Hypertension as a Risk Factor for Chronic Kidney Disease
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Abstract
Five decades back, high blood pressure (BP) was considered as an essential malady and not a treatable condition. Gradually, evidences started accumulating through major trials and now hypertension is the most common comorbidity and a powerful risk factor for chronic kidney disease (CKD) and coronary artery disease (CAD) and an independent risk factor for CKD progression. Although hypertension is the second most common cause of end-stage renal disease, next to diabetes mellitus, only few patients of primary hypertension develop renal dysfunction. The risk of hypertensive nephrosclerosis is high in African americans, independent of age, sex, and prevalence of hypertension. The clear-cut benefits of lowering BP in CKD patients are renoprotection and reducing the risk of CV complications. The less clear is the optimal BP targets and the best method for measuring and achieving the targets. Recent evidences suggest a BP goal of <130/80 mmHg irrespective of age and proteinuria, despite controversies. Home BP monitoring is gaining importance and it should be emphasized in all hypertensive patients.

Key words: Nephrosclerosis, hypertension, ESRD, BP goals, SPRINT

Introduction
Hypertension is one of the leading risk factors for death and disability, including stroke, accelerated coronary and systemic atherosclerosis, heart failure, and chronic kidney disease (CKD). The kidney is a major site of target end organ damage, and it is the second most common cause of end-stage renal disease (ESRD) next to diabetes mellitus. The threshold for diagnosing hypertension has declined over time, on the basis of major trials showing cardiovascular benefits of lowering blood pressure (BP) targets. Previously, hypertension has been defined as a BP of 140/90 mmHg or more, the 2017 ACC-AHA hypertension guideline adopted a lower threshold, in which hypertension is defined as a systolic blood pressure (SBP) of 130 mmHg or more or a diastolic BP of 80 mmHg or more. It has been shown that the risk ratio for CKD was 2.8 for a pre-treatment SBP of 166–180 mmHg and 7.6 for pre-treatment BP >180 mmHg. Lowering SBP by more than 2 mmHg was associated with a marked decrease in the relative risk (RR) of developing ESRD. Although hypertension was associated with an increased risk of developing ESRD, the overall rates of developing ESRD were low; approximately 15 cases per 100,000 person-years in the multiple risk factor intervention trial (MRFIT) study. Although hypertensive nephrosclerosis is the second most common cause of ESRD, the risk of developing ESRD in a hypertensive patient is <0.5%. In this paper, we review the epidemiology, pathophysiology of hypertensive CKD, and various trials on intensive BP control and renal outcomes, and controversies regarding the target BP goal.

Hypertension - cause and Consequence of CKD
High BP can be either a cause or a consequence of CKD. Estimating the prevalence of CKD attributable to hypertension alone is difficult as individuals with presumed hypertensive nephrosclerosis are rarely biopsied, and strict clinical criteria are not routinely followed to make a diagnosis. The reported incidence and prevalence of ESRD owing to hypertension is, therefore, likely an overestimate because of alternative diseases that are undiagnosed or overlooked. However, a strong...
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relationship was observed between both SBP and diastolic blood pressure (DBP) and ESRD. In men who were recruited in the MRFIT, the RR for ESRD was 20-fold higher for patients with Stage 4 hypertension (SBP 210 mmHg or DBP 120 mmHg) than for patients with optimal BP levels (SBP 120 mmHg and DBP 80 mmHg). The recent study by the Okinawa General Health Maintenance Association confirmed these results in women as well. A 17-year follow-up study by Tozawa et al. have demonstrated that high normal BP and mild, moderate, or severe hypertension, when compared to optimal BP, are independent risk factors for ESRD in men and women. The study, which included 46,881 men and 51,878 women undergoing dialysis, categorized BP as optimal (110 ± 6/68 ± 6 mmHg), normal (121 ± 4/75 ± 6 mmHg), high normal (131 ± 4/79 ± 6 mmHg), mild hypertension (142 ± 8/86 ± 7 mmHg), moderate hypertension (160 ± 11/94 ± 9 mmHg), and severe hypertension (181±16/105±12 mmHg). Age, body mass index, and adjusted relative risk for systolic and diastolic blood pressure for both men and women were measured. When these results were compared with an optimal blood pressure, the relative risk of development of end-stage renal disease for those with high-normal blood pressure and hypertension were significant in both men and women. Despite many studies, the level of blood pressure control that slows the progression and time course for the development of CKD remains disputed.

The debate on kidney being a cause of essential hypertension was resolved, after the proof-of-principle experiment, which demonstrated remission of essential hypertension in six African-American hypertensives with ESRD after they received successful kidney transplants from a normotensive donor. Hypertension develops early in the course of CKD and can be associated with worsening renal function and development of cardiovascular disease. Based on a national survey of representative sample of non-institutionalized adults in the USA, it is estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of Stage 1, 48.1% of Stage 2, 59.9% of Stage 3, and 84.1% of Stage 4–5 CKD patients

Pathogenesis

The renal pathology typically observed in majority of individuals with essential hypertension is benign nephrosclerosis, described as an accelerated aging of the renal vasculature, which is characterized by a very slow progressive thickening and sclerosis of the renal resistance vessels, whereas the glomerular capillaries are largely spared. Some ischemic glomerular loss does occur, but it is limited and happens slowly over decades. Thus, significant reduction in renal function and ESRD develops only after large losses of glomerular filtration surface area; hence, it is not too surprising that incidence of ESRD occurs infrequently in essential hypertension. In fact, except for some genetically susceptible groups such as African Americans, the only individuals with essential hypertension who develop sufficient hypertension-induced renal damage (HIRD) to cause ESRD are those in whom the hypertension becomes very severe and results in the development of malignant nephrosclerosis. In contrast to the relative resistance to HIRD in individuals with essential hypertension in the absence of genetic predisposition and malignant nephrosclerosis, individuals with CKD and diabetes mellitus seem to exhibit a much greater susceptibility to the adverse renal effects of even moderate hypertension. Moreover, in contradistinction to the largely vascular pathology of benign and malignant nephrosclerosis, the site of HIRD in CKD is predominantly glomerular, with a pattern of accelerated segmental or global glomerulosclerosis often superimposed on the intrinsic phenotype of the underlying renal disease.

Normally, episodic or sustained increases in BP result in proportionate autoregulatory vasoconstriction of the afferent arteriole (preglomerular vasculature) such that renal blood flow is maintained relatively constant within the autoregulatory range. The glomerular capillaries are protected from barotraumas as long as autoregulation is intact (Figure 2). Hence, vast majority of cases with essential hypertension usually do not exhibit glomerular injury and proteinuria. However, the resistance arterioles are exposed to chronic hypertension and slowly develop the pathology of benign nephrosclerosis. If the hypertension becomes very severe and exceeds the threshold for autoregulation, disruptive vascular injury occurs and malignant nephrosclerosis develops. The impairment of renal autoregulation associated with severe reductions in renal mass, as in established CKD, allows even moderate hypertension to be more freely transmitted to the glomerular capillaries with resultant barotraumas and progressive glomerulosclerosis (Figure 1). Vasodilatation alone with preserved autoregulation, observed after uninephrectomy only modestly increases the susceptibility to hypertensive injury.

The discovery of an association between MYH9 polymorphisms and kidney disease added insight into the underlying etiology of hypertensive nephrosclerosis. MYH9 polymorphisms result in podocyte dysfunction, leading to glomerulosclerosis. This might explain why BP control alone cannot reverse existing kidney damage or stop progression in AASK population (The African American study of kidney disease and hypertension).

The mechanisms of hypertension in CKD are multifactorial (Table 1). Failure of pressure natriuresis is one of the dominant mechanisms causing hypertension in CKD. Defective efferent arteriolar NO production during endothelial dysfunction states, such as diabetes mellitus and obesity, may exaggerate glomerular capillary pressure and increased susceptibility to glomerulosclerosis. Activation of the renin-angiotensin system (RAS) was proposed to be the mechanism in dialysis patients with uncontrolled hypertension despite optimized ultrafiltration. Bilateral nephrectomy or RAS blockers in such patients have been shown to control BP, suggesting failing kidneys as the source of excess renin. RAS activation may also contribute to hypertension by stimulating the sympathetic nervous system.

BP Goals

Whether intensifying the BP control in the prehypertensive stage will prevent the development of CKD and whether the use of
The best representation of natural history of hypertensive nephrosclerosis was the AASK cohort, which excluded patients with diabetes and marked proteinuria or alternative etiologies of renal dysfunction. The AASK study followed approximately 1100 individuals with baseline CKD (eGFR 20–60 ml/min/1.73 m²) and evaluated the effect of “strict” BP lowering on kidney disease progression. The intensive group targeted a mean arterial pressure (MAP) of 92 mmHg, whereas the control group targeted MAP of 102 mmHg. There was no significant difference in retarding CKD progression between the two groups on 10-year follow-up. However, a subgroup analysis in AASK cohort found that, in those who had a proteinuria of more than 300 mg/day, they demonstrated a slower decline in GFR at lower BP levels. Thus, the renoprotective effect of lower BP is actually evident in patients with higher proteinuria, thus providing additional support for recommending lower BP targets for these patients.

Non-diabetic Proteinuric Nephropathy

RCTs have shown that BP of <130/80 mmHg may reduce progression of CKD in patients with urine albumin excretion of more than 300 mg per 24 h (“macroalbuminuria”). In a subgroup analysis of MDRD study, which consisted of non-diabetic patients, showed that lowering mean BP to 92 mmHg (equivalent to 125/75 mmHg) preserved renal function in those with proteinuria of >3 g/day or >1 g/day in a subset with glomerular filtration rate of 25–55 ml/min/1.73m². The benefit of lowering BP target in patients with a PCR of more than 220 mg/g was also evident from the long-term follow-up data of AASK population. Thus, there is sufficient evidence to suggest a BP target of <130/80 mmHg for kidney protection in those with macroalbuminuria. KDIGO graded this suggestion as 2C, as the reported benefits in the AASK and the MDRD study were based on post hoc and subgroup analyses. However, it should be kept in mind that in both the MDRD study and AASK, MAP was targeted rather than systolic and diastolic BP, and a specific MAP may translate into different systolic and diastolic BP, depending on the individual patient.

Diabetic Nephropathy

The antiproteinuric effect of lowering BP is one of the most important mechanisms involved in the renoprotection, regardless of the type of drug administered, in both diabetic and non-diabetic kidney disease. The secondary analysis of the IDNT study, in type 2 diabetics, showed an optimal renoprotective effect when the SBP is between 120 and 130 mmHg, with no further benefits <120 mmHg. The normotensive ABCD trial compared intensive with moderate BP lowering in normotensive type 2 diabetic patients. BP attained in the intensive and moderate treatment arms were 128/75 and 137/81 mmHg, respectively, and the corresponding rates of microalbuminuria were 21% and 25%. There was no difference in the rate of progression.
decline of renal function; lesser degree of proteinuria was noted with intensive therapy. This is especially true from the results of ACCORD BP trial. This trial included a large number of diabetic patients, who had a mean serum creatinine of 0.9 mg/dl, with minimal proteinuria, with cardiovascular disease, or at least two risk factors for cardiovascular disease and evaluated the impact of lowering SBP <120 or 140 mmHg. While the intensive group attained an average SBP of 119 mmHg, the standard group attained an average SBP of 133 mmHg. There was no difference in the primary outcome between the two groups except for the reduction in non-fatal stroke in the intensive therapy group. The intensive control group had lower risk of stroke but at the expense of higher rates of serious side effects. KDIGO suggests that in diabetic patients with microalbuminuria, a BP goal of <130/80 mmHg and in those without microalbuminuria, KDIGO recommends a target of <140/90 mmHg.

Table 1: Factors causing hypertension in CKD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dominant mechanism</th>
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<tbody>
<tr>
<td>Impaired sodium excretion</td>
<td>Expansion of ECF volume</td>
</tr>
<tr>
<td>Activation of RAS</td>
<td>Direct vasoconstriction and sympathetic activation</td>
</tr>
<tr>
<td>Sympathetic activation</td>
<td>Direct vasoconstriction and renin release</td>
</tr>
<tr>
<td>Imbalance in prostaglandins or kinins</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Direct vasoconstriction, renal injury</td>
</tr>
<tr>
<td>Reduced nitric oxide</td>
<td>Loss of vasodilatory effect</td>
</tr>
</tbody>
</table>

Table 2: The change in BP goals before and after SPRINT trial

<table>
<thead>
<tr>
<th>Guideline</th>
<th>General population</th>
<th>CKD, No proteinuria</th>
<th>CKD, Proteinuria</th>
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<tr>
<td>JNC 7, 2003</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
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<tr>
<td>KDIGO, 2012</td>
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<td>ESC 2013</td>
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<td>JNC 8, 2014</td>
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<td>&lt;140/90</td>
<td>&lt;140/90</td>
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<tr>
<td>AHA 2017</td>
<td>&lt;130/80</td>
<td>&lt;130/80</td>
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Has the Sprint Introduced New BP Goal?

Before the SPRINT trial, optimal blood pressure control fell within the high-normal range (SBP/DBP 130–139/85–89 mmHg). The subject of debate was whether patients with prehypertension or mild hypertension need better BP control? In prehypertensives, the 10-year absolute risk of cardiovascular disease for middle-aged adults without diabetes is about 10%, and rises to 40% in the presence of diabetes and/or established cardiovascular disease. Use of antihypertensives in prehypertensives for secondary prevention decreased the CV disease and death by 15%.

The SPRINT trial included approximately 9000 non-diabetic patients, with an SBP of 130–180 mmHg, aged ≥50 years with a high CV risk, or an established CV disease (excluding stroke). Patients were randomly assigned to SBP targets of either <120 mmHg (intensive treatment) or <140 mmHg (standard treatment). The mean SBP in the intensive BP control group was 121.4 mmHg compared to 136.2 mmHg in the standard-treatment group. The trial was stopped prematurely after 3.26 years of follow-up because of a significantly lower rate of the composite primary end point in the intensive-treatment group compared with the standard-treatment group. No benefit was shown for secondary renal end points. Adverse effects were more with the intensive treatment, but serious adverse events were comparable in both groups. The generalization of the positive findings of the SPRINT trial has to be still evaluated, as it excluded diabetic and stroke patients, and the SPRINT cohort represents only 20–30% of all patients with hypertension [Figure 3].

Caveats of the Sprint Trial

The method used for the measurement of BP in SPRINT trial was different from the other studies. SPRINT used an automated, validated oscillometric device, and the BP was recorded thrice in a quiet and isolated room. This automated office blood pressure measurement (AOBP) was superior to conventional
office BP measurement, and it correlated well with the AMBP measurement (ABPM substudy in SPRINT) and target end-organ damage. The Spanish ABMP study shows that with a BP of <125 mmHg, the white coat hypertension and masked hypertension are very low. The other point to note is, SBP when assessed by AOBP was much lower than when measured with a manual BP instrument. Authors claim that the BP levels attained in the SPRINT intensive control group correspond to office SBP values of 136 mmHg, which is recommended as adequate BP control. Hence, it is still unclear how to translate the AOBP to conventional office BP. Whether that SPRINT trial has overestimated that the result is yet another question, as 50% of the SPRINT population was in prehypertensive stage. ABPM registry showed that among patients with characteristics like SPRINT, 42% of patients had daytime SBP <130 and 21% had 24 h SBP values <120 mmHg. Hence, many people receiving antihypertensive therapy are already within the SBP levels attained in the intensive BP control in SPRINT.

Why the difference compared to the HOPE 3 trial, which almost has a similar cohort like SPRINT? In HOPE trial, the intensively treated group did not benefit from lowering the BP, one major reason being, the population included was those with lower cardiovascular risk, in contrast to the SPRINT cohort.

**Effect on the Guidelines**

The SPRINT trial signaled the need for review of methodology of BP measurement in future clinical trials, and the importance of home AOBP to avoid masked and white coat hypertension. Although the New Australian hypertension guidelines[30] and latest Canadian guidelines[31] accepted the lowering of BP <120/80 mmHg, in patients with similar profile of SPRINT, the Latin American society of hypertension did not change their guidelines, quoting the methodology for BP measurement used in SPRINT trial.[32]

**Does Intensive BP Lowering Increases the Incidence of CKD? The Other Side of the Coin!!**

A very recent secondary analysis of two major trials ACCORD and SPRINT showed that intensive control of SBP increased the risk of incident CKD in patients with and without diabetes. This analysis included 4311 individuals from ACCORD and 6715 individuals with SPRINT. All participants had a baseline eGFR of 60 ml/min per 1.73 m² or higher (subgroup without CKD - 70% of SPRINT cohort and more than 90% of the ACCORD trial cohort). Baseline characteristics were comparable for intensive and standard SBP interventions within ACCORD trial and SPRINT trial. Compared with SPRINT population who did not have diabetes, ACCORD population was younger, having higher BMI, and higher eGFR and albuminuria. Both in the intensive and standard interventions in the ACCORD trial, an early steep in decline in eGFR was noted during the first 12 months, the decline being more pronounced with the intensive intervention. Incident CKD were lower in both intervention groups in SPRINT than in the ACCORD. At 3 years the cumulative incidence of CKD in the ACCORD trial was 10% with the intensive intervention and 4.1% with the standard intervention, corresponding SPRINT values were 3.5% and 1.0%. The absolute risk difference was slightly higher in the ACCORD trial than in SPRINT. This was even stronger in participants with a baseline urinary ACR of 3.4 mg/mmol or higher. Hence, the positive SPRINT results have to be cautiously extrapolated to the patients who are excluded, i.e., diabetic patients. Although ACCORD was underpowered to detect true difference in cardiovascular disease outcomes, participant level pooled meta-analysis of SPRINT and ACCORD showed decreased risk of cardiovascular disease events in the combined cohort. This study suggests the need for monitoring of renal function during intensive antihypertensive therapy, particularly in adults with diabetes. Hence, future studies are needed in this area to understand the clinical implication of treatment-related reductions in eGFR.

**Conclusion**

Hypertension is an important cause and a consequence of CKD. Proteinuric CKD is the target for more intensive intervention. Targeting to <130/80 mmHg definitely has benefit in terms of cardiovascular disease and in proteinuria CKD, but generalizing this statement to all hypertensive population is still questionable, weighing benefit versus risk. Home BP monitoring should be emphasized in all hypertensive patients. Additional studies characterizing the relationship between mild hypertension and subsequent risk of renal disease, standardizing the method of BP measurement is urgently needed.
References


