Prehypertension: is it relevant for nephrologists?

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Blood pressure (BP) in the prehypertensive range is associated with an increased risk for cardiovascular (CV) disease. Patients with co-morbidities are at greater risk for chronic kidney disease (CKD) development in the presence of prehypertension. Lifestyle changes can alter the natural history of prehypertension; however, long-term adherence is rare and thus, their impact on outcomes is limited. Pharmacological therapy in patients with prehypertension and demonstrable target organ damage with blockers of the renin-angiotensin system has demonstrated benefits on markers of CKD outcomes such as microalbuminuria. There are no data, however, on ‘hard end points’ such as doubling of creatinine or need for renal replacement therapy. In patients with diabetes, monitoring changes in albuminuria, along with assessment of BP in the prehypertensive range, is important to optimize early management and impact the attenuation of CKD progression. Data from natural history studies in patients with type 1 diabetes indicate that increases within the microalbuminuria range antedate increases in BP within the prehypertensive range. Even within the microalbuminuria range, however, systolic BP increases above 125 mm Hg are predictive of nephropathy. Thus, nephrologists need to ensure that their colleagues appreciate the importance of not only early BP intervention but also of monitoring albuminuria changes in order to have maximal impact on CKD prevention.

It is known that the relationship between the level of blood pressure (BP) and the risk of cardiovascular (CV) disease events is continuous, consistent, and independent of other risk factors. Observational studies involving more than 1 million individuals indicate that death from both ischemic heart disease and stroke increases linearly, starting at BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic upward.1 Epidemiological studies also support the hypothesis that the level of BP and risk of chronic kidney disease (CKD) progression is linear and extends into the normotensive range.2,3

The term ‘prehypertension’ was selected by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP to define a group at higher CV risk with BP readings not previously considered significant by clinicians.4 The range of BPs defined as prehypertension is 120–139/80–89 mm Hg. This range is based on two pieces of data: first, large epidemiological studies, as previously mentioned and second, data obtained from the focus groups of patients with hypertension as gathered by members of the executive committee of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP.1,4 The purpose of the focus groups was to define a term that resonates with the populace that would prompt them to ask for advice if they were told that they were prehypertensive. The epidemiological analyses provide evidence that the range of BPs defined as prehypertension are associated with an intermediate level of CV risk, higher than normotensive patients, that is, <120/80 mm Hg but less than those with stage 1 hypertension, that is, >140/90 mm Hg.5

The data for prehypertension contributing to development of CKD are weak. This review summarizes recent information on prehypertension that is relevant for nephrologists. It focuses on prehypertension as a CKD risk factor and its potential contribution to progression of CKD.

PREHYPERTENSION AND CO-MORBIDITIES

The presence of prehypertension, especially in the range of ≥130/80 mm Hg, is a harbinger of hypertension and risk of developing hypertension that increases with age.6 Normotensive individuals at 55–65 years of age have more than a 90% chance of developing hypertension by age 80.4,6 Thus, increases in BP are a reflection of advancing age as well as development of co-morbid conditions, such as obesity and
diabetes. All of these conditions are known to accelerate vascular aging by a variety of mechanisms, all converging on nuclear factor-κB and discussed later in this paper.\(^7\)\(^9\)

The prevalence of prehypertension is approximately 31–37% in the adult population of the United States, much higher than hypertension, which is about 20%.\(^10\) Prehypertension is most commonly associated with obesity and metabolic syndrome,\(^8\)\(^11\) the risk factors also appreciated to accelerate development and progression of CKD.\(^8\)\(^10\)\(^14\) A marker of CKD progression, proteinuria, is 43–56% higher in overweight and obese persons with nephropathy compared with individuals with body mass index (BMI) < 25 kg/m\(^2\).\(^15\) Moreover, there is epidemiological evidence from a large cohort study that body mass index is the strongest predictor of prehypertension in both men and women, relative to other variables tested.\(^16\)

The metabolic syndrome is an important factor in the pathogenesis of CKD.\(^11\) However, it is a compilation of risk factors that include hypertension, but not prehypertension. Analyses of large databases show an association between prehypertension, metabolic syndrome, and CKD, as well as increased CV risk. Prehypertension alone, however, was not found to increase the risk of CKD development.\(^6\)\(^17\)\(^18\) Data from the Metabolic Syndrome in Active Subjects in Spain Registry substudy further support this assertion. This substudy shows that prehypertension is an insulin resistance state and not the result of CKD.\(^8\) This suggests that alterations of kidney function are a consequence rather than a cause of elevated BP in the range of 120–139/80–89 mm Hg. Thus, one must judge prehypertension by the company it keeps.

Prehypertension is associated with a number of nontraditional risk markers, all of which are associated with endothelial dysfunction, accelerated vascular aging, and increased CV risk. Some of these factors include microalbuminuria,\(^12\) C-reactive protein, serum tumor necrosis factor-α, amyloid A, endothelin-1, homocysteine, advanced glycation end products, and higher white blood cell counts.\(^19\) A commonly measured marker of kidney function is microalbuminuria. It is a marker of endothelial dysfunction, and an independent risk marker for CV events, and not a marker of kidney disease as was previously thought.\(^20\) Increases in microalbuminuria over time, in the presence of BP either remaining in the prehypertensive range or well controlled, is associated with not only worsening endothelial function but also with worsening kidney function.\(^21\)

Many studies have tried to show a relationship between blocking increases in microalbuminuria and prevention of nephropathy. Blockers of the renin-angiotensin system are frequently used to achieve this aim. Unfortunately, all of these studies are confounded by reductions in BP, with none showing true prevention of nephropathy independent of BP reduction.\(^20\)\(^22\) Therefore, it is the prevention of BP rise that would slow or prevent nephropathy progression and not something specific to a drug class.\(^23\) This is not the case, however, once advanced nephropathy with proteinuria is present. In this setting of a BP being usually > 140/90 mm Hg, BP reduction using blockers of the renin–angiotensin system and ensuring maximal reductions in proteinuria are associated with slower CKD progression.\(^24\)

Prehypertension as a risk factor is relevant in the setting of concomitant diseases associated with it as well as the age of the patient. Recent data on aging show that mitochondrial production of reactive oxygen species, innate immunity, the local tumor necrosis factor-α-converting enzyme, and the renin–angiotensin system may underlie nuclear factor-κB induction and endothelial activation in aged arteries. Thus, multiple proinflammatory pathways converge on nuclear factor-κB in the aged arterial wall, and transcriptional activity of nuclear factor-κB is regulated by multiple nuclear factors.\(^25\) This is an important observation as prehypertension, as part of the aging process, may simply be the reflection of the magnitude of proinflammatory injury to the vessel.

A review of the data dealing with inflammatory markers, put into the perspective of vascular aging and prehypertension, notes that increased production of reactive oxygen species observed in aging and hypertension may provide the missing link interconnecting endothelin-1 and other inflammatory markers.\(^7\) These data are relevant to CKD progression, as the most common causes of CKD, diabetes, and hypertension are diseases of accelerated vascular aging. Hence, understanding these vascular changes in the context of prehypertension as a marker of these changes is an important first step in stopping CKD development associated with these diseases.

Evidence to support prehypertension as a marker of target organ injury comes from a cohort of adolescents with a high prevalence of obesity and diabetes. In this cohort, prehypertension was associated with increased cardiac output, peripheral resistance index, and evidence of increased arterial stiffness.\(^26\) This increase in arterial stiffness is associated with a lower kidney function even within the normal reference range and more importantly higher CV risk.\(^27\)

**PREHYPERTENSION AND CKD PROGRESSION**

**Epidemiologic evidence**

The majority of information regarding CKD progression or its development comes from advanced nephropathy studies in people with hypertension.\(^28\) All of the studies dealing with prehypertension, however, are epidemiological analyses of large databases\(^2\)\(^29\)\(^30\) or small limited-outcome studies and are summarized in Table 1. These epidemiological studies have a range of follow-up between 7 and 21 years and show a graded relationship between BP levels and the risk of CKD. These studies are consistent, however, in that they indicate that people with BP levels > 130/80 mm Hg over extended periods of follow-up have between 11 and 90% risk of worsening kidney function due to the prehypertension. It should be noted that many of the people in these studies did have concomitant risk factors, including hyperlipidemia and other metabolic disturbances.
A representative study to illustrate the relationship between CKD risk and prehypertension comes from the Multiple Risk Factor Intervention Trial. A clear relationship between the level of systolic and diastolic pressure over a 16-year follow-up period provided important information in the context of end-stage renal disease (ESRD) incidence. Indeed, the increase in risk was noticeable across the prehypertensive BP range, especially with a 43.6% higher likelihood of progressing to ESRD if it was in the 130–139/85–89 mm Hg range versus the lower range (Figure 1). Overall, the relative risk (RR) for the progression to ESRD related with any cause in 73,798 men, with baseline BPs of 120–129/80–84 mm Hg, was almost double, compared with optimal BP (RR 1.9, 95% confidence interval (CI) 1.4–2.7, P<0.001, Figure 1).2

Further support for the relationship between prehypertension and risk of ESRD comes from an analysis of the Kaiser Permanente group in northern California. Investigators evaluated 316,675 men and women who participated in health check-ups between 1964 and 1985. In a subset of 128,270 subjects (40.5%) with BPs in prehypertensive range, the adjusted RR for ESRD was significantly increased in both groups with BPs between 120 to 129/80 and 84 mm Hg (RR 1.62, 95% CI 1.27–2.07) and 130 to 139/85 and 89 mm Hg (RR 1.98, 95% CI 1.55–2.52), Figure 1,3 compared with those with a BP of <120/80 mm Hg. In addition, data from a prospective cohort study of 158,365 Chinese men and women over the age of 40 years,30 and the Physicians Health Study of 8093 healthy men without known kidney disease at baseline support this observation. In the Physicians Health Study, 25.1% of the total group (n=2037) of men had BPs in the prehypertensive range and this group had a 26% higher risk of having an estimated glomerular filtration rate of <60 ml/min per 1.73 m² compared with those with a BP of <120/80 mm Hg.29

Taken together, these studies support the notion that BP elevations above a systolic BP of 130 mm Hg is associated with a higher risk of CKD development or progression. This is further corroborated by data from the Kidney Early Evaluation Program. In a recent analysis in which 88,559 participants were evaluated, 20,500 (23.1%) were in the prehypertensive range. This analysis found that the greater the systolic BP levels, even in the prehypertensive range, 130–139 mm Hg, the greater is the probability of

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### Table 1 | Epidemiological studies of CKD/ESRD risk and prehypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects in the study</th>
<th>No. of subjects with prehypertension</th>
<th>Years or person-years of follow-up</th>
<th>Blood pressure levels</th>
<th>Risk of CKD</th>
<th>Final event</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRFIT study2</td>
<td>332,544 men</td>
<td>73,798 men</td>
<td>16 years follow-up</td>
<td>130–139/80–89 mm Hg</td>
<td>RR 1.9 (95% CI 1.4–2.7)</td>
<td>Incidence of ESRD</td>
</tr>
<tr>
<td>Hsu et al.3</td>
<td>316,675 men and women</td>
<td>128,270 men and women</td>
<td>21 years/8,210,431 person-years</td>
<td>BP 120–129/80–84 mm Hg</td>
<td>RR 1.62 (95% CI 1.27–2.07)</td>
<td>Incidence of ESRD</td>
</tr>
<tr>
<td>Physicians Health Study2</td>
<td>2037 men</td>
<td>14 years follow-up</td>
<td>130–139/85–89 mm Hg</td>
<td>OR 1.26 (95% CI 1.03–1.53)</td>
<td>Incidence of CKD</td>
<td></td>
</tr>
<tr>
<td>Reynolds et al.30</td>
<td>158,365 men and women</td>
<td>54,654 men and women</td>
<td>1,236,422 person-years</td>
<td>OR 1.11 (95% CI 0.89–1.31)</td>
<td>CKD</td>
<td></td>
</tr>
<tr>
<td>CLUE study32</td>
<td>23,534 men and women</td>
<td>46.3% higher risk*</td>
<td>20 years</td>
<td>Prehypertension</td>
<td>OR 1.30 (95% CI 0.98–1.74)</td>
<td>CKD</td>
</tr>
<tr>
<td>Obermay et al.31</td>
<td>17,375 men and women</td>
<td>~70% with normal BP and prehypertension</td>
<td>7 years</td>
<td>Prehypertension</td>
<td>OR 1.11 (95% CI 0.89–1.31)</td>
<td>CKD</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CKD, chronic kidney disease, glomerular filtration rate <60 ml/min per 1.72 m² using the abbreviated Modification of Diet in Renal Disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease, as recipient of renal transplantation or maintenance dialysis; HR, hazard ratio; MRFIT, Multiple Risk Factor Intervention Trial; NS, not significant; OR, odds ratio; RR, risk reduction; SBP, systolic blood pressure.

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**Figure 1** | Age-adjusted rates of end-stage renal disease (ESRD) for prehypertension in the Multiple Risk Factor Intervention Trial (MRFIT) and Hsu et al. analyses. *Between the MRFIT prehypertensive cohorts, the risk for ESRD development was increased.*
CKD being present (20% at <130 mm Hg, 28.5% at 130–139 mm Hg, \(P<0.001\)), a relationship that held regardless of race or sex.\(^\text{33}\)

It is clear that the relationship between prehypertension and CKD is weak, as smaller and shorter-term studies fail to show this association. A community-based, observational study of 23,534 people, followed for 20 years to evaluate CKD risk, found that the RR of developing CKD among those with high normal BP levels was 3.3 (95% CI 0.4–25.6) for men compared with individuals with optimal BP and 3.0 (95% CI 0.6–14.4) for women. The associations of high normal neared statistical significance (\(P = 0.075\)).\(^\text{32}\) A second longitudinal cohort study of 17,375 apparently healthy volunteers in Vienna, followed for a median of 7 years to evaluate the relationship between prehypertension and CKD, showed similar findings with the aforementioned study.\(^\text{31}\) Both these studies had very wide confidence intervals and helped to make the point that the associations between prehypertension and CKD risk are present but weak. As has been noted in many analysis, it is the presence of concomitant metabolic derangements that contributes to CKD development in addition to prehypertension.\(^\text{8,11}\)

Studies in pre-existing conditions, such as diabetes, provide stronger data about the relationship of prehypertension and CKD risk. In a population-based sample of adults with type I diabetes, lower BPs were protective against incident proteinuria and incident estimated glomerular filtration rate reductions to <60 ml/min per 1.73 m\(^2\). The maximum protective effect for both of these kidney disease-related outcomes was observed at BP levels of <120/80 mm Hg.\(^\text{34}\) In this study, those with a systolic BP between 120 and 129 mm Hg had a lower 16-year cumulative incidence of proteinuria, 0.76 (95% CI 0.53–1.09) compared with those with a systolic BP of >130 mm Hg (\(P<0.0001\)).\(^\text{34}\) Lastly, data from 137 patients with type I diabetes in Denmark showed that increases in systolic BP above 125 mm Hg predicted development of nephropathy.\(^\text{35}\) Moreover, it is established that people with type I diabetes with BP increases into the high prehypertensive range and who have increases in albuminuria from baseline, are more likely to have CKD progression. In the Diabetes Control and Complication trial, 19 of 21 (90%) progressors reached clinical diabetic nephropathy before the diagnosis of hypertension was made, that is, >140/90 mm Hg. In the intensive glycemic treatment group, the rise in diastolic BP preceded the rise in albuminuria by 1 to 2 years. Intensively treated progressors who developed hypertension did so before developing albuminuria, that is, >300 mg/day. Thus, in high-risk CKD patients, both the change in albuminuria within the microalbuminuria range and BP within the prehypertensive range need to be monitored.\(^\text{35,36}\)

**PREHYPERTENSION AND HISTOLOGICAL EVIDENCE OF CKD**

Data on the relationship between changes in mesangial proliferation and degree of arteriolar hyalnosis within the prehypertensive range are limited to only a few diseases. Diabetes and immunoglobulin A nephropathy have data showing changes in mesangial proliferation and degree of arteriolar hyalnosis in the prehypertensive range. Diabetes is confounded by glycemic effects on tissue; therefore, data evaluating vascular changes in type I diabetes, the best model to assess prehypertensive changes, are not very revealing. Immunoglobulin A nephropathy, being an immunologically mediated disease, may provide more insight.

A study of 332 consecutive renal biopsy specimens, coupled with clinical data from patients with immunoglobulin A nephropathy, describe changes in mesangial proliferation and arteriolar hyalnosis affecting the interlobular artery that correlated with BP levels in the prehypertensive range. A greater degree of mesangial proliferation and arteriolar hyalnosis was noted in prehypertensive range of <140/90 mm Hg, whereas no changes were noted among those with an optimal BP of <120/80 mm Hg.\(^\text{37}\) In a separate study by Hisayama et al.,\(^\text{38}\) 652 consecutive population-based autopsy samples without hypertension treatment were evaluated before death. The relationship between the severity of renal arteriosclerosis and BP levels was classified according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. Both hypertensive and prehypertensive subjects, after adjustment for age and gender, had significantly higher frequencies of renal arteriosclerosis than subjects with normal BP (normal 11.9%; prehypertension 28.5%; stage 1 hypertension 32.9%; stage 2 hypertension 58.2%). In a logistic regression model, those with prehypertension had a higher incidence of renal arteriosclerosis and arteriolar hyalnosis after adjustment for other CV risk factors. This significant association was observed across renal arterial vasculature.\(^\text{38}\)

Taken together, these data support the following concepts. First, increases in BP over time within the prehypertensive range are associated with morphological changes within the kidney as well as the behavior of the endothelium. Second, increases in albuminuria parallel BP increases and can antedate development of hypertension in type I diabetes. This is generally not the case in type II diabetes. Lastly, from natural history studies in type I diabetes performed by Mogensen (Mogensen, personal communication), it is clear that increases in systolic BP to levels >125 mm Hg are associated with development of nephropathy. Interestingly, only approximately 30% of the people studied by this group developed increases in pressure; this is the incidence of nephropathy in type I diabetes.\(^\text{35,39}\) Recent findings of candidate genes that identify patients with diabetes as high risk for nephropathy may also affect BP changes.\(^\text{40}\) Whether this susceptibility is mediated by changes within the kidney or emanate from the endothelium throughout the body is unknown.

**MANAGEMENT OF PREHYPERTENSION**

The current data support lifestyle intervention as the cornerstone of therapy for the general population: weight reduction to maintain normal body weight (body mass index 18.5–24.9), adopting the Dietary Approaches to Stop
Hypertension plan, reducing sodium intake to <100 mEq/l (2.4 g sodium or 6 g sodium chloride), increasing physical activity (at least 30 min per day, most days of the week), and limiting alcohol consumption to under 1 oz or 30 ml ethanol. These interventions have all been shown to reduce the risk of BP increases over time.

Evidence of the success of lifestyle modifications come from trials such as PREMIER, conducted in 810 adult participants volunteers with prehypertension or stage 1 hypertension to assess the effect of a behavioral intervention on BP. The intervention groups were successful in reducing BP and the prevalence of hypertension at 6 months. In the 18-month intervention, participants in both behavioral intervention groups had less hypertension, more weight loss, and better reduction in sodium and fat intake than those receiving only advice. However, the differences were not statistically significant. Physicians were more likely to recommend lifestyle modifications to obese people, even though they were neither more nor less likely to adhere to the advice than those with normal weight. Furthermore, individuals were less likely to follow advice on exercise and weight loss than sodium and alcohol restriction.

A few things are clear from all lifestyle intervention studies; they are effective for delaying the onset of hypertension in the short term, up to 1 year, but then there is regression to the mean. This is true for all studies of lifestyle modification, including weight loss studies as well as those requiring major decision making on the part of the patient. Thus, only a minority of individuals adhere to lifestyle recommendations derived from trials, as evidenced by obesity and diabetes being international epidemics. Moreover, nephrologists rarely see these patients early in their natural history. It is noteworthy that there are no such lifestyle interventions in early CKD, although because sustained increases in BP over time are well known to contribute to CKD progression, one could assume that keeping BP from rising with an exercise, low sodium lifestyle would be beneficial for preserving kidney function.

**PHARMACOLOGICAL MANAGEMENT**

There are very few trials that examine interventions to alter the natural history of disease within the prehypertensive range. No study has tested an intervention in this BP range to evaluate change in kidney function in the general population, although a recent study has examined this in early type I diabetes.44

The only trial that evaluated the natural history of hypertension in a general context was The Trial Of Preventing Hypertension. This was a randomized, placebo-controlled, double-blinded clinical trial designed to evaluate whether 2 years of treatment with the angiotensin receptor blocker candesartan cilexetil at 16 mg daily alters the natural history of hypertension development. A total of 809 individuals were randomly assigned to placebo or low-dose candesartan cilexetil for 2 years, followed by 2 years of placebo. The trial showed that pharmacological treatment can prevent or postpone the development of hypertension, with a 66.3% reduction in hypertension incidence relative to placebo over the first 2 years and a 26.8% absolute reduction at the end of 2 years. Over all 4 years, there was a 15.6% reduction in hypertension incidence relative to placebo and a 9.8% absolute reduction. The benefit of a lower BP over a longer time period was evident in the active treatment group, although there was some regression to the mean over the ensuing 2 years when patients were switched to placebo.

Perhaps, the majority of studies evaluate changes in the prehypertensive range in the setting of diabetes. More than 30 years ago, Marre et al. showed that in normotensive patients with type 1 diabetes (baseline BP 137/82 mm Hg), a reduction in BP with an angiotensin-converting enzyme inhibitor, enalapril, 20 mg/day for 6 months reduced persistent microalbuminuria, but there were no data on nephropathy progression. More recently, a multicenter, controlled trial involving 285 normotensive patients with type I diabetes and normoalbuminuria by Maurer et al. randomly assigned patients to receive losartan (100 mg daily), enalapril (20 mg daily), or placebo for 5 years. The primary end point was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The researchers noted no difference in mesangial fractional volume per glomerulus over the 5-year period between the placebo group (0.016 units) and either of the treatment groups. These changes were independent of differences in BP among the groups. Thus, they concluded that early blockade of the renin–angiotensin system in patients with type I diabetes did not slow nephropathy progression but slowed the progression of retinopathy. These data, taken together with outcome data, suggest that the effects of early pharmacological intervention even in early type I diabetes are not warranted beyond good glycemic and lipid management to slow nephropathy.

Interventions in type II diabetes, however, may be different (Table 2). The Appropriate Blood pressure Control in Diabetes ABCD trial examined the progression of nephropathy over a 5-year period, comparing intensive usual BP control in patients with type II diabetes. The unique intervention in this trial is that all patients were normotensive. The lower BP groups with an achieved systolic BP of <130/mm Hg showed slowed progression to incipient and overt diabetic nephropathy, decreased progression of diabetic retinopathy, and diminished incidence of stroke.

More recent evidence shows the effect of active treatment on CKD outcomes in the Action in Diabetes and Vascular disease Controlled Evaluation study. The data from this large trial in patients with predominantly stage 1 hypertension showed slowing of CKD development independent of the initial BP levels, even if within the normotensive range of <120/70 mm Hg. Moreover, those who were able to achieve a systolic BP level of <110 mm Hg systolic and 65 mm Hg diastolic have the greatest slowing of CKD. This trial further supports the notion of treating BP much earlier in the disease course to possibly stop nephropathy progression.
CONCLUSION

Those with prehypertension have an increased risk for CV disease. The totality of the evidence, largely from epidemiological studies, illustrates that BP in the prehypertensive range influences CKD progression but only to a minor extent. Its effect takes on greater relevance when present with concomitant metabolic risk factors or with target organ injury, especially in older patients. Studies of >5 years would be needed to fully assess the effect of prehypertension on CKD progression; however, given the current guideline recommendations for CV risk reduction coupled with early observations of Mogensen’s group of more than two decades of follow-up (personal communication), it is highly unlikely that anyone whose systolic BP remains below 130 mm Hg even without treatment is at risk for clinical nephropathy and certainly not ESRD. Given that nephrologists rarely see patients with prehypertension, they should be aware that pharmacological intervention at levels above a BP of 130/80 mm Hg will not dramatically alter nephropathy progression in people with normo or microalbuminuria, based on recent prospective data. One could speculate that the results might be more dramatic among those with albuminuria levels of >200 mg/day, as this has universally been the case in outcome studies.24 Individuals with target organ damage evidenced by albuminuria or elevated creatinine would be excellent candidates for drug therapy involving agents that block the renin-angiotensin system if their BP was in the prehypertensive range.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES


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**Table 2 | Studies in high-risk patients with diabetes and prehypertension: focus on CKD outcomes**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects in the study</th>
<th>Follow-up</th>
<th>Treatment with ACE inhibitor/ARB</th>
<th>Blood pressure levels</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marre et al.46</td>
<td>Double-blind study</td>
<td>20 normotensive patients with type I and II DM</td>
<td>6 months</td>
<td>Enalapril 20 mg/day or placebo</td>
<td>BP 132/81 mm Hg BP 137/82 mm Hg</td>
</tr>
<tr>
<td>ABCD study47</td>
<td>Randomized controlled intensive vs moderate study</td>
<td>480 normotensive patients with type II DM</td>
<td>5.3 years</td>
<td>Nisoldipine or enalapril as the initial treatment</td>
<td>BP 128/75 mm Hg</td>
</tr>
<tr>
<td>ADVANCE study48</td>
<td>Randomized controlled study</td>
<td>11,140 patients with type II DM</td>
<td>4.3 years</td>
<td>Perindopril-indapamide vs placebo</td>
<td>SBP &lt; 120 mm Hg SBP 120–139 mm Hg</td>
</tr>
<tr>
<td>Shimizu et al.49</td>
<td>Prospective controlled study</td>
<td>18 patients with IgA nephropathy</td>
<td>12 months</td>
<td>Losartan 12.5 mg/day</td>
<td>Normotensive</td>
</tr>
</tbody>
</table>

Abbreviations: ABCD, Appropriate Blood Pressure Control on Diabetes; ACE inhibitor, angiotensin-converting enzyme inhibitor; ADVANCE, Action in Diabetes and Vascular disease: Controlled Evaluation study; ARB, angiotensin receptor blocker; DM, diabetes mellitus; HR, hazard ratio; IgA, immunoglobulin A; SBP, systolic BP.


