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ORIGINAL RESEARCH

Causes of Chronic Kidney Disease and Their Associations with Cardiovascular Risk and Disease in a Sub-Saharan Low-Income Population

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Introduction: The causes of chronic kidney disease (CKD) in people living in Sub-Saharan Africa await identification. Also, whether cardiovascular risk and disease extent differ among patients with different CKD etiologies is uncertain.

Methods: In this prospective cross-sectional study, we examined the presumed causes of chronic kidney disease (CKD) and their relationships with cardiovascular risk and disease in 743 consecutive patients from a sub-Saharan low-income population.

Results: Hypertensive nephropathy (HNP) (60.2%), diabetic nephropathy (DNP) (24.4%), HIV associated CKD (20.0%) and glomerular disease (13.6%) comprised the major CKD etiologies upon enrolment at the hospital nephrology clinic. Pulse pressure was larger in patients with concurrent HNP and DNP than in those with HNP only ($p<0.001$). Pulse pressure and systolic blood pressure were larger in HNP or/and DNP patients than those with HIV associated CKD and glomerular disease ($p=0.04$ to <0.001). Cardiovascular disease was more prevalent in patients with HNP and concurrent HNP and DNP than those from other etiologic categories ($p<0.05$). HNP and DNP were associated with pulsatile pressures (pulse pressure and systolic blood pressure) independent of one another ($p\leq0.01$). In adjusted product of coefficient mediation analysis, mean arterial or distending pressure accounted fully for the potential impact of HNP on pulsatile pressures (103.9–115.7%) but not for that of DNP on the respective pressures (−2.0%-(-)7.5%).

Conclusion: HNP is by far the most prevalent presumed cause of CKD in this African population. Cardiovascular risk and disease differ markedly across CKD etiological categories.

Keywords: chronic kidney disease, low-income African population, etiological categories, cardiovascular risk and disease, pulsatile pressures, arterial stiffness

Introduction

Worldwide, the estimated prevalence of chronic kidney disease (CKD) is more than 10%.[1] CKD substantially impacts disability and mortality in both high income and low income countries.[2] In a recent meta-analysis of studies that were performed on the African continent, the overall prevalence was 15.8% (95% confidence interval (CI)=12.1–19.9%) for CKD stages 1 to 5 and 4.6% (95% CI=3.3–6.1%) for CKD stages 3 to 5.[3] The CKD prevalence in sub-Saharan African countries was three times larger than in those located in North Africa. Notably, even stage 2 CKD can impact atherosclerosis in black Africans.[4] Sub-Saharan Africa is currently undergoing an epidemiological transition that is engendered by rapid urbanization. Accordingly, the prevalence of major CKD risk factors including hypertension and diabetes is increasing.[5,6] The already sizeable burden of CKD in Africa is therefore bound to enlarge further in the foreseeable future.

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In North America as well as Latin America and Asia, the most prevalent presumed cause of CKD is diabetes and this is followed by hypertension.[7–9] By contrast, the relative contribution of different high-risk conditions that cause CKD in low-income black populations remain largely uncertain. In this regard, hypertension due to increased salt and fluid retention is more frequent and difficult to control in persons of black African ancestry than in other population groups.[10] In addition, South Africa accounts for 20% of new HIV infections as well as 20% of all people living with HIV globally.[11] HIV is complicated by CKD in 3.5% to 48.5% of cases.[12] Taken together, it is likely that etiologies of CKD differ in persons living in sub-Saharan Africa from those in previously reported studies.

CKD is associated with a markedly increased risk of cardiovascular disease.[13] In fact, CKD patients are more likely to die from cardiovascular disease than kidney failure in settings where dialysis is available. However, the extent of cardiovascular risk and disease in sub-Saharan Africans with CKD is largely unknown.

Whether cardiovascular risk and disease extent differs among patients with different CKD etiologies has also been rarely reported.[7,13] In this regard, in Norway, among patients undergoing a kidney biopsy, those with diabetic kidney disease experienced a poorer overall survival and more rapid progression to kidney failure than those with non-diabetic CKD.[7] Also, whereas HIV increases cardiovascular risk and disease incidence,[14] whether cardiovascular event rates differ in CKD induced by HIV compared to that due to other causes is uncertain.

The main cause of cardiovascular disease in patients with CKD is hypertension.[15] A bi-directional relationship between hypertension and CKD is well recognized.[16] Hypertension can cause CKD. Additionally, CKD development results in increased blood pressures. Both steady state pressure comprising mean or distending arterial pressure and pulsatile pressures including pulse pressure and, consequently, systolic blood pressure are increased in patients with CKD.[15,17–21] In this regard, pulse pressure is also a valuable marker of aortic stiffness.[22,23] Aortic stiffness is a core feature of cardiovascular disease and an independent risk factor for cardiovascular events in CKD.[24,25] The 2021 KDIGO Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease now recommends focusing on systolic blood pressure control in patients with CKD.[26] Whether blood pressure measures and their pathophysiology differ by CKD etiological categories requires further elucidation.

In the present study, we examined the presumed causes of CKD and their relationships with cardiovascular risk and disease in patients that were seen at Chris Hani Baragwanath Academic Hospital, a public health care facility that provides medical care to a large low-income African population.

Patients and Methods

Patients

This is a prospective cross-sectional study that was performed in agreement with the Helsinki declaration as revised in 2013. The study protocol was approved by the University of Witwatersrand Human (Medical) Research Committee (protocol number: M221013 MED22-09-043). Written informed consent was obtained from each study participant. All kidney transplants were donated voluntarily with written informed consent, and these were conducted in accordance with the Declaration of Istanbul. Seven hundred and thirty-four consecutive Patients with CKD were enrolled at the nephrology outpatient clinic in Chris Hani Baragwanath Hospital during the period 1 June 2023 to 30 September 2023. All patients met the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for CKD.[27] None of the participants were on dialysis. No exclusion criteria were applied. Chris Hani Baragwanath Hospital is an academic public health care facility that serves persons living in the South Western Townships (Soweto). It is the largest hospital on the African continent and the third largest hospital in the world. Typically, persons seeking health care at South African public health care hospitals do not have medical insurance. Public health care patients in South Africa represent a socioeconomically disadvantaged and low-income population.[28]

Methods

Recorded baseline characteristics included age, sex and race as demographic features, CKD duration, weight and height with body mass index (BMI) calculation as weight divided by height squared as anthropometric measures, and drug treatment comprising antihypertensive agents, statins, antidiabetic agents, antiretroviral therapy and immunosuppressive agents. CKD duration was defined as time since diagnosis.

Etiological categories were retrieved through patient record review. The KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease had been applied in each participant upon enrolment in the Chris Hani Baragwanath nephrology clinic and by or under the supervision of an experienced nephrologist.[27] Accordingly, presumed hypertensive nephropathy (HNP) and diabetic nephropathy (DNP) were diagnosed on clinical grounds and not confirmed through kidney biopsies. One or more diagnostic categories were recorded in each patient.

Recorded traditional cardiovascular risk factors comprised measured and calculated blood pressure and lipid variables and diabetes and smoking status. The overall traditional cardiovascular risk factor burden including low, moderate and high cardiovascular disease risk categories were determined by employing the Framingham score equation.[29] The Framingham is currently recommended for use in South Africa, this by the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA) dyslipidaemia guideline consensus statement: 2018 update.[29] Blood pressures, weight and height were measured by nurses prior to consulting with the involved doctor(s). Blood pressures were determined using a CRESCAPE V100 DINAMAP Vital Signs Monitor (GE Medical Systems Information Technologies, Inc., USA). Total cholesterol concentrations were determined using an enzymatic colorimetric test on a COBAS INTEGRA system (Roche Diagnostics Gmbh, Germany). High density lipoprotein (HDL) cholesterol levels were measured using a direct method on a cobas c analyser (Roche Diagnostics Gmbh, Germany). LDL cholesterol concentrations were quantified using a homogeneous enzymatic colorimetric assay on a COBAS INTEGRA analyser (Roche Diagnostics Gmbh, Germany). Triglyceride levels were determined using an enzymatic colorimetric test on a cobas c analyser (Roche Diagnostics Gmbh, Germany). Hypertension was defined as systolic or/and diastolic blood pressure of $\geq$140 mmHg and $\geq$90 mmHg, respectively. Uncontrolled systolic blood pressure was diagnosed when the systolic blood pressure was $\geq$130 mmHg. Total and HDL cholesterol were evaluated in 705 (96.0%) and 617 (84.0%) of the patients, respectively. The necessary data to calculate the Framingham score were available in all patients who had their HDL concentrations measured. Dyslipidemia was diagnosed in patients that were on statin treatment or/and had a total cholesterol/HDL cholesterol ratio of $\geq$4.[30] Remnant cholesterol was calculated as total cholesterol concentration minus HDL cholesterol level minus LDL cholesterol concentration. Diabetes was defined as a history of a previous diabetes diagnosis or/and antidiabetic medication use or/and a haemoglobin A1C of $\geq$6.5%. Haemoglobin A1C percentage was estimated in 706 (91.2%) study participants. Haemoglobin A1C percentage was estimated using ion-exchange high-performance liquid chromatography (HPLC) (Bio-Rad Laboratories, USA).

The non-traditional cardiovascular risk factors that were recorded included haemoglobin, albumin and uric acid concentrations. The creatinine clearance was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[31] No correction factor, as applies to American black individuals, should be used upon employing this equation in black persons living in Africa (4). The urine protein-creatinine ratio and human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, and gout with joint involvement status were also recorded. Albumin levels were quantified using colorimetric assay on a cobas c analyser (Roche Diagnostics Gmbh, Germany). Uric acid concentrations were measured using a colorimetric test (Roche Diagnostics Gmbh, Germany). Uric acid concentrations were evaluated in 584 (79.6%) patients. Creatinine levels were determined using a kinetic colorimetric assay based on the Jaffe method. (Hoffman-La Roche, Ltd, Switzerland). Urinary protein concentrations were estimated using a micro-turbidimetric assay on a COBAS INTEGRA 400 plus (Hoffman-La Roche, Ltd, Switzerland).

Established cardiovascular disease comprised ischemic heart disease (myocardial infarction or/and angioplasty or/and coronary artery bypass surgery) or/and cerebrovascular disease (cerebrovascular accident or transient ischemic attack), peripheral vascular disease and heart failure. Each of these diagnoses was confirmed by a cardiologist, neurologist or vascular surgeon or specialist physician as appropriate.

Data Analysis

Continuous patient characteristics were expressed as mean (SD) when normally distributed and median (interquartile range) when non-normally distributed. Categorical patient variables were expressed as proportions or percentages.

Patients with either only hypertensive nephropathy (HNP) or concurrent HPN and diabetic nephropathy (DNP) or diabetic nephropathy or HIV associated CKD or glomerular disease comprised the large majority (82.7%) of the study population. This allowed for comparing recorded baseline characteristics, cardiovascular risk factors and established cardiovascular disease among the main different etiological categories. For these multiple comparisons across etiological categories, we employed one way analysis of variance and the Kruskal Wallis and Chi squared test for normally and non-normally distributed and categorical or qualitative patient characteristics, respectively. Bonferroni correction for multiple comparisons was made in each instance. The association of etiological categories (ie HTN and concurrent HNP and DNP versus the other etiological categories) with the traditional cardiovascular disease risk burden as represented by the Framingham score and with uncontrolled systolic blood pressure was also assessed in non-modifiable traditional cardiovascular disease risk factor (age, sex and black population origin) adjusted multivariate linear and logistic regression models, respectively.

The mutually independent impact of HNP and DNP on pulse pressure and systolic blood pressure was determined in demographic characteristics together with and without mean arterial pressure adjusted linear regression models. The contribution of mean or distending arterial pressure[21] to the potential impact of HNP and DNP on pulse pressure and systolic blood pressure was assessed in demographic characteristic adjusted product of coefficient mediation analysis, which accounts for hierarchical structures.

The data were analysed using the IBM SPSS statistical program (version 27.0, IBM, USA) and Statistica 8.0 application package (version 14, TIBCO, USA).

Results

Baseline Recorded Characteristics in CKD Patients

The baseline recorded characteristics in the enrolled CKD patients are given in Table 1. Mean (SD) age was 52.8 (13.7) years, 54.8% were women and 98.1% were of black population origin. The body mass index was in the overweight range. Ninety two percent of patients were treated with antihypertensive agents. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers were employed to reduce proteinuria in the absence of hypertension in 4.3% of study participants. The mean (SD) number of antihypertensive agents was. 2.9 (1.4). Statins, insulin and

Table 1 Baseline Recorded Characteristics in CKD Patients

Characteristics	CKD Patients (n=734)
Demographics	
Age (years)	52.8 (13.7)
Female sex (%)	54.8
Black (%)	98.1
Mixed (%)	0.8
Asian (%)	0.4
White (%)	0.7
CKD duration (years)	3.5 (1.5–7.5)
Alcohol use (%)	5.9

(*Continued*)

Table 1 (Continued).

Characteristics	CKD Patients (n=734)
Anthropometry	
Weight (kg)	74.8 (16.0)
Height (cm)	162 (9.1)
BMI (kg/m^2)	28.7 (6.4)
Treatment	
Antihypertensive agent use (%)	92.0
Antihypertensives (n)	2.9 (1.4)
Diuretic agents (%)	77.8
Calcium channel blockers (%)	73.8
ACEI/ARB (%)	57.9
Alpha blockers (%)	35.7
Beta blockers (%)	32.4
Hydralazine (%)	12.9
Statins (%)	44.8
Oral hypoglycaemic agents (%)	2.0
Insulin (%)	20.4
Antiretroviral therapy (%)	36.5
Allopurinol (%)	6.4
Immunosuppressive agent use (%)	5.5
Kidney transplant recipients (%)	0.4

Notes: Data are expressed as mean (SD), median (interquartile range) or proportions.
Abbreviations: CKD, chronic kidney disease; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

antiretroviral agents were used in 44.8%, 20.4% and 36.5% of patients respectively. Kidney biopsy was performed in 15.4% of study participants.

Etiological Categories in CKD Patients

The presumed etiological categories are shown in Table 2. HNP (60.2%), DNP (24.4%), human immunodeficiency virus (HIV) associated CKD (20.0%) and glomerular disease (13.6%) comprised the main etiological categories. An extensive range of other etiological categories was present. However, the prevalence of each of these etiological categories was ≤4.5%. The mean (SD) number etiological categories were 1.51 (0.55). A kidney biopsy was performed in 94.0% of patients with glomerular disease and 13.1% of those with HIV associated CKD and none of those with HNP and DNP.

Cardiovascular Risk Factors and Disease in CKD Patients

The cardiovascular risk factors and established cardiovascular disease prevalence at the time of the study are given in Table 3. Among traditional cardiovascular risk factors, hypertension, dyslipidemia, diabetes and current smoking were

Table 2 Etiological Categories in CKD Patients

Etiological Categories	CKD Patients (n=734)
Hypertensive nephropathy (%)	60.2
Diabetic nephropathy (%)	24.4
HIV associated CKD (%)	20.0
Glomerular disease (%)	13.6
IgA nephropathy (%)	0.4
Post infectious glomerulonephritis (%)	1.0
Focal segmental glomerulosclerosis (%)	4.4
Lupus nephritis (%)	3.4
Minimal change disease (%)	0.9
Membranous glomerulonephritis (%)	2.6
Membranoproliferative glomerulonephritis (%)	0.8
Cystic disease (%)	4.5
Autosomal cystic disease (%)	4.2
Simple cyst (%)	0.3
Obstructive uropathy (%)	3.4
Uterine fibroids (%)	0.4
Urethral stricture (%)	2.3
Cervical cancer (%)	0.1
Schistosomiasis (%)	0.5
Prostate cancer (%)	0.5
Traditional medicine (%)	0.1
Tenofovir induced (%)	1.5
Lithium poisoning (%)	0.1
Amyloid A (AA) amyloidosis (%)	0.1
Renal cell carcinoma (%)	0.5
Malaria (%)	0.4
Etiological categories (n)	1.51 (0.55)

Notes: Data are expressed as proportions or mean (SD).
Abbreviations: CKD, chronic kidney disease; HIV, human immunodeficiency virus.

identified in 87.6%, 59.9%, 25.8% and 6.7% of the patients, respectively. Among patients with diabetes, 96.3% had hypertension. The median (interquartile range) Framingham score was 10.8 (5.1–18.9) %. As shown in Supplementary Table 1, among baseline characteristics and etiological categories, apart from minor differences in weight, BMI, statin use and DNP status, the recorded characteristics were similar in patients that had their Framingham score calculated as compared to those that had not.

Table 3 Cardiovascular Risk Factors and Disease in CKD Patients

CV Risk Factors and Disease	CKD Patients (n=734)
Traditional CV risk factors	
Hypertension (%)	87.6
Systolic blood pressure (mmHg)	140 (127–157)
Diastolic blood pressure (mmHg)	85 (16)
Pulse pressure (%)	56 (46–70)
Mean arterial pressure (mmHg)	102 (94–114)
Uncontrolled systolic blood pressure (%)	70.1
Dyslipidemia (%)	59.9
Total cholesterol (mmol/l)	4.7 (3.8–5.4)
HDL cholesterol (mmol/l)	1.31 (1.02–1.51)
LDL cholesterol (mmol/l)	2.4 (1.9–3.1)
Total chol-HDL chol ratio	3.4 (2.8–4.4)
Triglycerides (mmol/l)	1.60 (0.97–1.90)
Remnant cholesterol (mmol/l)	0.63 (0.42–0.81)
Diabetes (%)	25.8
Haemoglobin A1C (%)	6.0 (5.6–6.7)
Smoking (%)	6.7
Framingham score (%)	10.8 (5.1–18.9)
Low CV disease risk (%)	46.8
Moderate CV disease risk (%)	31.0
High CV disease risk (%)	22.2
Non-traditional CV risk factors	
Haemoglobin (g/dl)	12.9 (2.2)
Albumin (g/l)	43 (40–46)
Uric acid (mmol/l)	0.42 (0.12)
EGFR (mL/min/1.73m^2)	38.0 (21.3–57.3)
Urine protein-creatinine ratio (g/mmol)	0.047 (0.013–0.124)
Isolated low EGFR (%)	21.8
Isolated proteinuria (%)	22.4
Concurrent low EGFR and proteinuria	54.0
HIV virus infection (%)	39.4
Gout (%)	3.5
Systemic lupus erythematosus (%)	2.4

(*Continued*)

Table 3 (Continued).

CV Risk Factors and Disease	CKD Patients (n=734)
Established CV disease	
Ischemic heart disease (%)	0.9
CVA/TIA (%)	2.3
Peripheral vascular disease (%)	0.4
Heart failure (%)	2.0
Any cardiovascular disease (%)	5.6

Notes: Data are expressed as mean (SD), median (interquartile range) or proportions.
Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HDL, high density lipoprotein; LDL, low density lipoprotein; chol, cholesterol; EGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Regarding non-traditional cardiovascular risk factors, the median (SD) estimated glomerular filtration rate was 38.0 (21.3–57.3) mL/min/1.73m^2. Most patients (54%) had concurrent low estimated glomerular filtration rate and proteinuria. At the time of the study, 39.4% of the participants had HIV. Systemic lupus erythematosus was diagnosed in 2.4% of the patients. The prevalence of established cardiovascular disease was 5.6%.

Numerically, cerebrovascular disease and heart failure were more prevalent than ischemic heart disease and peripheral vascular disease.

Baseline Recorded Characteristics in the Isolated Major Etiological Categories

To determine whether isolated major etiological categories can impact cardiovascular risk and disease in the current population, we selected 607 patients who had either only (1) HNP (n=238) or (2) concurrent HNP and DNP (n=157) or (3) DNP (n=13) or (4) HIV associated CKD (n=99) or (5) glomerular disease (n=100). The baseline recorded characteristics in these different groups are given in Table 4. In this and the following section only significant intergroup differences after Bonferroni correction at p-value <0.05 are given. Among demographic characteristics, age, sex and

Table 4 Baseline Recorded Characteristics in the Isolated Major Etiological Categories Among 607 Patients with CKD

	Etiological Categories					
Characteristics	**HNP (n=238)**	**Concurrent HNP and DNP (n=157)**	**DNP (n=13)**	**HIV associated (n=99)**	**Glomerular Disease (n=100)**	**Intergroup Comparison p-value**
Demographics						
Age (years)	**55.0 (13.1)**	**61.0 (10.5)**	**45.7 (15.1)**	**48.8 (9.5)**	**40.5 (13.8)**	**<0.001**
Female sex (%)	**45.0**	**58.0**	**38.5**	**63.6**	**62.0**	**0.003**
Black (%)	98.3	98.1	92.3	99.0	96.0	0.3
Mixed (%)	0.8	0.6	7.7	1.0	0.0	0.08
Asian (%)	0.8	0.6	0.0	0.0	2.0	0.6
White (%)	0.0	0.6	0.0	0.0	2.0	0.2
CKD duration (years)	**4.5 (1.5–7.5)**	**2.5 (1.5–5.5)**	**2.5 (1.0–7.5)**	**4.5 (1.5–7.5)**	**4.5 (2.5–8.5)**	**0.003**
Alcohol use (%)	6.5	3.3	7.7	6.2	5.3	0.7

(*Continued*)

Table 4 (Continued).

Etiological Categories						
Characteristics	**HNP (n=238)**	**Concurrent HNP and DNP (n=157)**	**DNP (n=13)**	**HIV associated (n=99)**	**Glomerular Disease (n=100)**	**Intergroup Comparison *p*-value**
Anthropometry						
Weight (kg)	**75.3**	**79.1**	**67.0**	**68.2**	**74.0**	**<0.001**
Height (cm)	**163**	**163**	**165**	**161**	**161**	**0.04**
BMI (kg/m^2)	**28.6**	**29.8**	**24.8**	**26.6**	**28.8**	**<0.001**
Treatment						
Antihypertensive agent use (%)	**100**	**99.4**	**84.6**	**69.7**	**89.0**	**<0.001**
Antihypertensives (n)	**3.5 (1.2)**	**3.4 (1.0)**	**2.7 (1.5)**	**1.8 (1.5)**	**2.3 (1.4)**	**<0.001**
Diuretic agents (%)	**87.0**	**88.5**	**76.9**	**56.6**	**71.0**	**<0.001**
Calcium channel blockers (%)	**88.7**	**82.2**	**69.2**	**51.5**	**51.0**	**<0.001**
ACEI/ARB (%)	**63.9**	**67.5**	**53.9**	**29.3**	**68.0**	**<0.001**
Alpha blockers (%)	**46.6**	**37.6**	**46.1**	**20.2**	**21.0**	**<0.001**
Beta blockers (%)	**43.3**	**42.0**	**23.1**	**20.2**	**11.0**	**<0.001**
Hydralazine (%)	**20.2**	**18.5**	**0.0**	**5.0**	**4.0**	**<0.001**
Statins (%)	**45.8**	**54.8**	**69.2**	**31.3**	**54.0**	**0.001**
Oral hypoglycaemic agents (%)	**0.0**	**6.0**	**0.0**	**0.0**	**0.0**	**<0.001**
Insulin (%)	**0.0**	**79.6**	**84.6**	**0.0**	**0.0**	**<0.001**
Antiretroviral therapy (%)	**23.1**	**15.9**	**15.4**	**93.9**	**19.0**	**<0.001**
Allopurinol (%)	**9.2**	**9.6**	**0**	**2.0**	**2.0**	**0.01**
Immunosuppressive agent use (%)	**1.3**	**0.0**	**15.4**	**0.0**	**34.0**	**<0.001**
Kidney transplant recipient (%)	**1.3**	**0.0**	**15.4**	**0.0**	**0.0**	**<0.001**

Notes: Data are expressed as mean (SD), median (interquartile range) or proportions. Significant differences are shown in bold.
Abbreviations: CKD, chronic kidney disease; HNP, hypertensive nephropathy; DNP, diabetic nephropathy; HIV, human immunodeficiency virus; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

CKD duration differed between the groups. Patients with concurrent HNP and DNP were older than those with HNP only. Patients with HIV associated CKD (p-value < 0.001) and glomerular disease (p-value < 0.001) were younger than those with HNP and concurrent HNP and DNP. Patients with HIV associated CKD and glomerular disease were more often women than those with HNP and concurrent HNP and DNP. Disease duration was shorter in patients with concurrent HNP and DNP compared to those with HNP, HIV associated CKD and glomerular disease.

Among anthropometric measures, weight was lower in patients with HIV associated CKD compared to those with HNP and concurrent HNP and DNP. The BMI was smaller in HIV associated CKD than those with concurrent HNP and DNP.

Among treatment characteristics, patients with HNP and concurrent HNP and DNP used antihypertensive agents more frequently and in larger numbers than those in the other 3 etiological categories. The same applied to alpha blocker use. Diuretic agents, calcium channel blockers, beta blockers and hydralazine were more often employed in patients with HNP and concurrent HNP and DNP than in those with HIV associated CKD and glomerular disease. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers were used less frequently in patients with HIV associated CKD compared to those with HNP, concurrent HNP and DNP and glomerular disease. Statins were employed less often in HIV associated CKD than in those with concurrent HNP and DNP and glomerular disease. Immunosuppressive agents

were employed more often in patients with DNP (to prevent kidney transplant rejection) and glomerular disease than those in the other etiological categories.

Cardiovascular Risk Factors and Disease in the Isolated Major Etiological Categories

Cardiovascular risk factors and disease in the isolated major etiological categories at the time of the study are shown in Table 5. The differences in blood pressure measures among the etiological categories are also illustrated in Figure 1. Systolic blood pressure was larger in patients with HNP and concurrent HNP and DNP than in those with HIV associated CKD and glomerular disease (p-value <0.001 for all comparisons). Diastolic blood pressure was larger in patients with HNP compared to those with glomerular disease (p-value=0.002). Pulse pressure was larger in patients with concurrent HNP and DNP than in those with HNP only (p-value <0.001). Pulse pressure was also larger in patients with HNP and concurrent HNP and DNP compared to those with HIV associated CKD or glomerular disease (p-value=0.04 to <0.001). Mean arterial pressure was larger in patients with HNP compared to those with HIV induced CKD and glomerular disease (p-value <0.001 for both). Mean arterial pressure was also larger in patients with concurrent HNP and DNP compared to those with HIV induced CKD (p-value=0.02). Uncontrolled systolic blood pressure was more prevalent in patients with HNP and concurrent HNP and DNP than those in the other 3 categories.

Dyslipidaemia was observed more often in patients with concurrent HNP and DNP than in those with HIV associated CKD and glomerular disease. LDL cholesterol concentrations were lower in DNP than in than in those with HNP. Remnant cholesterol levels did not differ among etiological categories in pairwise comparisons.

As expected, diabetes was more frequent in patients with concurrent HNP and DNP and DNP than in those in the other 3 etiological categories. In line with this, haemoglobin A1C levels were larger in patients with concurrent HNP and DNP and DNP than in those in the other 3 etiological categories.

Blood pressure and diabetes are included in the Framingham algorithm, which is a measure of the traditional cardiovascular risk factor burden. Accordingly, and as illustrated also in Figure 2, the Framingham score was larger in patients with concurrent HNP and DNP than in those with HNP only (p-value=0.002). Likewise, the Framingham score was also larger in patients with HNP and concurrent HNP and DNP than in those with HIV induced CKD and glomerular disease (p-value <0.001 for all comparisons). Patients with DNP experienced a lower Framingham score than those with concurrent HNP and DNP (p-value=0.001). Low traditional risk factor mediated cardiovascular risk was less frequent in patients with concurrent HNP and DNP than in those in the 4 other etiologic categories. Low CV risk was observed less often in patients with HNP compared to those with HIV associated CKD and glomerular disease. Moderate cardiovascular risk was more frequent in patients with HNP and concurrent HNP and DNP than in those with glomerular disease. High cardiovascular risk was more frequently observed in concurrent HNP and DNP than those with HNP, HIV associated CKD and glomerular disease.

Regarding non-traditional cardiovascular risk factors, haemoglobin concentrations did not differ among groups in the 5 etiological categories in pairwise analysis. Uric acid levels were larger in patients with HNP compared to those with HIV associated CKD and glomerular disease and in patients with concurrent HNP and DNP compared to those with glomerular disease. Estimated glomerular filtration rate was larger in patients with glomerular disease than in those in the other 4 categories. Proteinuria was larger in patients with glomerular disease than in the other groups. However, differences in proteinuria were not significant among the groups in pairwise analysis. Isolated low estimated glomerular filtration rate was more frequent in patients with HNP and concurrent HNP and DNP than those with HIV associated CKD and glomerular disease. Isolated proteinuria was less often found in patients with HIV associated CKD than those with glomerular disease. Concurrent low estimated glomerular filtration rate and proteinuria was less frequent in patients with glomerular disease than in those with HNP, concurrent HNP and DNP and HIV associated CKD. HIV infection at the time of the study was more often observed in patients with HIV associated CKD than in those in the other 4 etiological categories. Systemic lupus erythematosus was diagnosed in patients with glomerular disease only.

Concerning established CV disease, peripheral vascular disease was more frequent in patients with DNP than in those with HNP. Any CV disease was more prevalent in patients with HNP than in those with glomerular disease. Patients with concurrent HNP and DNP and DNP experienced more frequent established CV disease than those with HIV associated CKD and glomerular disease.

Table 5 Cardiovascular Risk Factors and Disease in the Isolated Major Etiological Categories Among 607 CKD Patients

	Etiological Categories					
CV Risk Factors and Disease	**HNP (n=238)**	**Concurrent HNP and DNP (n=157)**	**DNP (n=13)**	**HIV Associated (n=99)**	**Glomerular Disease (n=100)**	**Intergroup Comparison *p*-value**
Traditional CV risk factors						
Hypertension (%)	**100**	**100**	**76.9**	**64.6**	**75.0**	**<0.001**
Systolic blood pressure (mmHg)	**142 (130–159)**	**147 (134–169)**	**141 (123–151)**	**134 (123–150)**	**130 (122–144)**	**<0.001**
Diastolic blood pressure (mmHg)	**88 (80–97)**	**85 (72–94)**	**87 (71–88)**	**84 (75–94)**	**83 (75–88)**	**0.001**
Pulse pressure (%)	**60 (46–69)**	**69 (54–82)**	**55 (48–67)**	**53 (43–62)**	**51 (42–61)**	**<0.001**
Mean arterial pressure (mmHg)	**106 (97–116)**	**105 (94–120)**	**105 (90–110)**	**99 (92–113)**	**100 (93–104)**	**<0.001**
Uncontrolled systolic blood pressure (%)	**75.2**	**83.4**	**69.2**	**59.6**	**53.0**	**<0.001**
Dyslipidemia (%)	**60.5**	**73.2**	**69.2**	**53.5**	**59.0**	**0.01**
Total cholesterol (mmol/l)	4.6 (3.9–5.4)	4.2 (3.6–5.5)	3.7 (3.3–4.2)	4.5 (4.0–5.4)	4.5 (3.6–5.7)	0.09
HDL cholesterol (mmol/l)	1.25 (1.03–1.52)	1.22 (0.98–1.44)	1.30 (1.08–1.44)	1.31 (1.03–1.49)	1.24 (1.04–1.61)	0.4
LDL cholesterol (mmol/l)	**2.5 (1.9–3.2)**	**2.3 (1.6–3.0)**	**1.8 (1.6–2.2)**	**2.4 (2.1–3.1)**	**2.9 (1.9–3.1)**	**0.02**
Total chol-HDL chol ratio	3.4 (2.7–4.5)	4.0 (2.9–4.5)	3.0 (2.4–3.5)	3.6 (2.8–4.2)	3.3 (2.8–4.6)	0.2
Triglycerides (mmol/l)	**1.33 (0.90–1.87)**	**1.54 (1.03–2.11)**	**1.18 (0.73–1.59)**	**1.48 (1.13–1.99)**	**1.24 (0.88–1.85)**	**0.04**
Remnant cholesterol (mmol/l)	**0.55 (0.39–0.78)**	**0.65 (0.46–0.88)**	**0.51 (0.34–0.72)**	**0.62 (0.48–0.85)**	**0.56 (0.32–0.79)**	**0.01**
Diabetes (%)	**1.3**	**100**	**100**	**0.0**	**4.0**	**<0.001**
Haemoglobin A1C (%)	**5.9 (5.4–6.3)**	**7.8 (6.7–9.3)**	**12.0 (9.0–12.5)**	**5.7 (5.4–6.0)**	**5.8 (5.5–6.2)**	**<0.001**
Smoking (%)	7.0	3.9	7.7	7.2	7.4	0.7
Framingham score (%)	**12.2 (6.3–19.4)**	**17.4 (10.2–29.9)**	**4.8 (2.1–12.8)**	**6.1 (3.8–12.7)**	**4.2 (1.6–8.2)**	**<0.001**
Low CV disease risk (%)	**39.5**	**23.5**	**66.7**	**66.7**	**79.8**	**<0.001**
Moderate CV disease risk (%)	**37.5**	**36.5**	**25.0**	**25.3**	**10.7**	**<0.001**
High CV disease risk (%)	**23.0**	**40.0**	**8.3**	**8.0**	**9.5**	**<0.001**
Non-traditional CV risk factors						

(*Continued*)

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Table 5 (Continued).

Etiological Categories						
CV Risk Factors and Disease	**HNP (n=238)**	**Concurrent HNP and DNP (n=157)**	**DNP (n=13)**	**HIV Associated (n=99)**	**Glomerular Disease (n=100)**	**Intergroup Comparison *p*-value**
Haemoglobin (g/dl)	**13.2 (2.3)**	**12.1 (2.0)**	**12.1 (2.7)**	**13.0 (2.2)**	**13.1 (2.2)**	**<0.001**
Albumin (g/l)	44 (40–46)	43 (39–46)	40.1 (35–44)	43 (39–46)	42 (38–46)	0.06
Uric acid (mmol/l)	**0.45 (0.12)**	**0.45 (0.12)**	**0.39 (0.30–0.45)**	**0.40 (0.12)**	**0.37 (0.10**	**<0.001**
EGFR (mL/min/1.73m^2)	**36 (20–52)**	**30.0 (21–50)**	**36 (32–59)**	**37 (17–49)**	**81 (42–129)**	**<0.001**
Urine protein-creatinine ratio (g/mmol)	**0.034 (0.012–0.117)**	**0.048 (0.015–0.119)**	**0.030 (0.006–0.142)**	**0.065 (0.029–0.144)**	**0.132 (0.015–0.185)**	**0.01**
Isolated low EGFR (%)	**30.6**	**22.9**	**38.5**	**14.2**	**8.1**	**<0.001**
Isolated proteinuria (%)	**17.7**	**17.0**	**23.1**	**8.2**	**61.6**	**<0.001**
Concurrent low EGFR and proteinuria	**51.7**	**60.1**	**38.4**	**77.6**	**30.3**	**<0.001**
HIV virus infection (%)	**26.0**	**17.8**	**15.4**	**100**	**19.0**	**<0.001**
Gout (%)	5.9	1.9	0.0	2.0	1.0	0.07
Systemic lupus erythematosus (%)	**0.0**	**0.0**	**0.0**	**0.0**	**18.0**	**<0.001**
Established CV disease (%)						
Ischemic heart disease	1.7	1.3	0.0	0.0	0.0	0.5
CVA/TIA (%)	3.4	4.5	7.7	0.0	0.0	0.05
Peripheral vascular disease (%)	**0.0**	**0.6**	**7.7**	**0.0**	**0.0**	**<0.001**
Heart failure (%)	2.5	3.2	0.0	2.0	0.0	0.5
Any CV disease	**7.6**	**9.6**	**15.4**	**2.0**	**0.0**	**0.01**

Notes: Data are expressed as mean (SD), median (interquartile range) or proportions. Significant differences are shown in bold.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HNP, hypertensive nephropathy; DNP, diabetic nephropathy; HIV, human immunodeficiency virus; HDL, high density lipoprotein; LDL, low density lipoprotein; chol, cholesterol; EGFR, estimated glomerular filtration rate; CVA, cerebrovascular accident; TIA, transient ischemic attack.

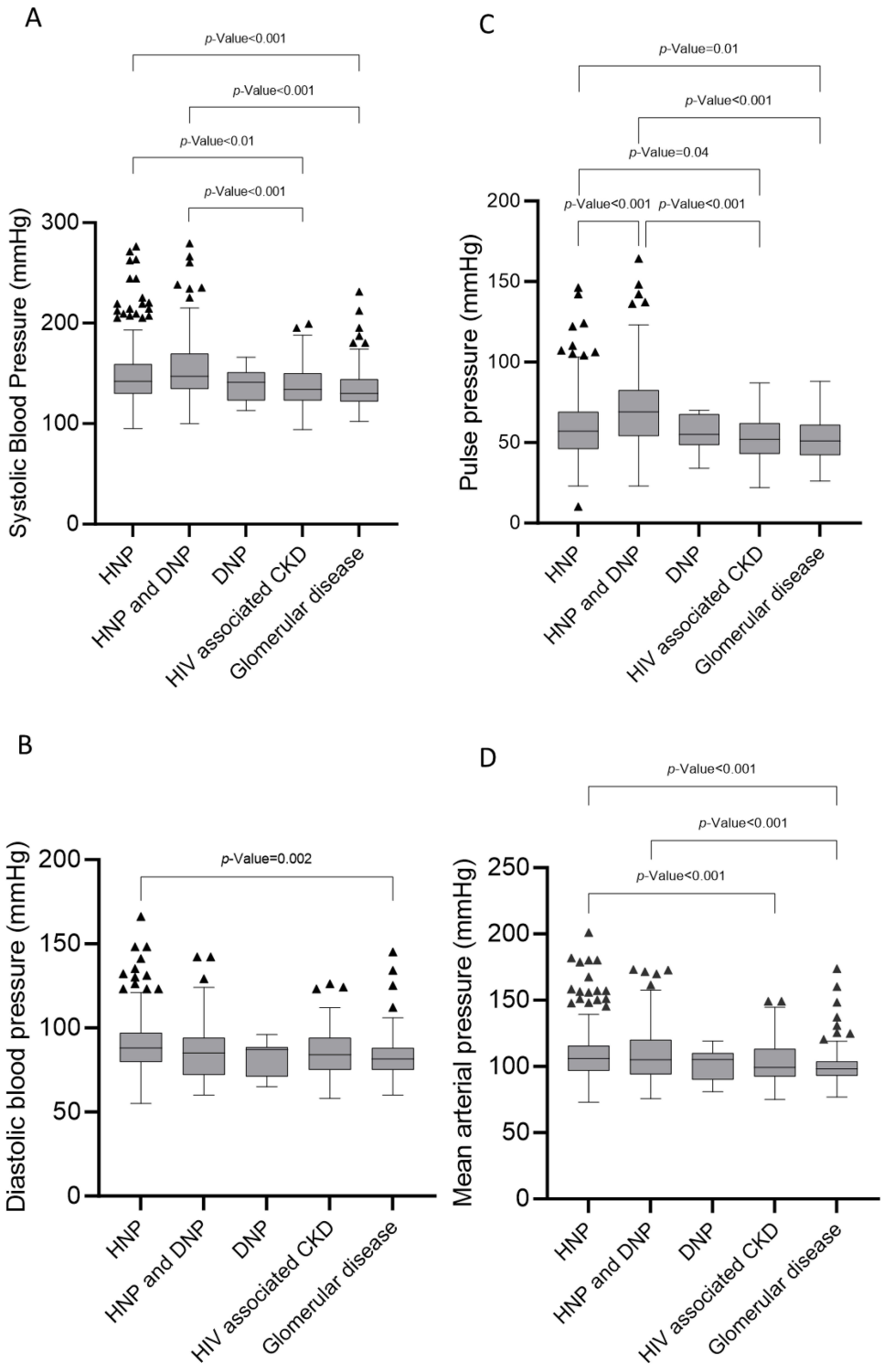


Figure 1 Box and whisker plots showing the differences across the main etiological categories for systolic blood pressure (**A**), diastolic blood pressure (**B**), pulse pressure (**C**) and mean arterial pressure (**D**). HNP, hypertensive nephropathy; DNP, diabetic nephropathy; HIV, human immunodeficiency virus.

The non modifiable cardiovascular risk factor profile comprising age and sex was more favourable in patients with HIV associated CKD and glomerular disease compared to those with HNP and concurrent HNP and DNP. Table 6 shows that the association of HNP or concurrent HNP or DNP with the Framingham score remained significant upon adjusting for demographic characteristics in a multiple regression model. Upon further adjustment for other baseline characteristics that differed among CKD etiological categories including BMI, CKD duration and kidney transplant recipient (see Table 4), the

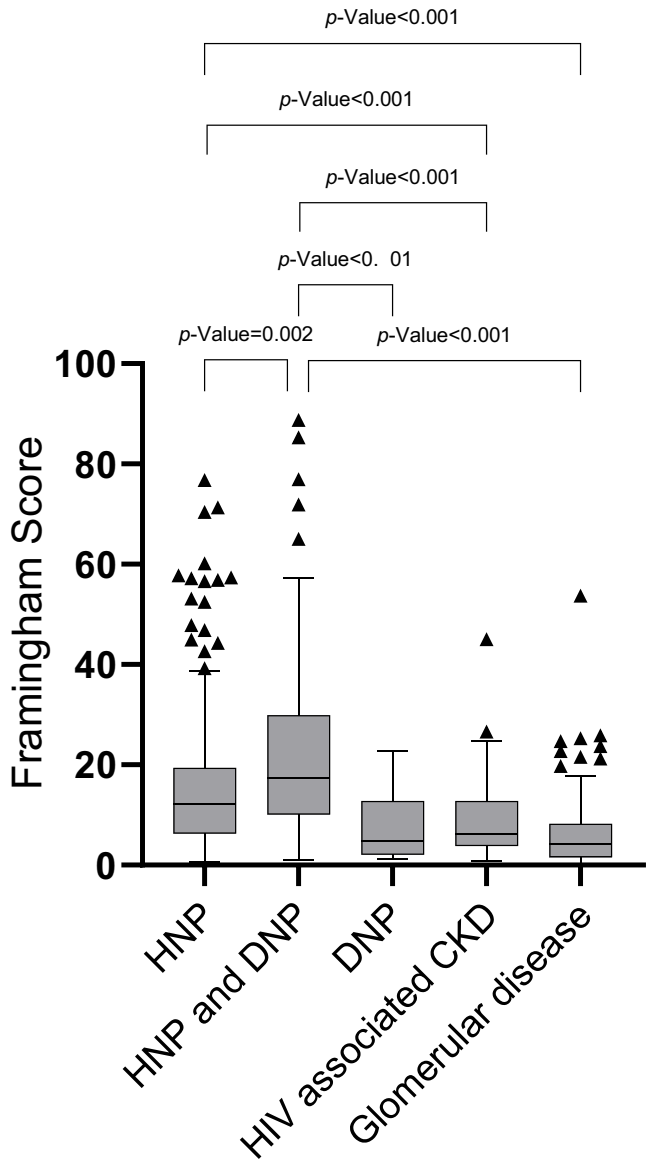


Figure 2 Box and whisker plots showing the differences across the main etiological categories for the overall traditional cardiovascular risk burden as represented by the Framingham score. HNP, hypertensive nephropathy; DNP, diabetic nephropathy; HIV, human immunodeficiency virus.

association of HNP or concurrent HNP or DNP with the Framingham score remained unaltered (Model R^2=0.477; β (SE) =1.812 (0.892); standardized β=0.064; *p*-value=0.04). Drug treatment was not adjusted for in the latter model as medications were intrinsically used in relation to CKD etiological categories (see Table 4). As given in Table 7, the relationship of HNP or concurrent HNP or DNP with uncontrolled systolic blood pressure was also independent of demographic characteristics.

Demographic Characteristic and Mutually Independent Potential Impact of HNP and DNP on Pulse Pressure and Systolic Blood Pressure in CKD Patients

The demographic characteristic and mutually independent potential impact of HNP and DNP on pulse pressure and systolic blood pressure in all patients are given in Tables 8 and 9, respectively. The partial correlation coefficients (95% CI) for the models in Tables 8 and 9 are given in Figure 3. HNP and DNP were each associated with pulse pressure (first model in Tables 8 and 9) and systolic blood pressure (second model in Tables 8 and 9). Both HNP and DNP were also associated with pulse pressure (third model in Tables 8 and 9) and systolic blood pressure (third model in Tables 8 and 9)

Table 6 Demographic Characteristic Independent Association of Hypertensive Nephropathy or Concurrent Hypertensive Nephropathy and Diabetic Nephropathy or Diabetic Nephropathy with the Framingham Score in CKD Patients

Characteristics	Model R^2	β	SE	Std. β	p-value
	0.465				
Age		**0.605**	**0.033**	**0.589**	**<0.001**
Female sex		**−6.385**	**0.838**	**−0.227**	**<0.001**
Black PO		−2.036	2.883	−0.021	0.5
HNP or concurrent HNP and DNP or DNP		**2.141**	**0.893**	**0.076**	**0.01**

Notes: Significant associations are given in bold.
Abbreviations: CKD, chronic kidney disease; β, regression coefficient; SE, standard error; Std. standardized; PO, population origin; HNP, hypertensive nephropathy; DNP, diabetic nephropathy.

Table 7 Demographic Characteristic Independent Association of Hypertensive Nephropathy or Concurrent Hypertensive Nephropathy and Diabetic Nephropathy or Diabetic Nephropathy with Uncontrolled Systolic Blood Pressure in CKD Patients

Characteristics	Odds Ratio	95% CI	*p*-value
Age	**1.02**	**1.00 to 1.03**	**0.006**
Female sex	0.81	0.58 to 1.13	0.2
Black PO	0.89	0.26 to 3.01	0.9
HNP or concurrent HNP and DNP or DNP	**1.86**	**1.31 to 2.63**	**<0.001**

Notes: Significant associations are given in bold.
Abbreviations: CKD, chronic kidney disease; CI, confidence interval; PO, population origin; HNP, hypertensive nephropathy; DNP, diabetic nephropathy.

Table 8 Demographic Characteristic and Mutually Independent Potential Impact of Hypertensive Nephropathy and Diabetic Nephropathy on Pulse Pressure in CKDpatients

Characteristics	Cumulative R^2	β	SE	Std. β	p-value
	0.104				
Age		**0.331**	**0.056**	**0.225**	**<0.001**
+female gender		−0.617	1.43	0.015	0.7
+black PO		3.55	5.18	0.024	0.5
+hypertensive nephropathy		**6.508**	**1.587**	**0.158**	**<0.001**
	0.122				
Age		**0.333**	**0.054**	**0.226**	**<0.001**
+female gender		−0.344	1.414	−0.008	0.8
+black PO		4.621	5.129	0.031	0.4
+diabetic nephropathy		**9.697**	**1.712**	**0.206**	**<0.001**
	0.130				
Age		**0.286**	**0.057**	**0.194**	**<0.001**
+female gender		0.044	1.417	0.001	0.9
+black PO		4.185	5.112	0.028	0.4
+hypertensive nephropathy		**4.249**	**1.638**	**0.103**	**0.01**
+diabetic nephropathy		**8.327**	**1.786**	**0.177**	**<0.001**

(*Continued*)

Table 8 (Continued).

Characteristics	Cumulative R^2	β	SE	Std. β	p-value
	0.401				
Age		**0.320**	**0.047**	**0.217**	**<0.001**
+female gender		0.376	1.177	0.009	0.7
+black PO		4.336	4.245	0.029	0.3
+hypertensive nephropathy		−0.666	1.387	−0.016	0.6
+diabetic nephropathy		**8.495**	**1.483**	**0.180**	**<0.001**
+mean arterial pressure		**0.586**	**0.032**	**0.532**	**<0.001**

Notes: Significant associations are given in bold.
Abbreviations: CKD, chronic kidney disease; β, regression coefficient; SE, standard error; Std., standardized; PO, population origin.

Table 9 Demographic Characteristic and Mutually Independent Potential Impact of Hypertensive Nephropathy and Diabetic Nephropathy on Systolic Blood Pressure in CKD Patients

Characteristics	Cumulative R^2	β	SE	Std. β	p-value
	0.068				
Age		**0.160**	**0.080**	**0.078**	**0.04**
+female gender		−0.174	2.029	−0.003	0.9
+black PO		2.134	7.347	0.010	0.8
+hypertensive nephropathy		**12.644**	**2.249**	**0.220**	**<0.001**
	0.045				
Age		**0.256**	**0.078**	**0.125**	**0.001**
+female gender		−1.560	2.051	−0.028	0.5
+black PO		3.684	7.438	0.018	0.6
+diabetic nephropathy		**8.882**	**2.483**	**0.136**	**<0.001**
	0.074				
Age		0.131	0.081	0.064	0.1
+female gender		−0.537	2.032	−0.010	0.8
+black PO		2.533	7.333	0.012	0.7
+hypertensive nephropathy		**11.216**	**2.349**	**0.195**	**<0.001**
+diabetic nephropathy		**5.266**	**2.562**	**0.080**	**0.04**
	0.862				
Age		**0.214**	**0.031**	**0.104**	**<0.001**
+female gender		0.251	0.784	0.004	0.7
+black PO		2.891	2.830	0.014	0.3
+hypertensive nephropathy		−0.444	0.924	−0.008	0.6
+diabetic nephropathy		**5.663**	**0.989**	**0.087**	**<0.001**
+mean arterial pressure		**1.391**	**0.022**	**0.908**	**<0.001**

Notes: Significant associations are given in bold.
Abbreviations: β, regression coefficient; SE, standard error; Std., standardized; PO, population origin.

independent of one another. Upon further adjustment for mean arterial or distending pressure (fourth model in Tables 8 and 9), the association of DNP with pulse pressure and systolic blood pressure persisted, whereas that of HNP was abolished.

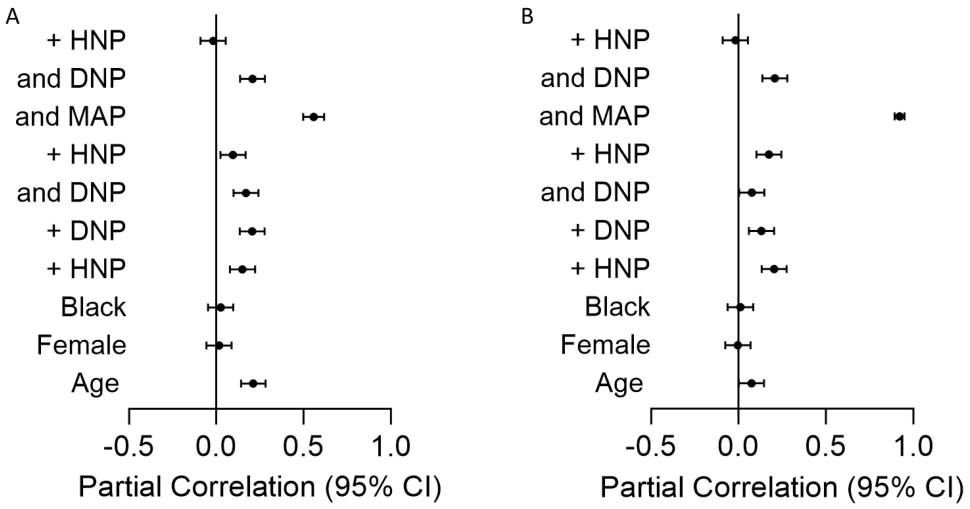


Figure 3 Partial correlations (95% CI) for the associations given in Table 8 (**A**) and Table 9 (**B**). HNP, hypertensive nephropathy; DNP, diabetic nephropathy; MAP, mean arterial pressure.

Mean arterial pressure as a mediator of the potential effects of hypertensive nephropathy and diabetic nephropathy on pulse pressure and systolic blood pressure in CKD patients.

As shown in Table 10, in adjusted product of coefficient mediation analysis, mean arterial pressure accounted for 115.7% of the potential effect of HNP on pulse pressure and 103.9 of the potential impact of HNP on systolic blood pressure. By contrast, mean arterial pressure did not mediate (−2.0% to −7.5% contribution) the potential effects of DNP on pulse pressure and systolic blood pressure.

Discussion

This study examined the presumed causes of CKD and their associations with cardiovascular risk and disease in a cohort of patients that form part of a large low-income African population. The main novel findings are sixfold. Firstly, the most

Table 10 Mean Arterial Pressure as a Mediator of the Potential Effects of Hypertensive Nephropathy and Diabetic Nephropathy on Pulse Pressure and Systolic Blood Pressure in CKD Patients

	Pulse Pressure			Systolic Blood Pressure		
Etiological Categories	**Estimate**	**95% CI**	**%Contribution**	**Estimate**	**95% CI**	**%Contribution**
Hypertensive nephropathy[a]						
Direct effect	−0.666	−3.389 to 2.056	−15.7	−0.444	−2.259 to 1.371	3.9
Indirect effect through MAP	**4.915**	**3.010 to 6.982**	**115.7**	**11.660**	**7.397 to 16.105**	**103.9**
Total effect	**4.249**	**1.034 to 7.464**	**100**	**11.216**	**6.603 25.829**	**100**
Diabetic nephropathy[b]						
Direct effect	**8.494**	**5.583 to 11.406**	**102.0**	**5.663**	**3.722 to 7.604**	**107.5**
Indirect effect through MAP	−0.167	−2.195 to 1.898	−2.0	−0.397	−5.137 to 4.396	−7.5
Total effect	**8.327**	**4.822 to 11.832**	**100**	**5.266**	**0.237 to 10.295**	**100**

Notes: Significant associations are given in bold. [a]Model adjusted for age, female sex, black population origin and diabetic nephropathy. [b]Model adjusted for age, female sex, black population origin and hypertensive nephropathy.
Abbreviations: CKD, chronic kidney disease; CI, confidence interval; MAP, mean arterial pressure.

prevalent presumed cause of CKD in this population was HNP by far and this was followed by less frequent DNP, HIV associated CKD and glomerular disease. Secondly, pulse pressure as a marker of aortic stiffness was larger in patients with concurrent HNP and DNP than in those with HNP only. Thirdly, pulse pressure and systolic blood pressure were larger in patients with HNP and concurrent HNP and DNP than in those with HIV associated CKD or glomerular disease. Fourthly, HNP and DNP were associated with pulse pressure independent of one another. Fifthly, in product of coefficient mediation analysis, mean or distending arterial pressure accounted fully for the potential impact of HNP on pulse pressure; by contrast, mean arterial pressure did not contribute at all to the potential effect of DNP on pulse pressure. Sixthly, HNP or concurrent HNP and DNP or DNP was associated with a markedly increased prevalence of uncontrolled systolic blood pressure. Taken together, in the current low-income African population, hypertension is the main presumed cause of CKD and cardiovascular disease risk differs markedly in relation to etiological categories.

The most striking finding in this study emanated upon exploring the contribution of HNP and DNP to the variation in pulse pressure. In demographic characteristic adjusted analysis, HNP and DNP were related to pulse pressure independent of one another. Aortic stiffness as represented by pulse pressure can develop because of arteriosclerosis that comprises replacement of elastin by collagen and arterial wall calcification.[22,23] However, importantly in the present context, due to mechanical properties of the arterial wall, arterial stiffness can also be produced by aortic distension that is mediated by mean arterial pressure.[21,32,33] Mean arterial pressure accounts for organ perfusion.[34] Aortic distension due to increased mean arterial pressure occurs through the recruitment of stiffer collagen fibres.[33] It is therefore particularly noticeable that upon adjustment for mean arterial blood pressure in addition to demographic characteristics and DNP, the association of HNP with pulse pressure was entirely abrogated in the present investigation. By contrast, upon adjustment for mean arterial blood pressure in addition to demographic characteristics and HNP, the association of DNP with pulse pressure was unaltered. Demographic characteristic and DNP adjusted product of coefficient mediation analysis confirmed that mean arterial pressure fully explained (115.7%) the potential effect of HNP on pulse pressure. Contrary to this, mean arterial pressure did not mediate any (−2.0%) of the potential impact of DNP on pulse pressure. Pulse pressure determines systolic blood pressure.[35] In keeping with this, upon replacing pulse pressure by systolic blood pressure as the dependent and outcome characteristic in the analysis, our findings on systolic blood pressure paralleled those on pulse pressure.

The above-mentioned findings have treatment implications. Aortic stiffness is a key component of CKD induced cardiovascular disease.[25] Intrinsic aortic stiffness due to structural arterial wall changes remains largely untreatable at this stage. By contrast, mean arterial pressure mediated aortic stiffness should be treatable with currently recommended antihypertensives.[36–38] Indeed, mean arterial pressure depends on not only on volume load as represented by cardiac output but also systemic or peripheral vascular resistance.[34] Antihypertensive agents including angiotensin converting enzyme inhibitors,[36] angiotensin receptor blockers[37] and calcium channel blockers[38] as well as thiazide diuretics[39] ultimately reduce blood pressure by decreasing systemic vascular resistance. Given that mean arterial pressure simultaneously depends on volume load,[34] the use of loop diuretics in volume overloaded patients with CKD would also be expected to decrease the impact of HNP on pulse pressure. The potential role of the more novel sodium glucose co-transporter 2 inhibitors in the present context merits future study.[40] Collectively, reported data together with our findings suggest that aortic stiffness may respond to the use of agents that decrease systemic vascular resistance or/and volume overload in patients with HNP but not in those with DNP.

In the population at large, circa 70% of patients with diabetes have comorbid hypertension[41] that increases cardiovascular risk.[42,43] In the present patient cohort, 93.6% of patients with diabetes had concurrent hypertension. In this regard, the second most noticeable result in the present study was that pulse pressure as a measure of aortic stiffness was larger in CKD patients with concurrent HNP and DNP than in those with HNP only. Our results indicate that comorbid hypertension in diabetes exacerbates cardiovascular disease risk in CKD patients.

In relation to traditional cardiovascular risk factors, dyslipidaemia was more prevalent in patients with concurrent HNP and DNP than in those with HIV associated CKD and glomerular disease. However, the foremost differences in traditional cardiovascular risk factors across the main etiological categories comprised more prevalent hypertension, larger pulse pressure and systolic blood pressure and more frequent uncontrolled hypertension in patients with HNP and concurrent HNP and DNP compared to those from other etiological categories. Independent of demographic

characteristics, HNP, concurrent HNP or DNP or isolated DNP was associated with a 1.86 fold increased risk of uncontrolled hypertension. Hypertension is the most frequent modifiable cause of premature death.[44] Hypertension is also the leading contributor to incident cardiovascular disease in CKD patients.[15,45] Apart from a larger glomerular filtration rate in patients with glomerular disease compared to the other groups, no marked differences in non-traditional risk factors across the etiological categories were noted. Our results suggest that adequate cardiovascular disease risk management in the current setting should be strongly focused on adequate blood pressure control.[46]

The prevalence of established cardiovascular disease was larger in patients with concurrent HNP and DNP and isolated DNP than in those with HIV associated CKD and glomerular disease. Regardless of these findings, the most salient feature that emerged in our analysis on established cardiovascular disease was that the prevalence was overall remarkably low at 5.6%. This contrasts sharply to the reported prevalence of cardiovascular disease among patients with CKD from high income populations, which ranges from 26.8% to 47.2%.[47] Conceptually, this could represent a decreased susceptibility to cardiovascular disease in black Africans from low-income populations. An alternative and presumably more likely and concerning interpretation of these findings is that the low prevalence of established cardiovascular disease represents a survival or selection bias in that patients with cardiovascular disease may have died earlier and prior to enrolling into the present study. Future studies are urgently needed to determine which one of these scenarios applies in CKD patients that belong to low-income African populations.

Globally, diabetes is the most common presumed cause of CKD.[7–9] Notably, hypertension is more prevalent, severe, and resistant to treatment in persons with a black population origin.[10] This is due to genetically determined salt and fluid retention that is accompanied by low plasma renin activity.[10] In a recent population study that was performed in rural South Africans,[48] diabetes status appeared more strongly (odds ratio (95% CI)=4.1 (2.0–8.4)) associated with CKD than was hypertension (odds ratio (95% CI)=2.8 (1.8–4.3)). However, the median (interquartile range) age in that study was as young as 35 (27–48) years and most participants presented with persistent microalbuminuria in the absence of a reduced estimated glomerular filtration rate. In contrast to these reported data, in the present investigation, presumed HNP was found in 60.2% of participants and was 2.5-fold more prevalent than that of DNP. A substantial proportion of patients had HIV associated CKD (20.0%) or glomerular disease (13.6%), whereas other etiological categories were uncommon. These findings suggest that particularly adequate blood pressure control as well as lifestyle measures that decrease diabetes incidence are likely to be the most important strategies to prevent CKD and its associated cardiovascular disease in low-income black Africans.

A strength of the present study is its large size and the overall limited number of missing data. Notwithstanding this, the current investigation has limitations. Firstly, in view of its cross-sectional design, no inferences can be made on cause-effect relationships. Secondly, the over great majority (98.1%) of the included CKD patients was derived from an African low-income population. Therefore, our findings on the potential determinants of pulse pressure as an aortic stiffness marker and systolic blood pressure may not apply to CKD patients from other population origins. We however believe that this is unlikely to be the case. Thirdly, presumed HNP and DNP were determined based on clinical features and not confirmed by kidney biopsy as was systematically done in patients with glomerular disease. Although a kidney biopsy represents a mostly safe procedure,[49] its routine performance in patients with suspected HNP or DNP would likely be unacceptable to patients and physicians and considered unethical,[7] particularly where no clinical benefit is anticipated.

In conclusion, the most prevalent presumed cause of CKD in black Africans from a low-income population was found to be HNP. This was followed by less frequent DNP and HIV associated CKD and glomerular disease. Etiologic categories have a marked potential impact on cardiovascular risk in patients with CKD particularly as relates to aortic stiffness and hence pulsatile pressures, which comprise the major cause of cardiovascular disease in patients with CKD. Mean arterial or distending pressure accounts entirely for the impact of HNP on pulsatile pressures. Contrary to this, mean arterial pressure does not contribute at all to the effects of DNP on pulsatile pressures.

Ethics Statement

This study was conducted in line with the principles of the Helsinki declaration. The study protocol was approved by the University of Witwatersrand Human (Medical) Research Committee (protocol number: M221013 MED22-09-043). Participants gave informed, written consent.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013;382(9888):260–272. doi:10.1016/S0140-6736(13)60687-X
2. Kassebaum NJ, Arora M, Barber RM, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1603–1658. doi:10.1016/S0140-6736(16)31460-X
3. Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. *BMC Nephrol*. 2018;19(1):125. doi:10.1186/s12882-018-0930-5
4. Dessein PH, Hsu HC, Tsang L, et al. Kidney function, endothelial activation and atherosclerosis in black and white Africans with rheumatoid arthritis. *PLoS One*. 2015;10(3):e0121693. doi:10.1371/journal.pone.0121693
5. Kaze AD, Schutte AE, Erqou S, Kengne AP, Echouffo-Tcheugui JB. Prevalence of hypertension in older people in Africa: a systematic review and meta-analysis. *J Hypertens*. 2017;35(7):1345–1352. doi:10.1097/HJH.0000000000001345
6. Werfalli M, Engel ME, Musekiwa A, Kengne AP, Levitt NS. The prevalence of type 2 diabetes among older people in Africa: a systematic review. *Lancet Diabetes Endocrinol*. 2016;4(1):72–84. doi:10.1016/S2213-8587(15)00363-0
7. Øvrehus MA, Oldereid TS, Dadfar A, et al. Clinical phenotypes and long-term prognosis in white patients with biopsy-verified hypertensive nephrosclerosis. *Kidney Int Rep*. 2020;5(3):339–347. doi:10.1016/j.ekir.2019.12.010
8. Correa-Rotter R, Méndez Durán A, Vallejos A, et al. Unmet Needs of CKD in Latin America: a review from expert virtual working group. *Kidney Int Rep*. 2023;8(5):954–967. doi:10.1016/j.ekir.2023.02.1082
9. Liyanage T, Toyama T, Hockham C, et al. Prevalence of chronic kidney disease in Asia: a systematic review and analysis. *BMJ Glob Health*. 2022;7(1):e007525. doi:10.1136/bmjgh-2021-007525
10. Spence JD, Rayner BL. Hypertension in blacks: individualized therapy based on renin/aldosterone phenotyping. *Hypertension*. 2018;72(2):263–269. doi:10.1161/HYPERTENSIONAHA.118.11064
11. Ugwu CLJ, Ncayiyana JR. Spatial disparities of HIV prevalence in South Africa. Do sociodemographic, behavioral, and biological factors explain this spatial variability? *Front Public Health*. 2022;10. doi:10.3389/fpubh.2022.994277
12. Naicker S, Rahmania S, Kopp JB. HIV and chronic kidney disease. *Clin Nephrol*. 2015;83(Suppl 1):S32–S38. doi:10.5414/CNP83S032
13. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation*. 2021;143(11):1157–1172. doi:10.1161/CIRCULATIONAHA.120.050686
14. Feinstein MJ. HIV, subclinical cardiovascular disease, and clinical progression: insights from immunologic heterogeneity. *JAMA*. 2022;328(10):931–932. doi:10.1001/jama.2022.15226
15. Ameer OZ. Hypertension in chronic kidney disease: what lies behind the scene. *Front Pharmacol*. 2022;13. doi:10.3389/fphar.2022.949260
16. Burnier M, Damianaki A. Hypertension as cardiovascular risk factor in chronic kidney disease. *Circu Res*. 2023;132(8):1050–1063. doi:10.1161/CIRCRESAHA.122.321762
17. Magriço R, Bigotte Vieira M, Viegas Dias C, Leitão L, Neves JS. BP reduction, kidney function decline, and cardiovascular events in patients without CKD. *Clin J Am Soc Nephrol*. 2018;13(1):73–80. doi:10.2215/CJN.05510517
18. Briet M, Boutouyrie P, Laurent S, London GM. Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int*. 2012;82(4):388–400. doi:10.1038/ki.2012.131
19. Maeda T, Yokota S, Nishi T, et al. Association between pulse pressure and progression of chronic kidney disease. *Sci Rep*. 2021;11(1):23275. doi:10.1038/s41598-021-02809-8
20. Raina R, Polaconda S, Nair N, et al. Association of pulse pressure, pulse pressure index, and ambulatory arterial stiffness index with kidney function in a cross-sectional pediatric chronic kidney disease cohort from the CKiD study. *J Clin Hypertens*. 2020;22(6):1059–1069. doi:10.1111/jch.13905
21. Safar ME, Asmar R, Benetos A, et al. Interaction Between Hypertension and Arterial Stiffness. *Hypertension*. 2018;72(4):796–805. doi:10.1161/HYPERTENSIONAHA.118.11212
22. Mitchell GF, Rong J, Larson MG, et al. Longitudinal hemodynamic correlates of and sex differences in the evolution of blood pressure across the adult lifespan: the Framingham heart study. *J Am Heart Assoc*. 2023;12(12):e027329. doi:10.1161/JAHA.122.027329
23. Mitchell GF, Lacourcière Y, Ouellet JP, et al. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation*. 2003;108(13):1592–1598. doi:10.1161/01.CIR.0000093435.04334.1F

24. Hsu HC, Norton GR, Robinson C, Woodiwiss AJ, Dessein PH. Potential determinants of the E/e' ratio in non-dialysis compared with dialysis patients. *Nephrology*. 2021;26(12):988–998. doi:10.1111/nep.13948
25. Pickup L, Radhakrishnan A, Townend JN, Ferro CJ. Arterial stiffness in chronic kidney disease: a modifiable cardiovascular risk factor? *Curr Opin Nephrol Hypertens*. 2019;28(6):527–536. doi:10.1097/MNH.0000000000000535
26. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2021;99(3S):S1–S87. doi:10.1016/j.kint.2020.11.003
27. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825–830. doi:10.7326/0003-4819-158-11-201306040-00007
28. Solomon A, Christian BF, Woodiwiss AJ, Norton GR, Dessein PH. Burden of depressive symptoms in South African public healthcare patients with established rheumatoid arthritis: a case-control study. *Clin Exp Rheumatol*. 2011;29(3):506–512.
29. Klug E. South African Heart Association (S A Heart), Lipid and Atherosclerosis Society of Southern Africa (LASSA). South African dyslipidaemia guideline consensus statement. *S Afr Med J*. 2012;102(3 Pt 2):178–187. doi:10.7196/samj.5502
30. Hsu HC, Robinson C, Norton GR, Woodiwiss AJ, Dessein PH. The optimal haemoglobin target in dialysis patients may be determined by its contrasting effects on arterial stiffness and pressure pulsatility. *Int J Nephrol Renovasc Dis*. 2020;13:385–395. doi:10.2147/IJNRD.S285168
31. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612. doi:10.7326/0003-4819-150-9-200905050-00006
32. Cox RH. Pressure dependence of the mechanical properties of arteries in vivo. *Am J Physiol*. 1975;229(5):1371–1375. doi:10.1152/ajplegacy.1975.229.5.1371
33. Avolio A. Arterial Stiffness. *Pulse*. 2013;1(1):14–28. doi:10.1159/000348620
34. DeMers D, Wachs D. Physiology, mean arterial pressure. In: *StatPearls*. StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK538226/. Accessed January 7, 2024.
35. Mitchell GF. Arterial stiffness and hypertension: chicken or egg? *Hypertension*. 2014;64(2):210–214. doi:10.1161/HYPERTENSIONAHA.114.03449
36. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation*. 1998;97(14):1411–1420. doi:10.1161/01.cir.97.14.1411
37. Abraham HMA, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. *Drug Saf*. 2015;38(1):33–54. doi:10.1007/s40264-014-0239-7
38. Schiffrin EL. Circulatory therapeutics: use of antihypertensive agents and their effects on the vasculature. *J Cell & Mol Med*. 2010. doi:10.1111/j.1582-4934.2010.01056.x
39. Rapoport RM, Soleimani M. Mechanism of thiazide diuretic arterial pressure reduction: the search continues. *Front Pharmacol*. 2019;10:815. doi:10.3389/fphar.2019.00815
40. Adam CA, Anghel R, Marcu DTM, Mitu O, Roca M, Mitu F. Impact of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibitors on Arterial Stiffness and Vascular Aging—What Do We Know So Far? (A Narrative Review). *Life*. 2022;12(6):803. doi:10.3390/life12060803
41. Naseri MW, Esmat HA, Bahee MD. Prevalence of hypertension in Type-2 diabetes mellitus. *Ann Med Surg*. 2022;78:103758. doi:10.1016/j.amsu.2022.103758
42. Naha S, Gardner MJ, Khangura D, Kurukulasuriya LR, Sowers JR. Hypertension in Diabetes. In: Feingold KR, Anawalt B, Blackman MR, et al. editors. *Endotext*. MDText.com, Inc.; 2000. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279027/. Accessed January 7, 2024.
43. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001;37(4):1053–1059. doi:10.1161/01.hyp.37.4.1053
44. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16(4):223–237. doi:10.1038/s41581-019-0244-2
45. SPRINT Research Group. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2021;384(20):1921–1930. doi:10.1056/NEJMoa1901281
46. Georgianos PI, Agarwal R. Resistant hypertension in Chronic Kidney Disease (CKD): prevalence, treatment particularities, and research Agenda. *Curr Hypertens Rep*. 2020;22(10):84. doi:10.1007/s11906-020-01081-x
47. Yuan J, Zou XR, Han SP, et al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). *BMC Nephrol*. 2017;18(1):23. doi:10.1186/s12882-017-0441-9
48. Fabian J, Gondwe M, Mayindi N, et al. Chronic kidney disease (CKD) and associated risk in rural South Africa: a population-based cohort study. *Wellcome Open Res*. 2022;7:236. doi:10.12688/wellcomeopenres.18016.2
49. Poggio ED, McClelland RL, Blank KN, et al. Systematic review and meta-analysis of native kidney biopsy complications. *Clin J Am Soc Nephrol*. 2020;15(11):1595–1602. doi:10.2215/CJN.04710420

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