REVIEW ARTICLE

Hypertensive kidney disease: a true epidemic or rare disease?

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KEY WORDS

arterionephrosclerosis, chronic kidney disease, hypertensive kidney disease, kidney biopsy, renal pathology

ABSTRACT

In the industrialized world, hypertension affects approximately 30% of the general population. Hypertensive kidney disease is considered one of the consequences of long-term and poorly controlled hypertension. According to renal databases, it is a leading cause of end-stage renal failure, second only to diabetic kidney disease. We challenge this dogma by emphasizing lack of specificity of both clinical and morphological presentations of hypertension-related kidney disease and very low prevalence of hypertensive kidney disease that is diagnosed based on kidney biopsy findings in registries. In most cases of concomitant hypertension and chronic kidney disease (CKD), the sequence of events (ie, which came first, CKD or hypertension) cannot be established. Arterial hypertension plays a role in the pathogenesis of chronic vascular disease and may occasionally lead to arterionephrosclerosis, but its general significance in the evolution of CKD and prevalence among CKD patients appear to be highly overestimated. Studies of the morphology of kidney biopsies have indicated that arterionephrosclerosis, classically considered a morphological equivalent of the clinical term "hypertensive kidney disease" (previously referred to as "hypertensive nephropathy"), most commonly superimposes upon variable chronic renal diseases, even in the absence of elevated blood pressure. To date, no prospective controlled clinical trials have been conducted in primary hypertension patients with renal events as primary endpoints. Data from available clinical trials with renal events that serve as secondary endpoints suggest that lowering blood pressure below current targets may provide additional cardiovascular benefits but may be harmful to the kidneys.

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Introduction The kidneys regulate body fluid status and sodium balance and release several blood pressure (BP)-regulating hormones that play an important role in essential and secondary hypertension. The kidneys are also affected by high BP. However, accumulating evidence indicates that this complex interdependence of the kidneys should be considered the culprit rather than the victim of high BP. The present review discusses the true significance of the so-called "hypertensive kidney disease" (HKD) (ie, renal consequences of essential and secondary nonrenal hypertension). Based on a search of recent literature, we believe that such term should be abandoned, with very few specific exceptions.

Hypertensive kidney disease: definitions and epidemiology The prevalence of HKD remains a subject of debate. Some researchers believe that this is a true epidemic, a frequent complication of, and the second most common cause (after diabetic kidney disease [DKD]) of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Other researchers, however, deny the existence of such a diagnosis at all.[1,2] Indeed, several classic studies of hypertension treatment (from the era when placebo could still be used as a control for active treatment) clearly demonstrated that long-term poorly controlled hypertension damages the kidneys, and both BP and the duration of hypertension are correlated with the risk of CKD and ESRD. The same message comes from large observational trials, in which renal damage is defined as a decrease in glomerular filtration rate (GFR), increase in serum creatinine, or ESRD.[3-5] A more recent analysis by the National Heart and Nutrition Examination Study found an association between the severity of hypertension and risk of an estimated GFR (eGFR) drop below 60 ml/min/1.73 m^2. A more detailed analysis

TABLE 1 Clinical criteria for the diagnosis of hypertensive kidney disease

Schlessinger criteria	AASK (apply to African-Americans)
Family history of hypertension (first degree relatives)	Age, 18–70 y
Left ventricular hypertrophy (on echocardiography or ECG)	Diastolic blood pressure >95 mm Hg
Proteinuria less than 0.5 g/d in urinalysis or max. ++ in dipstick test	Urine protein to creatinine ratio <2.0 g/g
Long-term hypertension with BP exceeding 140/90 mm Hg before the onset of proteinuria and/or serum creatinine >1.2 mg/dl	No evidence of clinically relevant kidney disease with immunological background and/or diabetes
No history of exposition to nephrotoxic agents or known clinically relevant kidney disease	

SI conversion factors: to convert creatinine to μmol/l, multiply by 88.4.

Abbreviations: AASK, African-American Study of Kidney Disease and Hypertension; BP, blood pressure; ECG, electrocardiography

showed that such a relationship remains significant only in patients with concomitant urinary albumin-to-creatinine ratio of 30 mg/g or more. No association between BP and CKD was observed below this threshold of the urinary albumin-to-creatinine ratio.[6]

The key argument that is made by supporters of the "HKD epidemics" concept is that hypertension is the second most common cause (after DKD) of ESRD. Most renal registries state that up to 30% of all patients who are on renal replacement therapy developed ESRD because of HKD. This argument can be easily refuted by simply applying the strict definition of HKD. The classic definition (ie, Schlessinger criteria) states that HKD is renal damage that develops in patients with long-term and poorly controlled hypertension, in which other causes of kidney disease are excluded (TABLE 1).[7] However, in most patients in whom a diagnosis of HKD is established, these criteria are not met because the workup to exclude "other causes" is usually not performed. With the exception of a few situations in which a definitive diagnosis of renal pathology that leads to CKD can be established based on imaging modalities (eg, polycystic kidney disease, vesico-urinary reflux, advanced bilateral renal artery stenosis, and staghorn nephrolithiasis) or a specific biomarker (eg, metabolic errors with genetic background), the gold standard in the diagnosis of kidney disease is core biopsy. The vast majority of patients with advanced CKD and ESRD have never been biopsied; therefore, the true etiology of their disease cannot be defined. A similar myth applies to DKD. Most patients with type 2 diabetes and any renal symptoms (eg, albuminuria, proteinuria, elevated serum creatinine, and lower GFR) will be diagnosed with DKD, and DKD is considered the leading diagnosis in patients who start dialysis. The clinical diagnosis of DKD, however, cannot be established based on clinical signs or symptoms without kidney biopsy, which is not routinely performed in diabetic patients. The results of the available studies suggest an overestimation of DKD as a sole cause of ESRD.[8]

Most patients who undergo renal biopsy have hypertension, but hypertension is almost never considered a single or leading indication for biopsy. Interestingly, in large biopsy registries, HKD is reported sporadically or not reported at all (except in the United States, where it also does not, in general, exceed 8%–10%), despite a high prevalence of hypertension in the general population and an even higher prevalence in patients with symptoms of kidney disease.[9-12]

To increase the specificity of an HKD diagnosis, attempts were made to develop criteria that allowed recognition of this entity. Schlessinger criteria were developed for individuals of non-African descent, and the AASK (African-American Study of Kidney Disease and Hypertension) criteria for those of African descent (TABLE 1). The poor application of these criteria, however, was revealed by Zarif et al,[13] who carefully analyzed medical histories of a multiethnic group of dialyzed patients with HKD that was diagnosed as the cause of ESRD. Detailed analysis indicated that Schlessinger criteria were met in 1.5% and AASK criteria in 13.5% of the respective groups of patients. In many cases, predialysis medical data raised suspicions of renal diseases other than HKD, such as DKD, chronic or acute glomerulonephritis, interstitial nephritis, HIV-associated nephropathy, renal cell carcinoma, and even kidney myeloma. Renal biopsy results were available for only 4 patients, among whom there was one case in which morphologic picture could have corresponded to HKD.[14] These data, although very limited in size, illustrate the worldwide trend of labelling patients with HKD instead of trying to identify the true cause of renal dysfunction. A total of 35%–50% of patients who start renal replacement therapy are referred for renal care in less than 4 months prior to hemodialysis initiation.[14,15] In most of them, any attempt to establish a credible diagnosis of underlying kidney disease cannot be made. Hypertension is almost always present, and it is tempting to blame it as a cause of CKD, although the sequence of events (eg, hypertension first, followed by CKD, or vice versa) usually cannot be established. In the United Kingdom, Finland, and Austria, the reported percentage of patients with hypertension as an apparent cause of ESRD varies between 5% and 10%.[16] These discrepancies in the reported prevalence of HKD may be related to the influence of ethnicity but appear to primarily reflect differences in the type and quality of healthcare systems.[16] Epidemiological studies indicate that 30% of the overall Polish population have hypertension (ie, ~10 million individuals). It is reported that of all patients who undergo dialysis (~22 000 individuals), approximately 30% (~6000–7000 individuals) progressed to ESRD through HKD. These numbers suggest that ESRD that is attributable to hypertension is an extremely rare event (even after including kidney transplant recipients). This number is probably even lower because of the presumed misclassification of many

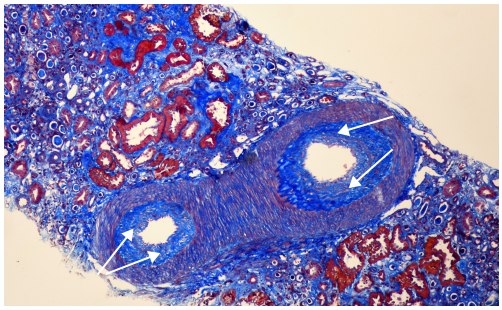

FIGURE 1 Arterionephrosclerosis. Significant arterial lumen reduction due to the presence of fibrotic neointima (arrows). Severe tubulointerstitial scarring related to chronic ischemia. Trichrome stain (original magnification × 100)

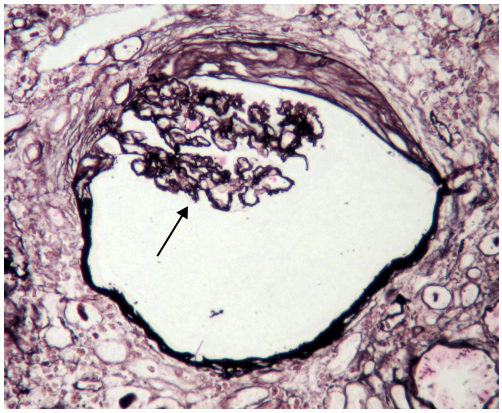

FIGURE 2 Chronic glomerular ischemia. Glomerular tuft simplification, capillary collapse, glomerular basement membrane wrinkling (arrow), Bowman space extension. Silver stain (original magnification ×400).

patients who are simply labeled with a diagnosis of HKD without biopsy confirmation.

In summary, the true dimension of the epidemic of HKD cannot be credibly estimated. However, with the exception of African-American ethnicity and extreme cases of long-term, severe, untreated, uncontrolled, or malignant hypertension, this entity as an isolated phenomenon does not constitute an important cause of CKD, although hypertension definitely contributes to the progression of CKD of any cause.

Pathogenesis of hypertension-related kidney damage

Under physiological conditions, intraglomerular pressure is relatively constant, at least in the range of systemic systolic blood pressure (SBP) between 80 and 160 mm Hg. The adequate constriction of an afferent arteriole in response to BP rise (ie, the mechanism of autoregulation) protects the glomerulus from hypertension and also "smooths" the difference between systolic and diastolic BP, thus guarding the glomerulus against pulsation. Indeed, the systolic-to-diastolic change in glomerular volume is minimal. According to current knowledge, 2 distinct mechanisms of renal damage occur in hypertension. In the first, autoregulatory properties of renal microcirculation are progressively lost, with resultant abnormal dilatation of the afferent arteriole and a secondary increase in intraglomerular pressure, paralleled by a rise in SBP. The direct transmission of hypertension from larger vessels to glomerular structures causes pulsation, stretching, and endothelial injury. Apart from oxidative stress, these hemodynamic changes activate the renin-angiotensin-aldosterone system (RAAS), nuclear factor κB transcription, and the synthesis of profibrotic growth factors, the leading one of which is transforming growth factor b.[17,18]

The second mechanism is considered by some authors to be an alternative to the first process, but others consider it simply as the second phase of the first process. This mechanism may be recognized as an adaptive reaction of renal microcirculation with resultant arteriolar wall hypertrophy, lumen narrowing, and flow reduction. This mechanism may be compared with pulmonary hypertension in response to greater blood flow in the pulmonary circulation that is caused by cardiac shunt or arterio-venous fistulas. Similar to the first mechanism, this second mechanism is strongly related to RAAS activation, greater endothelin 1 stimulation, and the expression of proinflammatory cytokines and profibrotic growth factors.[19]

Hypertensive kidney disease and arterionephrosclerosis: not equivalent terms Hypertensive kidney disease is a clinical, not morphological, term. It is traditionally used to describe a syndrome that is characterized by long-term essential hypertension, hypertensive retinopathy, left ventricular hypertrophy, minimal proteinuria (usually of less than 0.5 g/d or urinary albumin to creatinine ratio of less than 0.5 g/g), and progressive renal insufficiency. At the microscopic level, HKD manifests as either acute thrombotic microangiopathy that is caused by the accelerated or malignant phase of hypertension or a chronic arterionephrosclerosis process.[20] Arterionephrosclerosis is defined as a combination of arteriosclerosis (ie, intimal fibrosis), accompanied by either media thickening (attributable to smooth muscle cell hyperplasia) or thinning (attributable to vascular wall remodeling or media atrophy), afferent arteriole hyalinization, secondary chronic glomerulopathy (ischemic or hypertrophic), and tubulointerstitial scarring (FIGURES 1-3). The evolution of chronic glomerular lesions depends on the pattern of afferent arteriole hyalinization. In the obstructive type of hyaline deposition, glomeruli exhibit progressive ischemic lesions, manifested by evolving simplification of the glomerular tuft that is associated with wrinkling of the glomerular basement membrane (GBM), capillary collapse, and the distension of the Bowman space (FIGURE 2). In the other form, hyalinization is accompanied by arteriolar smooth muscle cell atrophy and secondary lumen dilatation, which lead to glomerular tuft hypertrophy. Dilatation of the afferent arteriole reflects an impairment in its myogenic response and loss of the autoregulation mechanism.[21,22] In both forms of glomerulopathies, the ultimate outcome is secondary tuft sclerotization, which is an obsolescent type in the case of ischemia (characterized by the preservation of the Bowman capsule; FIGURE 3A) and a solidified form (with Bowman capsule not preserved) as a complication of glomerulomegaly (FIGURE 3B).[23] Ischemic glomerulopathy and the obsolescent

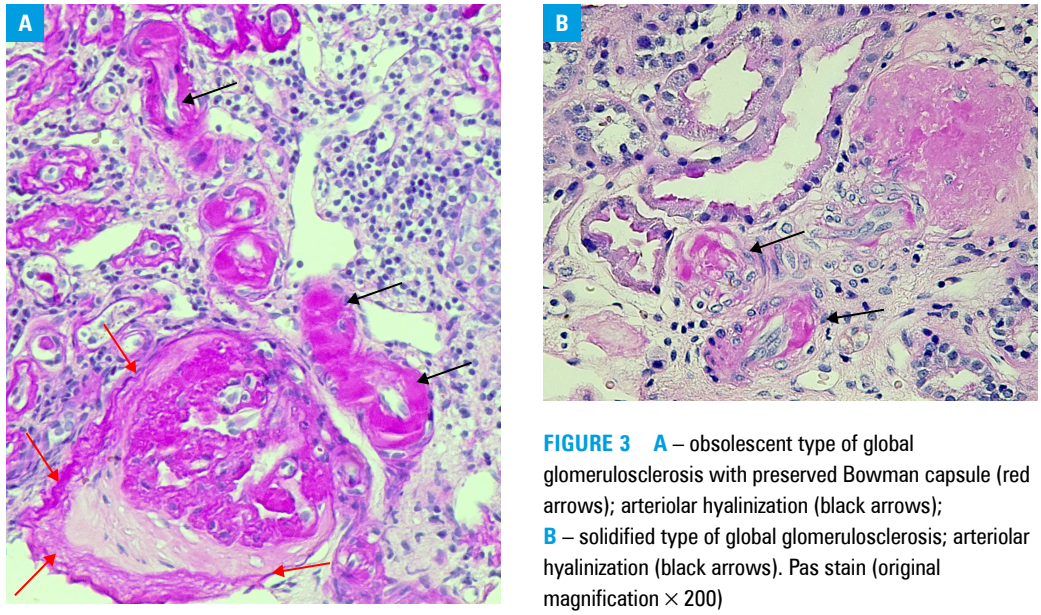

FIGURE 3 **A** – obsolescent type of global glomerulosclerosis with preserved Bowman capsule (red arrows); arteriolar hyalinization (black arrows); **B** – solidified type of global glomerulosclerosis; arteriolar hyalinization (black arrows). Pas stain (original magnification × 200)

type of glomerulosclerosis generally dominate, except in patients of African American descent, among whom glomerulomegaly and the solidified type of tuft sclerotization are more common.[24]

Arterionephrosclerosis is a disease of all renal tissue compartments. Blood is supplied to tubules and interstitial tissue by post-glomerular (efferent) arterioles, and glomerular ischemia leads to tubulointerstitial ischemia, which gradually translates into progressive interstitial fibrosis and tubular atrophy (FIGURE 1). Additionally, proteins that leak through the damaged glomerulus are reabsorbed by tubules, promoting tubulointerstitial scarring.[20]

In the case of severe or malignant hypertension, its deleterious impact on the kidney is mostly seen in glomeruli, arterioles, and interlobular arteries. The lesions may vary in terms of severity, ranging from widening of the subendothelial region of the vascular wall (an ultrastructural phenomenon) to the fibrinoid necrosis of glomerular capillaries and arteriolar and arterial walls and the presence of thrombi (revealed by light microscopy). Additionally, with regard to the aforementioned lesions, a reduction of the vascular lumen may be complicated by glomerular ischemia, manifested by capillary collapse, GBM wrinkling and ultimately glomerulosclerosis. The other scenario that results in the sclerotization of glomerular tuft is initiated by the increase of the filtration pressure that leads to mesangiolysis, glomerulomegaly, and ultimately, to the so-called hypertrophic glomerulosclerosis. With time, also the nonglomerular acute lesions evolve into chronic ones: arteriolar hyalinization, and "onionskin" fibrotic thickening of the arteriolar and arterial walls. Glomerular and vascular injury is initially accompanied by acute tubular epithelium injury, interstitial edema (with interstitial hemorrhage and necrosis in more severe cases), and a mild inflammatory response. In later phases, the tubulointerstitial compartment exhibits more or less extensive scarring.[20]

The causal relationship between accelerated or malignant hypertension and kidney injury is usually quite apparent because they temporally coincide, and this relationship is further supported by the simultaneous evolution of retinopathy. Although most commonly discussed in the context of HKD, lesions that define the phenomenon of arterionephrosclerosis are nonspecific in nature and occur under various physiological and pathophysiological conditions.

Studies of peri-implantation kidney transplant biopsies have shown that arteriosclerosis and arteriolar hyalinization are common lesions in donor kidneys. They almost always occur together and evolve in parallel, reflected by similar stages of progression.[25] Arteriosclerosis and arteriolar hyalinization have been reported to be strongly correlated with age and hypertension. However, analyses of donor kidney morphology have shown that they are generally not accompanied by tubulointerstitial or glomerular lesions that are typical of nephrosclerosis (FIGURE 4).[25,26] Moreover, the relationship between the severity of these lesions and the risk of nephrosclerosis has not been confirmed.

The rare occurrence of arterionephrosclerosis as a dominant or isolated type of kidney injury, even in the elderly population, has been confirmed by data from kidney biopsy registries. Studies that analyzed the prevalence of kidney biopsy–based diagnoses showed that the proportion of cases in which arterionephrosclerosis is a dominant microscopic finding ranged from 0.7% in Polish cohorts to up to 3.4% in Czech cohorts.[9,10,27] Among Polish elderly patients who underwent kidney biopsy, only 1% were diagnosed with arterionephrosclerosis, although as many as 80.6% of the patients aged 65 years or older had hypertension.[9] According to other published kidney biopsy registries, the frequency of arterionephrosclerosis as a dominant or isolated pathology in elderly patients varies from 1.53% in the Chinese cohorts to 7.1% in the United

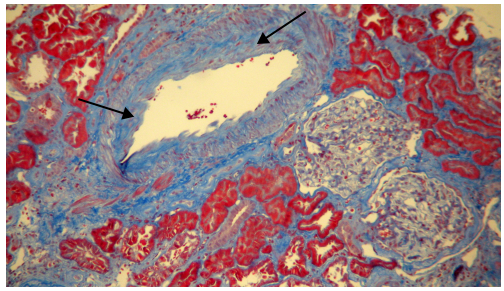

FIGURE 4 Arteriosclerosis. Despite intimal fibrosis (arrows) and arterial lumen reduction, tubulointerstitial and glomerular morphology is preserved. Donor kidney. Trichrome stain (original magnification ×400)

States cohorts.[28-30] The fact that the prevalence of arterionephrosclerosis in the United States population is distinctly higher than in populations from other regions of the world is related to the greater susceptibility of African Americans to arterionephrosclerosis relative to whites.[24] In African Americans, arterionephrosclerosis may even precede the occurrence of hypertension, demonstrating that it is a pure manifestation of genetic renovasculopathy in some instances (see below).[31] To date, no studies have demonstrated any qualitative differences in the morphological characteristics of evolving arterionephrosclerosis during the course of long-term hypertension compared with age-related lesions in elderly patients with no history of high BP.

Advanced sclerotization of the intrarenal arteries (ie, the major component of arterionephrosclerosis) is commonly present in various chronic nephropathies, even in the absence of hypertension. Various types of chronic glomerular injuries, such as diabetic glomerulopathy, immunoglobulin A nephropathy, membranous glomerulonephritis, disparate etiological forms of focal segmental glomerulosclerosis (FSGS), and chronic interstitial inflammation, are commonly accompanied by severe chronic arterial lesions, even before the occurrence of hypertension.[32] At the time of end-stage renal insufficiency, both native and transplant kidneys almost always exhibit morphological features of arterionephrosclerosis, independent of the nature of the original kidney disease. Data indicate that chronic injurious processes enhance tissue aging, which may at least partially explain arterionephrosclerosis being a constant part of progressive kidney disease.[33] In conclusion, with the exception of patients in whom the clinically apparent episode of malignant hypertension is further confirmed by the morphological presentation of arterionephrosclerosis in kidney tissue, HKD cannot be unambiguously diagnosed based on kidney biopsy because of the lack of sensitivity and specificity of morphological findings.

Genetic factors in hypertensive kidney disease Currently available methods for analyzing potential links between specific gene variants and disease phenotypes allow the identification of potential genetic backgrounds that predispose individuals to kidney damage that results from hypertension. One gene candidate is the gene that encodes uromodulin (*UMOD*). The protein is considered kidney-specific because it is synthetized exclusively by epithelial cells of the thick ascending limb. This protein has several physiological functions, including the control of sodium-potassium--chloride cotransporter activity in this region of nephron, which might be relevant to BP regulation.[34,35] Animal studies recently showed that *THP* gene knockout or *THP* gene mutations were associated with the marked upregulation of RAAS and oliguria and hypertension that are unresponsive to furosemide.[36,37] Another gene candidate may be the gene that encodes MYH9. The A isoform of type II myosin heavy chain is an important structural component of the podocyte cytoskeleton. Abnormal MYH9 expression may promote foot process effacement (ie, the universal sign of podocyte dysfunction or damage). Both the *THP* and *MYH9* genes, in addition to the gene that encodes apolipoprotein L1 (*APOL1*), appear to affect the susceptibility of renal parenchyma to hypertension--related damage in patients of African descent. Certain *MYH9* gene polymorphisms promote renal damage in hypertensive African Americans, although its influence is much weaker than *APOL1*. Moreover, the influence of *MYH9* gene polymorphisms nearly disappeared when controlled for *APOL1* risk alleles.[38] A large study that analyzed the prevalence and progression of CKD showed a strong relationship between the risk of CKD onset, the rate of CKD progression, and *APOL1* gene variants in African Americans.[39] Such a relationship was not observed among hypertensive Americans of European descent, in which the prevalence of risk alleles did not exceed 3% of the European white population.[40] Interestingly, variants of the *APOL1* gene that increase the susceptibility to CKD were protective against Trypanosoma, an infection that is transmitted by tsetse (*Glossina*) flies in sub-Saharan Africa.

APOL1 risk alleles have been reported to promote renal damage through several mechanisms, leading to primary FSGS, increasing the progression of renal damage in adaptive FSGS, promoting kidney injury in HIV-associated nephropathy, increasing the susceptibility of kidney tissue to interferon, and leading to arterionephrosclerosis, which is considered a morphological characteristic of HKD.[41,42] The link between *APOL1* risk alleles and distinct renal pathology has been identified, thus creating a new clinical entity, APOL1 nephropathy.

Congenital low nephron number as a factor that programs the development of hypertension and CKD Congenitally low nephron number and low renal mass are considered major determinants of the future development of hypertension or CKD. Histomorphometric analysis indicated that the number of nephrons in apparently healthy

TABLE 2 Blood pressure targets in patients with chronic kidney disease according to current guidelines

Guideline	Year published	Office BP, mm Hg	
		Systolic	Diastolic
European Society of Cardiology / European Society of Hypertension[48]	2018	130–139	70–79
American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines[68a,b]	2018	<130	<80
Joint National Committee 8[69a]	2014	<140	<90
Hypertension Canada (nondiabetic CKD)[70]	2018	<140	<90
Hypertension Canada (all diabetics)[70]	2018	<130	<80
NICE: CKD without diabetes and/or albuminuria[71,72]	2019[c]	120–139	<90
NICE: CKD with diabetes and/or albumin to creatinine ratio of ≥70 mg/mmol[71,72]	2019[c]	120–129	<80
KDIGO (no albuminuria)[73]	2012	≤140	≤90
KDIGO (albuminuria >30 mg/24 h)[73]	2012	≤130	≤80

a Target blood pressure values do not differ in CKD vs no-CKD populations. In all remaining guidelines, targets for CKD are different as compared with the general population.

b Targets recommended if concomitant known cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk of 10% or higher; if no additional markers of increased cardiovascular disease risk, targets may be reasonable; CKD, particular values of: glomerular filtration rate, serum creatinine, or proteinuria not included into the American College of Cardiology/American Heart Association risk calculator

c 2019 NICE guidelines on hypertension do not discuss BP targets in CKD but refer the reader to the CKD guidelines published in 2014 (last updated in 2017, but without change in BP targets).

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute of Health and Care Excellence

people may vary between 200 000 to more than 2.5 million per kidney. Autopsy-based studies have shown than a low nephron number is associated with hypertension (which is usually sodium-dependent), hyperfiltration, proteinuria, and CKD.[43,44] A low nephron number at birth is also linked to a higher risk of overweight, obesity, metabolic syndrome, and diabetes later in life. Final development of the kidney and the establishment of nephron number occur late in the last trimester of pregnancy. Therefore, key risk factors of low nephron number at birth (also referred to as "nephron underdosing" or oligonephronia) include prematurity and intrauterine growth retardation. These 2 conditions, in turn, depend on several socioeconomic and medical factors, including suboptimal prenatal care, maternal nutrition deficits, smoking, alcohol intake, drug abuse, low vitamin A status, infection, hypertension, CKD, gestational diabetes mellitus, and genetic background.[45,46] Up to 15% of all neonates are small for gestational age, and up to 10% of all deliveries are premature. Therefore, fetal programming may be an important risk factor for hypertension and CKD in the general population. Many of these adverse outcomes remain preventable with improved prenatal care. Interestingly, some studies questioned the importance of glomerular number in renal damage secondary to hypertension, at least in African Americans. Glomerular volume rather than glomerular number was identified as an independent risk factor for renal damage in patients with hypertension.[47]

Treatment of hypertension and hypertensive kidney disease Interestingly, current European guidelines on the detection and treatment of high BP now recommend looser control of BP in patients who have CKD as compared with other patient groups. The universal goal of SBP less than 130 mm Hg and diastolic BP between 70 and 79 mm Hg has been established. Target SBP is set at 130 to 139 mm Hg in individuals who are 65 years or older. Maintaining these target values is believed to prevent end-organ damage (including kidney protection) with the simultaneous avoidance of untoward adverse effects of treatment. The European Society of Cardiology and European Society of Hypertension guidelines accept more liberal targets of BP control also in patients with established CKD (ie, SBP of 130–139 mm Hg for all age ranges).[48] Currently, RAAS blocking agents are considered the treatment of choice not only for patients with hypertension and concomitant albuminuria or proteinuria but also for all patients with hypertension. Patients who use 2 or more BP-lowering drugs should be treated with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor type 1 blocking agents (ARB), unless contraindicated. In other hypertension patients, monotherapy can sometimes be attempted. In patients with established CKD, the initial treatment should always consist of 2 drugs including either an ACEI or ARB.[48] Recent United States guidelines, endorsed by many key medical associations, including the American Heart Association, suggest achieving a universal target BP less

than 130/80 mm Hg, independent of any comorbidity, age group, etc.[48] These criteria apply to all patients with a calculated 10-year risk of cardiovascular disease of 10% or more.[49] According to the Kidney Disease: Improving Global Outcomes expert panel, patients with proteinuria of more than 30 mg/d are suggested to maintain BP values of 130/80 mm Hg or less.[50] Patients with albuminuria that ranges from 30 to 300 mg/d are recommended to use RAAS blocking agents. This turns into a stronger recommendation once albuminuria exceeds 300 mg/d.[50] According to all available guidelines, double RAAS blockade is contraindicated (eg, ACEI, ARBs, and direct renin inhibitors in any combination). In patients with albuminuria of less than 30 mg/d, no first-choice BP-lowering drug is specified. Theoretically, dihydropyridine-type calcium channel blockers are not best suited for the initial treatment of hypertension in the setting of renal disease because they additionally dilate the afferent arteriole. However, no long-term trials have reported the inferiority of this drug group with regard to kidney function protection, aside from studies that used indirect (surrogate) renal outcome measures, such as a reduction of albuminuria. Additionally, cardiovascular protection is a priority in the treatment of hypertension. Thus, comorbidities other than CKD would usually determine the choice of drugs.[50] A summary of selected guidelines dealing with target BP values in patients with CKD is presented in TABLE 2.

Chronic kidney disease is a frequent cause of treatment-resistant hypertension. A total of 20% to 30% of all patients with hypertension experience resistance to treatment, and this percentage rises to 80% to 90% in patients with advanced CKD, which is inversely correlated with the loss of GFR and parallels an increase in proteinuria (albuminuria).[51] Thus, debates about the choice of the third drug (assuming ACEI/ARB plus calcium channel blocker or a diuretic are the first choice) are purely academic. Most hypertensive patients with CKD will receive 3 drugs from the aforementioned list. Any other drug that is added to this regimen should be based on general rules of hypertension treatment. Unfortunately, in patients with more advanced CKD, the use of a preferred "number 4" drug, spironolactone, is commonly limited by the risk of hyperkalemia.

Impact of blood pressure control in essential hypertension on chronic kidney disease and patient survival

To our knowledge, no clinical studies have evaluated the impact of essential hypertension control with CKD as a primary endpoint (ie, the primary prevention of CKD in essential hypertension). The only published clinical trial in which CKD progression served as a primary endpoint for assessing the effectiveness of BP-lowering therapy in hypertensive African American patients with already established CKD (ie, secondary prevention) was the AASK study.[52] One key finding of the AASK trial was that intensive BP lowering did not inhibit the rate of CKD progression. No difference was detected in the rate of GFR loss between patients who were randomized to therapeutic arms with a dihydropyridine-type calcium channel blocker, b-blocker, or ACEI.[52] The only renal benefit was found in patients with baseline proteinuria who were treated with a RAAS inhibitor, which is a common finding in trials that are devoted to nephroprotection. Interestingly, among African American patients, the effectiveness of BP-lowering drugs was independent of *APOL1* risk allele status.[38] The AASK study may pave the way toward new thinking about the relationship between kidney disease and hypertension in an attempt to resolve the "chicken-and-egg" dilemma. Originally designed to demonstrate protection against renal consequences of essential hypertension, The AASK study turned into a key study demonstrating that primary kidney disease (ie, APOL1 risk allele-triggered arterionephrosclerosis) precipitates the onset of hypertension. A similar conclusion emerged from a meta-analysis of 11 trials that included 5308 patients with cryptogenic or nonhypertensive CKD upon enrollment. Additional SBP lowering of 7.7 mm Hg and diastolic BP lowering of 4.9 mm Hg compared with standard BP targets did not influence the rate of CKD progression in patients without proteinuria, whereas it reduced the risk of progression by 27% in patients with protein loss of more than 300 mg/d or more than 0.22 g/g of urine creatinine. One should, however, interpret these data very cautiously since the studies included into this meta-analysis comprised very diverse patient groups (ie, children, older patients, African American patients from AASK, diabetics, and patients without diabetes; importantly, all were diagnosed with CKD).[53] Additionally, tight BP control reduced albuminuria or the rate of GFR loss. In patients with established baseline CKD, however, tight BP control had little impact on the cardiovascular or cerebrovascular event rate or overall survival.[53] Some studies, however, reported that BP-lowering interventions may be equally effective in preventing cardiovascular events also in patients with a lower baseline GFR. This was further demonstrated in another meta-analysis of 25 prospective hypertension trials that included 152 900 patients with CKD. Both groups (ie, patients with and without CKD) experienced similar benefits in terms of lower mortality rate and fewer cardiovascular events, regardless of baseline CKD status and eGFR level. This benefit did not depend on the type of BP-lowering drug that was used or the presence or absence of proteinuria. Notably, however, the vast majority of patients with CKD were in CKD stages 1 to 3 (ie, eGFR >30 ml/min/1.73 m^2). Patients with eGFR lower than 30 ml/min/1.73 m^2 constituted 0.3% of the overall study sample.[54]

One of the most important recent clinical hypertension studies was the SPRINT (Systolic Blood Pressure Intervention Trail). This trial provided new arguments to the ongoing

discussion of target BP values in different populations and significantly influenced the recent United States guidelines for hypertension treatment. The SPRINT study showed that aggressive BP management had a significant beneficial effect on all-cause mortality, cardiovascular mortality, and heart failure rate but was also associated with a significant reduction of eGFR, with the risk of kidney function worsening being 3.49-fold higher in patients with target SBP of less than 120 mm Hg as compared with patients whose target BP was established at the level of 135 to 140 mm Hg.[55] The findings of the SPRINT may not be fully applicable to most hypertensive patients due to unique method of BP assessment (ie, unattended automatic blood pressure measurement that virtually eliminated the white-coat effect). The substantial difference in BP between routine and automatic unattended BP assessment was also confirmed by other authors.[56]

One long-lasting dogma in nephrology is that albuminuria reduction equates with nephroprotection. Indeed, in the natural evolution of many kidney diseases, albuminuria or proteinuria precedes reduction of GFR. However, in many cases, the gradual loss of GFR is not preceded or even accompanied by urine protein loss. The dynamics of the eGFR reduction (usually 25% or 50% relative to baseline), the time to doubling baseline serum creatinine, or reaching eGFR of less 45 or 15 ml/min/1.73 m^2 (of note, the latter is considered equivalent to ESRD) seem to better define the CKD progression. A drop in urine albumin loss may simply reflect a hemodynamic effect of certain drugs that lower intra-glomerular pressure (eg, RAAS inhibiting agents—ACEI, ARB). In several prospective randomized trials, subsequent to BP lowering, albuminuria reduction was not followed by a decrease in the rate of GFR drop.[57-60] The results of the ACCOMPLISH (The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) trial showed that more pronounced effect of antihypertensive therapy on GFR loss and the rate of cardiovascular events was associated with lower efficacy with regard to reducing albuminuria and vice versa.[61] These findings were codified by a joint conference of experts from the Food and Drug Administration and National Kidney Foundation, who recommended to not equate a reduction of albuminuria with nephroprotection.[62]

Conclusions The true prevalence, diagnostic criteria, prevention, and treatment of HKD are poorly defined. Hypertensive kidney disease became a popular label for patients with CKD in whom proper diagnostic tests of renal disease were not performed or in whom the disease was difficult to define because of the multifactorial nature of kidney tissue damage. With the exception of patients in whom the clinically apparent episode of malignant hypertension is further confirmed by the morphological presentation of arterionephrosclerosis in kidney biopsies, HKD cannot always be unequivocally diagnosed even by microscopic examination, but kidney biopsy is always helpful for at least narrowing the differential diagnosis. Currently we are not able to formulate any indications to perform kidney biopsy in patients with essential hypertension and renal involvement extending beyond classical indications based on urine sediment findings, proteinuria, albuminuria, and GFR. It is, however, of paramount importance to promote liberal approach to kidney biopsy, for example, not to postpone it even in patients with mild, otherwise unexplained proteinuria. Noninvasive assessment of kidney disease should certainly be also considered. For example, patients with long-lasting, poorly controlled essential hypertension can be subjected to functional magnetic resonance imaging—the growing body of evidence indicates the relationship between functional magnetic resonance imaging findings and features of kidney damage on microscopic assessment and even an insight into renal metabolism provided by this technique (although such a relationship still awaits validation).[63] Another technique that seems promising in noninvasive assessment of renal damage is an ultrasound-based analysis of intrarenal blood flow that seems to be ideally suited for an assessment of kidney vasculature.[64] Finally, it seems that we enter the new era of nephroprotection due to the increasing role of sodium-glucose cotransporter type 2 inhibitors in therapy. These drugs, initially developed to lower glucose in patients with poorly controlled type 2 diabetes, have also been demonstrated to have a protective effect on cardiovascular events and mortality in patients with and without diabetes, and are also used to improve blood pressure control in patients with well-controlled diabetes (not as glucose-lowering, but as BP-lowering drugs). Given the wide range of nephro- and cardio-protective mechanisms, one can expect that sodium-glucose cotransporter type 2 inhibitors will shape the new future of patients with hypertension and kidney disease with or without diabetes.[65-67]

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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