.17*	–2.42±0.17*†
Amlodipine	+4.03±0.64	–3.22±0.33	–1.60±0.34

*Numbers are mean changes in GFR ± SEM from baseline. Acute phase refers to the first 3 months after random assignment, and chronic phase refers to the period from 3 months to 4 years (metoprolol and ramipril) and 3 years (amlodipine). Total change was computed from combined changes in GFR during acute and chronic phases. P≤0.02 compared with *amlodipine and †ramipril. Data from reference 13*

CKD patients with proteinuria, the evidence for a BP target lower than 130/80 mmHg is supported by renal outcomes in a subgroup of patients enrolled in the MDRD trial (20).

Other major issues that remain to be addressed with regard to BP targets in patients with nondiabetic CKD include: whether a lower BP target translates into improved cardiovascular outcomes in this population; whether a lower BP target should be widely applied to elderly patients (older than 75 years of age) with CKD, because these patients were not included in the above trials or the targets for their BP were significantly higher (see MDRD); and whether this target applies to patients with ESRD.

BP-lowering therapy for patients with nondiabetic CKD

The evidence for the recommendation of blockers of the RAS as the initial treatment of hypertension for patients with diabetic CKD is relatively robust and based on RCTs with hard renal end points in high-risk patients, as well as on RCTs with surrogate end points in those with diabetic renal disease in its early stages (18,19,30,31). In contrast, in patients with nondiabetic CKD, the evidence in favour of a particular class of antihypertensive drugs is much more limited.

Renal outcomes

With regard to renal outcomes, in the AASK (13) trial, treatment with ramipril, compared with metoprolol, during the acute but not chronic period of follow-up resulted in a slower decline in GFR from baseline to up to four years. Compared with both metoprolol and ramipril, amlodipine caused an increase in GFR during the acute phase, followed by a significantly faster decline in GFR during the chronic phase (13). However, the total decline in GFR in the amlodipine group was actually less than in the metoprolol group and was not significantly different from the ramipril group (Table 1) (13). Stratification according to baseline proteinuria showed different patterns of changes in GFR. In those with proteinuria less than 300 mg/day, changes in GFR during the acute and chronic phases were similar, as described above, for the whole group (13). In contrast, in those with proteinuria more than 300 mg/day, amlodipine did not cause an initial increase in GFR, but caused a rate of decline in GFR that was nearly two times faster than with ramipril, and 1.2 times faster than with metoprolol (13). As for hard renal end points, the risk for ESRD was reduced equally by 59% (95% CI 36% to 74%) by ramipril and metoprolol compared with amlodipine (13). The secondary clinical composite outcome (ESRD, a decline in GFR of 50% or more, and death) was reduced by 22% (95% CI 1% to 38%; P=0.04) and by 38% (95% CI 14% to 56%; P=0.004) with ramipril compared with metoprolol or amlodipine, respectively (13). Finally, to fully evaluate the effects of BP control and primary antihypertensive regimens, subgroup analysis was performed. Whereas there were no differences in the rates of decline in GFR between the usual and lower BP control groups, a significantly lower risk of ESRD and/or death, as well as ESRD alone, was observed among patients randomly assigned to amlodipine and lower BP compared with those on amlodipine and usual BP control (13,24). For patients assigned to metoprolol or ramipril, there was no difference in renal outcomes between lower and usual BP control (13,24).

In conclusion, the AASK trial indicated that hypertensive African-Americans with nondiabetic CKD benefit from BP-lowering with regimens including an ACE inhibitor. In African-Americans with nondiabetic proteinuric CKD, treatment of hypertension (in the absence of an ACE inhibitor) with a dihydropyridine calcium channel blocker is associated with inferior renal outcomes. In the same group, however, lower BP could partially reverse the negative impact on renal outcomes associated with amlodipine (13,24).

The meta-analysis of 11 RCTs by Jafar et al (9) showed that antihypertensive regimens that included ACE inhibitors compared with conventional antihypertensive drugs decreased development of ESRD (7.4% versus 11.6%; P=0.002), and the combined outcome of doubling of the serum creatinine level or ESRD (13.2% versus 20.5%; P=0.001) over a mean follow-up period of 2.2 years. However, BPs were lower in the ACE inhibitor arm (decrease in BP from 148/90 mmHg to 139/85 mmHg versus 149/91 mmHg to 144/87 mmHg in the non-ACE inhibitor arm), partly because five studies compared ACE inhibitors with placebo (9). In addition, there was a high prevalence of proteinuric CKD, as indicated by baseline proteinuria of 1.8 g/day (9). Indeed, based on results of stratification of patients according to baseline urinary protein excretion, the conclusion is that a significant benefit of ACE inhibitor-based regimens is seen in those with proteinuria more than 0.5 g/day, but not in those with proteinuria less than 0.5 g/day (9).

Finally, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT [12]) was designed to test the hypothesis that 'newer' antihypertensive agents are superior to a thiazide diuretic for cardiovascular outcomes. Hypertensive patients (older than 55 years of age) with at least one additional risk factor for coronary artery disease were randomly assigned to treatment with chlorthalidone, amlodipine or lisinopril, and were followed for a mean of 4.9 years (12). Patients with serum creatinine levels higher than 176.8 µmol/L at baseline were excluded. However, if the serum creatinine drawn at the time of random assignment was found to exceed this value, patients were maintained in the trial. Urinary protein excretion was not assessed during enrolment or during the trial. However, patients with proteinuria of

TABLE 2
Recommendations for the treatment of hypertension in patients with nondiabetic chronic kidney disease

	Proteinuria <0.5 g/24 h (ACR <30 mg/mmol)	Proteinuria ≥0.5 g/24 h (ACR ≥30 mg/mmol)
Blood pressure target	<130/80 mmHg (C)	<130/80 mmHg (C)
Specific antihypertensive drug	None	Angiotensin-converting enzyme inhibitor (A)
		Angiotensin II receptor blocker (D)
Diuretic as part of the regimen	Most likely (D)	Most likely (D)
Thiazide diuretic	GFR >30 mL/min/1.73 m^2	GFR >30 mL/min/1.73 m^2
Loop diuretic	GFR ≤30 mL/min/1.73 m^2	GFR ≤30 mL/min/1.73 m^2
Combination therapy	Most likely (D)	Most likely (D)

Letters in parentheses indicate the grading of evidence. ACR Urinary albumin to creatinine ratio

1 g/day or more were likely excluded from the enrolment from 1994 to 1998, because the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (32) recommended the use of ACE inhibitors in patients with type 2 diabetes and nephropathy, as well as in patients with renal dysfunction (32). Post hoc subgroup analysis of renal outcomes in the ALLHAT according to baseline GFR revealed no differences between the lisinopril, amlodipine and chlorthalidone arms in the risk of development of ESRD or the composite end point (a 50% or greater decline in GFR or ESRD) (33). These data suggest that in hypertensive, mostly Caucasian patients with presumably nonproteinuric CKD at baseline (GFR of less than 60 mL/min/1.73 m^2) at mean achieved BPs of 130-140/70-80 mmHg, and with 66% of patients achieving BPs of lower than 140/90 mmHg, there is no difference in renal outcomes associated with the use of either thiazide diuretics, dihydropyridine calcium channel blockers or ACE inhibitors.

Cardiovascular outcomes

Post hoc subgroup analysis of data from the ALLHAT revealed that 3774 nondiabetic patients (mean age 70±8 years) with an initial GFR of less than 60 mL/min/1.73 m^2 had much higher six-year rates of fatal coronary artery disease or nonfatal myocardial infarction (10.9%) and combined cardiovascular disease (fatal coronary artery disease, nonfatal myocardial infarction, coronary revascularization, hospitalized angina, stroke, other treated angina, heart failure, peripheral artery disease) (32.0%) than in ESRD (2.8%) (12). There were no differences in fatal coronary artery disease or nonfatal myocardial infarction between patients randomly assigned to chlorthalidone, amlodipine and lisinopril (12). However, higher rates of heart failure were observed among those randomly assigned to lisinopril and amlodipine than among those on chlorthalidone (12). In conclusion, this study did not demonstrate superiority of ACE inhibitors over thiazide diuretics for cardiovascular outcomes in nondiabetic patients with presumably nonproteinuric CKD.

In conclusion, while not robust, evidence from a meta-analysis of 11 RCTs and the AASK study suggests that multidrug BP-lowering regimens that include ACE inhibitors slow the progression of nondiabetic proteinuric CKD to ESRD. Whether this translates into improved cardiovascular outcomes remains to be studied. In contrast, in nondiabetic, nonproteinuric CKD patients, there appears to be no additional benefit from any specific BP-lowering drug class with regard to renal and cardiovascular outcomes beyond the benefit from BP-lowering per se.

Combination therapy to reach the target BP

In all the above studies, the majority of patients required two or more BP-lowering drugs to reach a BP of lower than 140/90 mmHg (9,12,13,20,25,31). Thus, achieving BP control to the current recommended target of lower than 130/80 mmHg usually requires a combination of BP-lowering drugs.

Diuretic use in patients with CKD

Extracellular fluid volume expansion is a major contributor to hypertension in patients with CKD. Thus, diuretics should be part of the BP-lowering regimen in most patients with CKD. Indeed, in the majority of patients in the above trials, diuretics were used in the BP-lowering regimens. For example, in the AASK trial, patients required, on average, two to three antihypertensive drugs to reach their target BP, and 70% to 80% of them were receiving a diuretic as add-on therapy (13). Thiazide diuretics reduce their efficacy with advanced nephron loss and may therefore need to be replaced with loop diuretics in those with advanced CKD (GFR of less than 30 mL/min/1.73 m^2).

Emerging concepts in the treatment of hypertension in nondiabetic patients with CKD and proteinuria

Despite the application of the above measures to decrease BP, and reduce renal and cardiovascular risks in patients with nondiabetic CKD, a significant number of subjects are left with proteinuria and a fast rate of renal function loss. In this population, new concepts to decrease BP and proteinuria have been and/or are tested. These include combinations of an ACE inhibitor and angiotensin II receptor blocker (34), addition of aldosterone antagonists, such as spironolactone, to the BP-lowering regimen with blockers of the RAS (35,36), and doses of ACE inhibitors or angiotensin II receptor blockers exceeding those recommended for BP-lowering effects (37). Although the results of some of these studies have been very encouraging with regard to the reduction of urinary protein excretion and the above combination therapies appear to be safe, these regimens have not yet been endorsed by the CHEP.

CONCLUSION

Evidence for recommendations for BP targets and treatment of hypertension in patients with nondiabetic CKD, as outlined in Table 2, is limited compared with diabetic CKD patients. However, because CKD is now recognized as a major independent risk factor for cardiovascular morbidity and mortality, more patients with CKD are likely to be included in large RCTs. This will likely strengthen our recommendations for treatment of hypertension in this population.

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