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COLLEGE OF MEDICINE & HEALTH SCIENCES

SCHOOL OF MEDICINE & PHARMACY

A prospective cohort study in a Rwandan referral hospital of the incidence of rapid GFR decline and its risk factors in patients with hypertension.

Submitted in partial fulfillment of the requirements for the award of the Degree of Master of Medicine in Internal Medicine, University of Rwanda.

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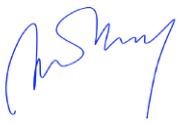
Declaration

I hereby declare that the work titled *"A prospective cohort study in a Rwandan referral hospital of the incidence of rapid GFR decline and its risk factors in patients with hypertension."* is my original work. I have not copied from any other colleagues' work or from any other sources except where due reference or acknowledgement is made explicitly in the text, nor has another person written any part of this work on my behalf.

April 4, 2019



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Dedication

To Aya and Mumu, in you I found the meaning of unconditional love.

To Lily, Didy and Prince, you are more than family to me; you are true friends.

To mum and dad, thank you for inspiring me to be the best version of myself, and for having your heart in the right place.

Abstract

Introduction: Hypertension, behind diabetes mellitus, is second most common cause of ESRD. It is estimated that one-third of Rwandans between the age 55 and 64 years have hypertension. In a country where access to renal replacement therapy is very limited, understanding the role of traditional risk factors for rapid GFR decline, and other modifiable factors related to access to medications and adherence to treatment may help prevent loss of kidney function among hypertensive patients.

Methods: We enrolled 137 outpatients – having hypertension as sole diagnosis – followed-up at Centre Universitaire Hospitalier de Kigali. Measurements at Month 0: demographics, BMI, socioeconomic status, level of education, baseline BP, baseline creatinine (baseline GFR calculated using CKD-EPI equation), proteinuria, HbA1c, BP control over 12 months, questionnaire administration for adherence to treatment and access to medications. Month 12: GFR. The primary outcome was the incidence of rapid GFR decline – defined as a decline of >= 4ml/min/1.73m^{2}over one year. Secondary outcomes were traditional factors associated with rapid GFR decline; and exploratory outcomes were measures of adherence to treatment and access to medications and their association with rapid GFR decline. We used binary logistic regression (univariate and multivariate analysis) to identify independent factors.

Results:24 participants were lost to follow-up. The mean age was 56 years and the median age was 58 years; women made the majority (65%) of the study population; 56% were either overweight or obese; 83.7% had at least finished primary school; and two-third were in the middle socioeconomic status category. The incidence of rapid GFR decline was 28.1%; 18.5% of participants with rapid GFR decline progressed to incident CKD. Fourteen participants (10.8%) were newly diagnosed with diabetes mellitus and 18 participants (13.3%) were found to have proteinuria. We found that 43% of the study population had no full access to medications; 63% had good adherence; and 52% had uncontrolled blood pressure. The association between rapid GFR decline and age, socioeconomic status, baseline GFR or access to medications was statistically significant in univariate analysis, however, in multivariate analysis, there was no statistically significant association.

Limitations: Short duration of follow-up and low statistical power. Measurements of creatinine are influenced by a number of factors.

Conclusion and recommendations: We found a high incidence of rapid GFR decline; more studies with larger sample size and longer follow-up periods are needed to understand the problem. We emphasize the need for regular routine screening of diabetes and proteinuria among hypertensive patients. In-depth analysis of root causes of shortage of antihypertensive medications is recommended.

List of abbreviations

BMI: Body Mass Index

BP: Blood Pressure

BSA: Body Surface Area

CHUK: Centre Universitaire Hospitaliere de Kigali/Kigali University Teaching Hospital

CKD: Chronic Kidney Disease

DBP: diastolic blood pressure

DM: Diabetes Mellitus

EDTA: Ethylene diamine tetra acetic acid

GFR: Glomerular Filtration Rate

HBA1C: Glycated Hemoglobin

IRB: Institutional Review Board

KDIGO: Kidney Disease: Improving Global Outcomes

KDOQI: Kidney Disease Outcomes Quality Initiative

LVEDD: Ventricle End Diastolic Diameter

OPD: Outpatients department

OR: Odds Ratio

PI: Principal Investigator

SBP: Systolic Blood Pressure

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1 Introduction

Starting in their early 30s, healthy individuals on average lose their kidney function —estimated by the decline of the glomerular filtration rate (GFR) — at a rate of 1ml/min/1.73m^2 per year.[1]The Kidney Disease Outcomes Quality Initiative (KDOQI) defines rapid GFR decline as a decline of more than 4ml/min/1.73m2 per year.[2] Rapid GFR decline leads to end-stage renal disease (ESRD) at young age. Losing the kidney function at young age results in loss of productivity, increased health expenditure, poor quality of life, and ultimately, sometimes preventable, deaths.

The problem of ESRD presents a different and difficult challenge in Rwanda. Renal transplant cannot be offered and only four tertiary level hospitals, with a dozen of hemodialysis machines, take care of patients from all over the country. For lack of better alternative, patients on the community-based insurance scheme, who make the majority of patients, can only receive a limited number of hemodialysis sessions.

Hypertension is prevalent in Rwanda and poses a public health concern. It is estimated that 9.5% of Rwandans above the age of 15 years and 33.2% of those between the age of 55 and 64 years have hypertension.[3]Hypertension, behind diabetes mellitus, is second most common cause of ESRD.[4]It is important to pay even more attention to the progression of hypertensive renal disease in the black population, because in this group the onset of hypertension is earlier and is associated with faster GFR decline.[5]

Control of hypertension is the cornerstone of preserving renal function in patients with hypertension as progression of hypertensive renal disease may be clinically silent. The eighth joint national committee (JNC-8) recommendation, concerning the general population, is to initiate anti-hypertensive treatment if systolic blood pressure (SBP) ≥150 mmHg and ≥140 mmHg for patients above the age of 60 years and below the age of 60 years respectively.[6]

Hypertension is difficult to manage. Short appointments limit outpatient management, difficult adherence to treatment, and poor health literacy. Patients rarely check their blood pressures at

home, and there is much literature to support that infrequent office-based measurements are unreliable.[7,5,6]Home-based blood pressure measurement is recommended to monitor blood pressure control.[8]From anecdotal observations, in the outpatient department (OPD), the assessment of kidney function by GFR and proteinuria is not routinely done and/or not documented. Despite the scale of the problem, interventions to address it often lag behind.

In addition to poor hypertension control, there are other risk factors for rapid GFR decline. Baseline glomerular filtration rate (GFR) and proteinuria have been found to be important risk factors for rapid GFR decline.[9,10] The quantification of proteinuria is cheap, rapid, and can be a reliable marker of renal damage.[11–13] Urine dipstick can be used to rule out proteinuria of >30mg/day with a negative predictive value of 96%. A cutoff dipstick proteinuria value of 3+ has the best combination of sensitivity and specificity (96% and 87%, respectively) in predicting a protein-creatinine ratio of 1g/g (equivalent to 1g/day) or greater.[14–16]Other factors found to be associated with rapid GFR decline are: age, income, blood pressure(BP), SBP slope, diabetes mellitus (DM), and level of education.[9,10,17]

We suspect that, in addition to factors found in other studies, unavailability of antihypertensive medications in the hospital, unaffordability of the medications in private pharmacies, and non-adherence to treatment are risk factors for rapid GFR decline.

Knowing the incidence of rapid GFR decline and factors associated with it may help in having targeted screening of patients at risk, providing adequate education, treatment and follow up, hence prevent progression to CKD and ESRD. In addition to better direct patients care, the new knowledge may help healthcare administrators plan better in terms of availing and allocating resources (i.e. human resources, laboratory tests, and medications). We undertook the present study to determine the incidence of rapid GFR decline and identify its risk factors among hypertension patients in our setting.

2 Objectives of the study

2.1 Research Questions:

1. Among hypertensive patients followed-up at a single referral hospital in Rwanda, what is the incidence of rapid GFR decline?

2. Among hypertensive patients followed-up at a single referral hospital in Rwanda, what are the risk factors associated with rapid GFR decline?

2.2 Hypothesis

We hypothesized that in Rwanda, although similar risk factors for rapid GFR decline are operating here as elsewhere, the additional challenges of access to medications and adherence to treatment would be significantly associated with rapid GFR decline and would also lead to a greater proportion of patients with HTN experiencing a rapid GFR decline.

2.3 Primary Outcome

Incidence of rapid GFR decline among hypertensive patients followed at a referral hospital in Rwanda.

2.4 Secondary Outcomes

Association of traditional risk factors, such as, baseline GFR, baseline proteinuria and BP control, with rapid GFR decline among hypertensive patients followed-up at a referral hospital in Rwanda; defined by univariate and multivariate analysis.

2.5 Exploratory Outcomes

Association of measures of access and adherence to anti-hypertensive medications with rapid GFR decline.

3 Methods

3.1 Ethical consideration

We obtained ethical clearance from the University of Rwanda – College of Medicine and Health Sciences' Institutional Review Board (IRB); we also obtained ethical clearance from Centre Hospitalier Universitaire de Kigali(CHUK) ethical committee. All participants were informed about the study procedures and gave written informed consent prior to enrollment.

3.2 Study design

This is a prospective cohort study with a follow-up of 12 months. The primary outcome is the incidence of rapid GFR decline. The secondary outcome is factors associated with rapid GFR decline. Studied factors are baseline GFR, baseline proteinuria, baseline BP, BP over 12 months, age, sex, BMI, level of education, and socio-economic status. The exploratory outcome is the association of measures of access and adherence to anti-hypertensive medications. We administered a questionnaire to measure self-reported access and adherence to anti-hypertensive medications.

3.3 Study population

We used convenience-sampling method to enroll participants over the period of 3 months. They were outpatients followed-up at CHUK's OPD for hypertension as sole diagnosis. The inclusion criteria were:

- Being 18 years of age and above
- Having a documented diagnosis of hypertension

- Willing to keep consulting CHUK's OPD for at least one year
- Signing the informed consent

Exclusion criteria were:

- Having documented diagnosis of secondary hypertension
- Having documented diagnosis of CKD
- Being diagnosed with Diabetes Mellitus (HbA1c >6.5% –measured at the beginning of the study).
- Having conditions known to be associated with CKD (Example: heart failure, chronic liver disease, etc.)

Sample size estimation

Assuming the proportion (p*) of patients with rapid GFR decline among hypertension patients to be 10%, we used Kish's approximate formula to calculate the sample size (n) for a 95% confidence and a margin of error (E) of 0.05. Z score for a 95% confidence = 1.96

$n=p^* (1-p^*) (Z/E)^2$ $n=0.05(1-0.05) (1.96/0.05)^2= 138$

Our target was to enroll 167 participants over a three-month period to account for an estimated 20% potential loss to follow-up.

3.4 Definition of variables and outcomes

3.4.1 Age and sex

We subdivided our study population into two groups: elderly (60 years and older) and young (younger than 60 years). Hypertension studies which serve as basis for the Joint National Committee (JNC) formulation of the Evidence-based Guideline for the Management of Hypertension in Adults, uses the age 60 years as a cut-off between young and elderly population.[18] The second variable is sex (male vs. female).

3.4.2 Body Mass Index

The BMI was calculated using the formula: BMI = weight (in kg)/height (in m)^2. We measured the weight and height during the first visit using a mechanical weighing scale. We used an Up-to-date online calculator to get BMI values. We grouped participants into three groups: underweight (below 18), normal (18 to 24.99), overweight (25 to 29.99), and obese (30 and above).

3.4.3 Level of education

We recorded participants' self-reported level of education. We asked participants to choose what among four options –no formal education, primary education, secondary education and tertiary education– is the level of education they completed.

3.4.4 Socio-economic status

We used the local governments' Ubudehe categories (1 through 4) as a measure of participants' socioeconomic statuses. We access the information on Ubudehe category from the hospital's electronic medical record. Participants in Ubudehe category 1 were classified in the "low" socioeconomic category; those in Ubudehe category 2 were classified in the "low-middle" category; same for "high-middle" and "high" categories.

3.4.5 Access to medications

We asked participants to answer by yes or no if over the previous 7 days, they missed at least one dose of antihypertensive medication (1) because they could not find the medication(s) in the hospital's pharmacy; and (2) because the medications were too expensive in pharmacies outside the hospital. In case "yes" was the answer to both sub-questions, the participant was considered as not having full access to medications; otherwise, the participant was considered as having full access to medications.

3.4.6 Adherence to treatment

We studied adherence to antihypertensive medications using "Extent of non-adherence" validated tool.[19] It is a self-report measure of non-adherence comprised of three Likert scale items. Participants are asked to rank statements from "strongly disagree" to "strongly agree" regarding how often they took or missed their doses over the past 7 days. A total score reflecting non-adherence is calculated by averaging responses to items 1 (reverse-scored), 2, and 3. For the sake of simpler presentation of results in terms of "poor", "moderate" and "good" adherence, we presented results on a scale of 12 instead of 5. For item 1, which is reverse-scored, the contribution is 5 minus the scale position; for positive items (2 and 3) the score contribution is the scale position minus 1. The maximum score is 12 and represents the highest extent of non-adherence. The minimum score is 0 and represents the lowest extent of non-adherence. We categorized the extent of non-adherence into three groups: low (0 to 4), moderate (5 to 8) and high (9 to 12). To avoid double negatives, instead of reporting "low extent of non-adherence" we reported "good adherence"; "moderate adherence" instead of "moderate extent of non-adherence"; and "poor adherence" instead of "high extent of non-adherence." A professional translator translated the questionnaire to Kinyarwanda.

3.4.7 Blood pressure control

We took monthly, automated office blood pressures (AOBP) for 12 consecutive months using a validated electronic equipment. Though manual sphygmomanometer were recommended in the past, current guidelines recommend AOBP instead of auscultation method.[20,21] All blood pressure measurements were taken in nursing station; participants were in seated position, forearm lying on the table. Participants sat in the waiting room for at least 30 minutes before having their measurements taken. We took both right and left arm blood pressures, but for analysis, we used the right arm measurements. We considered baseline blood pressure as normal if SBP was below 140 mmHg and DBP below 90 mmHg for participants younger than 60 years. For participants aged 60 years and older, Blood pressure was considered normal if SBP was below 150 mmHg and DBP below 90 mmHg. Values of 140 mmHg and 150 mmHg and above were considered elevated for participants younger than 60 years and 60 years of age and older respectively. Blood pressure

over 12 months was considered poorly controlled for participants who had three or more BP measurements above 140 mmHg for participants younger than 60 years and 150 mmHg for participants aged 60 years and older.

3.4.8 Diabetes mellitus

A registered nurse (research assistant) collected blood samples in Etylenediaminetetraacetic acid (EDTA) tubes (purple top), put on mixer and analyzed within 2 hours. Patients with a glycated hemoglobin (HbA1c) of 6.5% or above were considered as having diabetes mellitus. As per protocol, for the sake of minimizing confounders, having diabetes mellitus was an exclusion criterion. Hence, we excluded diabetic participants' data from analysis looking at factors associated with GFR decline among patients having hypertension.

3.4.9 Rapid GFR decline

In accordance with KDOQI, rapid GFR decline was defined as drop of more than 4 ml/min/1.73m^2 or more from the baseline over 12 months. As recommended by KDIGO Clinical Practice Guidelines, we calculated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$eGFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993Age * 1.018 \text{ [if female]} * 1.159 \text{ [if black]}.$$

Scr is serum creatinine (mg/dL),
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr/κ or 1
max indicates the maximum of Scr/κ or 1.

We used an online calculator to get GFR values from UpToDate website.[22]

For creatinine measurement, the registered nurse collected blood samples in dry tubes (red top), centrifugation was done within 3 hours of collection. In cases where sera samples were not

analyzed immediately after centrifugation, they were stored under 2 – 8 degrees Celcius, to be analyzed within 7 days.

Baseline GFR was calculated at the beginning of the study; we collected a second set of blood samples for GFR at the 12th month of follow-up. We classified GFR into 5 categories, Category 1: >= 90 ml/min, Category 2: 60ml/min – 89.99 ml/min, Category 3: 30ml/min – 59.99 ml/min, Category 4: 15ml/min – 29.99 ml/min, Category 5: <15ml/min.

3.4.10 Proteinuria

We collected and analyzed urine samples in the OPD clinic. We used "Urine-3" strips made by Cypress Diagnostics. We analyzed urine samples within 5 minutes of collection, reading results exactly 60 seconds after dipping. We classified results into two groups: no proteinuria and positive proteinuria.

3.5 Follow-up

The registered nurse who works in the Internal Medicine OPD kept a list of all participants and identified them as they come for regular monthly follow-up. For the sake of minimizing loss to follow-up, we made a copy of a follow-up card for each participant –one copy for the participant and another for the investigator. The information on the follow-up card was OPD file archive code, two telephone numbers of the participant, names and telephone number of the principal investigator (PI). In case a participant missed a follow-up visit, we called him/her and tried to reschedule an appointment on the closest date possible.

3.6 Data security

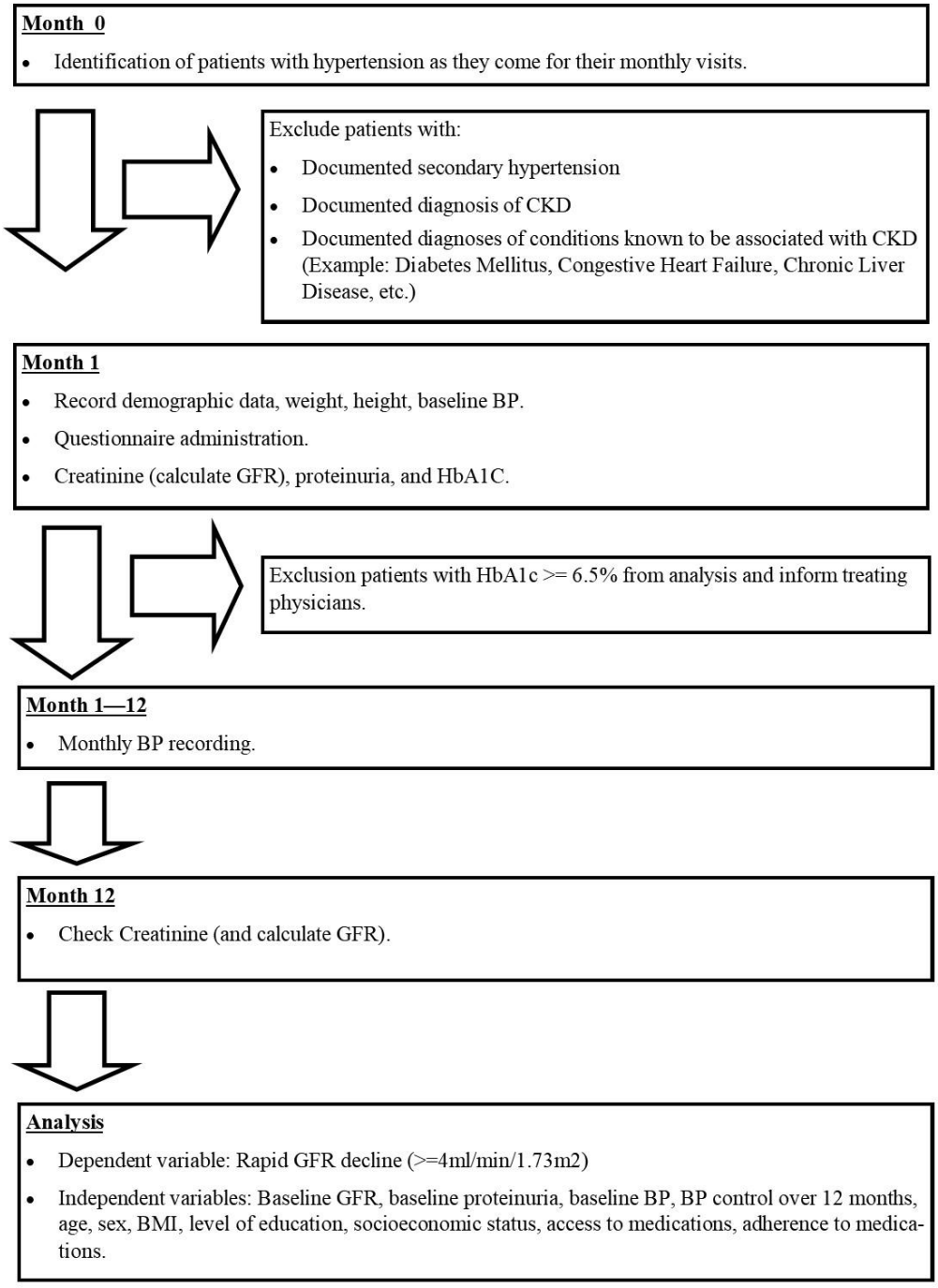
The PI created a dataset password and each enrolled participant had a unique identifier for recording the data. The data was therefore de-identified and stored electronically in password-protected files on a password-protected computer. The PI was responsible for overseeing data management.

All paper-based data was stored in locked cabinets under the co-investigator's custody. The PI will ensure that all paper-based data collection tools are shredded and disposed of appropriately as soon as the study is completed. Only de-identified data untraceable to participants will be retained after the study completion.

3.7 Statistical analysis

We analyzed the data using IBM SPSS Statistics' version 23. In descriptive statistics, we reported continuous data as means with standard deviations and categorical data as frequencies (percentages). We used binary logistic regression; the dependent variable was rapid GFR decline with two possible values (No=0, Yes=1). First, we used univariate logistic regression analyses to identify variables associated to rapid GFR decline, and then we used multivariable logistic regression analysis to identify independent variables associated to rapid GFR decline. Results were presented as odds ratios (OR) with their p values –OR in univariate analysis and adjusted OR in multivariate analysis. Though odds ratios are often used in case-control studies, they can be used in prospective cohort studies as well; we only have to be aware of not overestimating the effect size by mistakenly considering them as risk ratios.[23] Variables with a p value <0.10 in the univariate logistic regression analyses were included in the multivariable logistic regression analysis; and a $p<0.05$ was considered statistically significant.

Figure 1: Study Design



4 Results

4.1 Baseline characteristics

4.1.1 Age, sex and BMI

Over the period of 3 months, we enrolled 137 participants to the study. The age distribution of the study population was normal. The mean age was 56.79 years, the standard deviation being 12.68, and the median 58 years. Participants were evenly distributed between the two age groups; 73 (53.3%) were young and 64 (46.7%) were elderly. The proportion of women was almost double that of men –89 (65%) women vs. 48 (35%) men. Most participants were either overweight or obese, 64 participants, making 49.6% of the study population; 43 were overweight and 21 were obese. Participants with normal BMI were 58 (44.6%) and 8 participants were underweight, making the smallest proportion (5.8%) of the study population.

4.1.2 Level of education and socioeconomic status

The vast majority of the study population had completed primary education, the count being 65 (48.1%). 39 (28.9%) participants had completed secondary education; nine (6.7%) had completed tertiary education; and 22 (16.3%) had no formal education. Two-third of participants were classified in the middle socioeconomic categories, 72 being in the high-middle category and 29 in the low-middle category. Participants in the low socioeconomic category were 22 (16.3%), and those in the high socioeconomic category were only 11 (8%).

4.1.3 Blood pressure control

We found that blood pressure control was a major issue. More than a half of baseline blood pressure measurements were above the recommended limits, 71 (51.8%) high vs 66 (48.2%) normal. Regarding monthly blood pressure measurements over 12 months, 44 (37.9%) were classified as well controlled and 72 (62.1%) as poorly controlled.

4.1.4 Laboratory results

Among the 130 participants whose HbA1c was done, 14 (10.8%) were newly diagnosed with diabetes mellitus. Four out of five participants had their baseline GFR classified as either normal (Category 1) or mildly decreased (Category 2). Participants classified as Category 3 were 28 (20.6%). No one was classified as Category 4 or 5. Proteinuria was positive in 18 (13.3%) participants and negative in 117 participants (86.7%).

4.1.5 Access and adherence to medications

We found that access to medications was problematic. The number of participants without full access to medications was as high as 59 making 43.1% of the study population. They reported missing at least one dose, in the previous week, due to lack of medications in the hospital's pharmacy, and medications being too expensive outside the hospital. Among those who did not find medications in the hospital's pharmacy, only 8 (12%) reported being able to afford medications in pharmacies outside the hospital. The majority (63.5%) of the study population had good adherence to treatment; one-third of participants had either moderate or poor adherence, the proportion of those having poor adherence being the smallest (13.1%).

Table 1: Baseline characteristics

		Number (%)
Age	Young	73 (53.3%)
	Elderly	64 (46.7%)
Sex	Female	89 (65%)
	Male	48 (35%)
BMI	Underweight	8 (5.8%)
	Normal	58 (44.6%)
	Overweight	43 (33.1%)
	Obese	21 (16.2%)
Level of education	No formal education	22 (16.3%)
	Primary	65 (48.1%)
	Secondary	39 (28.9%)
	University	9 (6.7%)
Socioeconomic status	Low	25 (18.2%)
	Middle-low	29 (21.2%)
	Middle-high	72 (52.6%)
	High	11 (8%)
Baseline BP	Normal	66 (48.2%)
	High	71 (51.8%)
BP control over 12 months	Controlled	44 (37.9%)
	Poorly controlled	72 (62.1%)
Diabetus mellitus	No	116 (89.2%)
	Yes	14 (10.8%)
Baseline GFR	Category 1	38 (27.9%)
	Category 2	70 (51.5%)
	Category 3	28 (20.6%)
Proteinuria	Negative	117 (86.7%)
	Positive	18 (13.3%)
Access to medications	Access	78 (56.9%)
	No access	59 (43.1%)
Adherence to treatment	Good	87 (63.5%)
	Moderate	32 (23.4%)
	Poor	18 (13.1%)

Age: young (60 yrs), old (>= 60 yrs). BMI: underweight (below 18), normal (18 to 24.99), overweight (25 to 29.99), obese (30 or above). Education level: highest level of schooling completed. Socioeconomic status:low(ubudehe 1), low-middle(ubudehe 2), high-middle(ubudehe 3), high(ubudehe 4). Baseline BP: high (above 140/90 if younger than 60 or above 150/90 if aged

60 years and above). BP control over 12 months: poorly controlled (3 or more times having BP above 140/90 if younger than 60 or above 150/90 if aged 60 years and above). Diabetes mellitus: HbA1C above 6.5%. Baseline GFR. Category 1: >= 90 ml/min, Category 2: 60ml/min – 89.99 ml/min, Category 3: 30ml/min – 59.99 ml/min. Proteinuria: positive: positive on urine dipstick. Access to medications: access (participant did NOT miss a dose of anti-hypertensive medication(s), over the previous 7 days, due to lack of medications in the hospital's pharmacy or medications being too expensive in pharmacies outside the hospital). No access (participant missed at least one dose, over the previous 7 days, due to lack of medications in the hospital's pharmacy and medications being too expensive in pharmacies outside the hospital). Adherence to treatment: Scores on Extent of Non-adherence tool (0-4: good adherence, 5-8: moderate adherence, 9-12: poor adherence).

4.2 Incidence of rapid GFR decline

Among 137 participants we had at the beginning of the study, 24 (20 non-diabetics, 3 newly diagnosed with diabetes and 1 for whom HbA1C was not done), making 17.5% of the study population, were lost to follow-up. We remained with 113 participants at the end of the study. For analysis of factors of rapid GFR, we excluded 17 participants (11 newly diagnosed with diabetes and 6 for whom HbA1c was not done). The incidence of rapid GFR decline was 28.1% (27 out of 96). Further analysis showed that among participants with rapid GFR decline, 18.5% (5 out of 27) progressed to CKD (GFR below 60 ml/min/1.73m^2), while 4.3% (3 out of 69) of those without rapid GFR decline progressed to CKD.

4.3 Factors associated with rapid GFR decline

4.3.1 Univariate analysis

In the univariate analysis, age, socioeconomic status, access to medications and baseline GFR were identified as variables to be included in the multivariate analysis ($p<0.10$). Findings for sex, BMI, level of education, adherence to treatment, BP control, and proteinuria were not statistically significant.

Age

Elderly participants were less likely to have rapid GFR decline compared to young participants. The odds for rapid GFR decline were 62% lower (OR=0.38, CI 90%, 0.17 to 0.85, p=0.05) in the elderly group compared to the young group.

Socioeconomic status

Participants in the high socioeconomic status category were more likely to have rapid GFR decline compared to those in the low socioeconomic status category; the odds were 5 times higher (OR=5.41, CI 90%, 1.1 to 26). Participants in low-middle and middle-high categories were less likely to have rapid GFR decline compared to the low socioeconomic status group; the odds were 68% lower (OR=0.32, CI 90%, 0.1 to 1.2) in the middle-low group and 18% lower (OR=0.82, CI 90%, 0.3 to 2.1) in the middle-high group. The p value for the socioeconomic status variable was 0.06.

Access to medications

The odds for rapid GFR decline were double in the group without access to medications compared to that with access to medications (OR=2.26, CI 90%, 1.06 to 4.8, p=0.07).

Baseline GFR

The odd for rapid GFR decline in the group with normal GFR (Category 1) was higher than that of Category 2 and Category 3. The odds for rapid GFR decline in Category 2 were decreased by 54% (OR=0.46, CI 90%, 0.29to 0.89, p=0.024) compared to GFR category 1, and the odds for rapid GFR decline in Category 3 group were decreased by 84% (OR=0.16, CI 90%, 0.07 to 0.674, p=0.037). The p value for the baseline GFR variable was 0.023.

Other variables

Sex

The odds for rapid GFR decline were 50% higher (OR = 1.5, 0.68 to 3.1, p=0.41) in male participants compared to female participants.

BMI

Compared to the underweight group, the odds for rapid GFR decline in the overweight group were 17% higher; they were 45% lower in the normal BMI group; and 78% lower in the obese group. The p value for the BMI variable was 0.18.

Level of education

The higher the level of education, the lower the odds for rapid GFR decline were. Compared to the no formal education group, the odds were 69% lower and 17% lower in the secondary education group and university education categories respectively. The odds for the primary education group were slightly higher (10%). The p value for the level of education variable was 0.92.

Adherence to treatment

Participants with poor and moderate adherence to treatment were more likely to have rapid GFR decline. The odds for poor adherence were 53% higher and 82% higher in the moderate adherence group compared to the good adherence group. The p value for the adherence to treatment variable was 0.47.

Baseline blood pressure

The odds for rapid GFR decline for the high baseline blood pressure group were double that of the low baseline blood pressure group, 54% vs. 26.3%. The p value for the baseline blood pressure variable was 0.11.

Blood pressure control over 12 months

The odds for rapid GFR decline in the group with poorly controlled blood pressure over 12 months were 21% higher compared to the group with controlled blood pressure; the p value was 0.71.

Proteinuria

The odds ratio of positive proteinuria was 35% lower in the positive proteinuria group compared to the negative proteinuria group; the p value was 0.42.

4.3.2 Multivariate analysis

Variables with a p value less than 0.10, in the univariate analysis, were included in the multivariate analysis to identify independent factors of rapid GFR decline ($p < 0.05$). Variables included in the multivariate analysis were age, socioeconomic status, access to medications and baseline GFR. None of the factors included in multivariate analysis was statistically significant (see table 2).

Table 2: Incidence of rapid GFR decline

			Univariate analysis (95% CI)		Multivariate analysis (95% CI)	
		Odds for rapid GFR decline (%)	Odds ratio for rapid GFR decline	p-value	Adjusted Odds ratio for rapid GFR decline	p-value
Age	Young	19/33 (57%)	1	0.05	1	0.48
	Elderly	8/36 (22%)	0.38		0.61	
Sex	Female	16/47 (34%)	1	0.41		
	Male	11/22(50%)	1.47			
BMI	Underweight	3/5 (60%)	1	0.18		
	Normal	9/27 (33%)	0.55			
	Overweight	12/17 (70%)	1.17			
	Obese	2/15 (13%)	0.22			
Level of education	No formal	4/10 (40%)	1	0.92		
	Primary	14/31 (45%)	1.1			
	Secondary	7/22 (31%)	0.31			
	University	2/6 (33%)	0.83			
Socioeconomic status	Low	6/13 (46%)	1	0.06	1	0.33
	Low-middle	3/20 (15%)	0.32		0.1	
	Low-high	13/34 (38%)	0.82		0.7	
	High	2/5 (40%)	0.87		0.5	
Baseline BP	Normal	10/38		0.11		
	High	17/31 (54%)	2.08			
BP control over 12 months	Controlled	9/27 (26%	1	0.71		
	Poorly controlled	12/38 (31%)	1.21			
Baseline GFR	G1	6/20 (30%)	1	0.02	1	0.06
	G2	6/44 (14%)	0.46		0.26	
	G3	1/19 (5%)	0.16		0.96	
Proteinuria	Negative	24/57 (42%)	1	0.42		
	Positive	3/11 (27%)	0.65			
Access to medications	Yes	11/42 (26%)	1	0.07	1	0.10
	No	16/27(59%)	2.26		2.7	
Adherence to treatment	Good	15/46 (32%)	1	0.47		
	Moderate	9/15 (60%)	1.84			
	Poor	3/6 (50%)	1.53			

Rapid GFR decline: drop of 4ml/min/1.73m^2 or more from the baseline over 12 months. Age: young (60 yrs), old (>= 60 yrs). BMI: underweight (below 18), normal (18 to 24.99), overweight (25 to 29.99), obese (30 or above). Education level: highest level of schooling completed. Socioeconomic status:low(ubudehe 1), low-middle(ubudehe 2), high-middle(ubudehe 3), high(ubudehe 4). Baseline BP: high (above 140/90 if younger than 60 or above 150/90 if aged 60 years and above). BP control over 12 months: poorly controlled (3 or more times having BP above 140/90 if younger than 60 or above 150/90 if aged 60 years and above). Diabetes mellitus: HbA1C above 6.5%. Baseline GFR. Category 1: >= 90 ml/min, Category 2: 60ml/min – 89.99 ml/min, Category 3: 30ml/min – 59.99 ml/min. Proteinuria: positive: positive on urine dipstick. Access to medications: access (participant did NOT miss a dose of anti-hypertensive medication(s), over the previous 7 days, due to lack of medications in the hospital's pharmacy or medications being too expensive in pharmacies outside the hospital). No access (participant missed at least one dose, over the previous 7 days, due to lack of medications in the hospital's pharmacy and medications being too expensive in pharmacies outside the hospital). Adherence to treatment: Scores on Extent of Non-adherence tool (0-4: good adherence, 5-8: moderate adherence, 9-12: poor adherence).

5 Discussion

In the present study, the mean age was 56 years and the median age was 58 years; females made the majority (65%) of the study population; 56% were either overweight or obese; 83.7% had at least finished primary school; and two-third were in the middle socioeconomic status category. The incidence of rapid GFR decline was 28.1%; 18.5% of participants with rapid GFR decline progressed to incident CKD. Fourteen participants (10.8%) were newly diagnosed with diabetes mellitus and 18 participants (13.3%) were found to have proteinuria. We found that 43% of the study population had no full access to medications; 63% had good adherence; and 52% had uncontrolled blood pressure. The association between rapid GFR decline and age, socioeconomic status, baseline GFR or access to medications was statistically significant in univariate analysis, however, in multivariate analysis, there was no statistically significant association.

We highlight some of the strengths of the study -- We used a guideline-based criterion to define our primary outcome; rapid GFR decline, as defined in KDOQI clinical practice guidelines, is not used only for research purposes but has clinical implications as well. As this was a prospective cohort study, it allowed us to calculate the incidence, recall bias was minimized, and allowed us to study all hypothesized risk factors. Less than 17.5% of participants were lost to follow-up, though not ideal, it does not cause serious threat to the validity of the results. We used a validated

tool to assess self-reported measure of adherence to treatment. There was no interference with practitioners' decision-making regarding treatment. We ensured the integrity of the dataset by collecting data several times per week, as participants came for monthly visits, and corrected errors soon after data entry. All laboratory samples were collected by one qualified personnel and analyzed by one laboratory, fulfilling national and international laboratory standards.

Confirming our hypothesis, the incidence of rapid GFR decline was greater than 10%. Though non-access to medications and poor adherence were proposed as factors for greater incidence, and even though patients with no access to medications and/or poor adherence were more likely to have rapid GFR decline, the association was not statistically significant in multivariate analysis. A possible explanation is that the study was powered to detect the incidence of rapid GFR but underpowered for detecting the hypothesized risk factors; a bigger sample size would give greater power. The findings, though not statistically significant, are clinically significant; non-access to anti-hypertensive medications, poor adherence and uncontrolled BP can lead to various poor health outcomes.

Among participants with rapid GFR decline, 18.5% (5 out of 27) progressed to CKD, while only 4.3% (3 out of 70) of those without rapid GFR decline progressed to CKD. This is to emphasize that, in our study population, rapid GFR is clinically relevant – patients with declining GFR will eventually end-up needing renal replacement therapy. Over 12 months, these participants moved from normal kidney function to decreased GFR (below 60 ml/min/1.73m^2). Again, with a longer follow-up duration, we can better visualize the GFR decline over many years, but still, with due reservations, we can predict that our participants will continue to lose their kidney function given the factors remain constant.

The prevalence of undiagnosed diabetes (10.8%) was remarkable. Two studies conducted in sub-Saharan countries, found that the prevalence of undiagnosed diabetes was 14.8% and 14.7% among patients with hypertension.[24,25] Even though, we found a lower prevalence of diabetes, it is still very concerning that 1 in 10 patients with hypertension have undiagnosed and understandably untreated. Our findings on proteinuria are similar to findings in sub-Saharan Africa. In a systematic

review of studies conducted in 20 sub-Saharan countries, the prevalence of proteinuria ranged between 6% and 24%.[26]

According to World Health Organization's *Stepwise approach to NCD surveillance*, the prevalence of hypertension among women in Rwanda is slightly lower than that of men.[3] Yet, we found that women made 65% of those attending the outpatient clinic for hypertension. Our findings are similar to those in two other sub-Saharan countries where the proportion of women in hypertension clinics were 76% and 78.7%.[24,25] The finding reflect the "men's health gap". Despite the fact that men have more financial and social opportunities than women do, they still have poorer health outcomes. In sub-Saharan Africa women live 5 years longer than men, the difference is even bigger in developed countries, such as Russia, where women outlive men by 11 years. One of the reasons why men have poor health outcomes is that they are less likely to see a doctor when they are sick.[27]

The study population is older than the Rwandan general population, whose proportion of elderly people, above the age of 65 years, is only 5%. Elderly people are more likely to develop non-communicable diseases including hypertension. Even though our Rwandan hypertensive population is older than the average Rwandan general population, it is still younger than the hypertensive population in the middle-income and high-income countries.[28,29]According to the World Bank, the life expectancy in Rwanda rose from 48.4 years to 67.3 years from the year 2000 to 2016.[30]With the increasing life expectancy, we can only expect to have more of non-communicable diseases including hypertension. We found that more than a half of the study population was either overweight or obese and 4 out 5 had finished primary school. On average, the general Rwandan population has limited formal education (67% finished primary school) and less overweight/obese (17.1%). Hence, our findings do not reflect the general Rwandan population, but rather the population in an urban area.[4,29]

Our study has a number of limitations. The major limitations are short follow-up duration and low statistical power. A longer period of follow-up would paint a complete picture of rapid GFR decline, and an enrolment period longer than 3 months could have allowed us to enroll more participants to gain statistical power. After publishing these preliminary results and given the

resources, we intend to continue the follow-up of the cohort for more years to see the trend of their GFR and other metrics of target organ damage due to hypertension. The outcome of GFR is not ideal; a number of factors, including muscle mass, physical activity, recent illness, etc., can influence the measurement of creatinine. To try to alleviate this, we enrolled stable OPD participants in a steady state and excluded participants with conditions known to be associated with kidney disease.

6 Conclusion and recommendations

The incidence of rapid GFR decline is high among Rwandan adult hypertensive patients followed-up in a referral hospital clinic in an urban area. The understanding of the problem is far from being complete. More studies with larger sample size and longer follow-up period are needed for better understanding of the problem. The high rates of non-access to medications and poorly controlled blood pressure is concerning, not only for poor renal outcomes, but also for other target organs damage not studied here. Moving towards full access to antihypertensive medications, in-depth analysis of the root causes of shortage of the medications is paramount. Our findings on newly diagnosed cases of diabetes mellitus and proteinuria remind us of the importance of regular screening of diabetes and proteinuria among hypertensive patients. The men's health gap is evident in our population, as it is worldwide; we need educational/awareness interventions to have more male patients consult clinics. Finally, the Rwandan population is aging, and the rate of overweight and obese persons is increasing; we can only expect the number of patients with hypertension to increase. More is required from healthcare workers, hospitals and national health authorities to understand the problem of hypertension and its complications among Rwandan population and to avail antihypertensive medications.

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8 Appendices

8.1 Informed consent

8.1.1 Kinyarwanda version

Kugira uruhari mu bushakashatsi kubushake

Nitwa MUCYO Willy. Turashaka gukora ubushakashatsi bwo kwiga ku mpamvu zitera kugabanuka kwihuse k'ubushobozi bw'impyiko bwo kuyungurura amaraso mu bantu bafite umuvuduko w'amaraso bivuriza mu bitaro bya kaminuza y'u Rwanda. Icyo ubu bushakashatsi bugamije ni ugusobanukirwa impamvu mu barwayi b'umuvuduko w'amaraso, bamwe barware impyiko mu buryo bwihuse ariko abanda ntibarware. Ibizava muri ubu bushakashatsi bishobora kuzafasha mu gukurikirana abarwayi b'umuvuduko w'amaraso neza bityo bikababuza kugira uburwayi bw'impyiko.

Turabasaba kugira uruhari muri ubu bushakashatsi. Nimuramuka mubyemeye, turabasaba gusinya mwemezako mwabyemeye kubushake bwanyu.

Ibirimo

Iyo umuvuduko w'amaraso udakurikiranywe neza ushobora gutera ingaruka mbi. Zimwe muri izo ngaruka harimo gutakaza imikorere y'impyiko. Mu Rwanda hari ubumenyi budahagije kubitera impyiko gutakaza ubushobozi bwo kuyungurura amaraso. Ububushakashatsi buzadufasha kurushaho gusobanukirwa n'igitera ubu burwayi bw'impyiko mu bafite umuvuduko w'amaraso mu Rwanda.

Ukobizakorwa

Abantu bazagira uruhari muri ububushakashatsi ni abarwayi b'umuvuduko w'amaraso bivuza bataha mu bitaro byakaminuza y'u Rwanda. Tuzababaza ibibazo bijyanye n'uburwayi bwanyu nyuma yahoo tubapime umuvuduko w'amaraso. Ikizakurikiraho ni ukubafata amaraso n'inkari tugapima imikorere y'impyiko na diyabete. Tuzakomeza gupima umuvuko w'amaraso buri kwezi kugeza amezi cumi n'abiri ashize. Nyuma y'ayomezi cumin'abiri tuzongera tubapime impyiko kugirango tugererenye ibyo bipimo n'ibya mbere.

Ingarukazishoboka

Niba mutwemereye gutanga umusanzu wanyu muri ubu bushakashatsi, amaraso tuzayafata dukoresheje urushinge, kubera urworushinge ruzakoreshwa mu gufata amaraso umuntu uzafatirwa ibizamini ashobora kuzagira ububabare budakabije aho tuzafata amaraso. Gusa ubwo bubabare bumara igihe gito kandi bushira ntamuti umuntu afashe.

Inyungu z'ububushakashatsi

Ubumenyi tuzakura muri ubu bushakashatsi bushobora kuzadufasha gukurikirana neza birushijeho abarwayi b'umuvuduko w'amaraso, namwe murimo, no gukumira ingaruka zijyanye n'uburwayi bw'impyiko buturuka k'umuvuduko w'amaraso.

Niba mwasobanukiwe neza kandi mukumva bibafitiye akamaro mwakuzuza inyandiko ikurikira kandi mukadushyiriraho n'umukono wanyu.

Mufite uburenganzira bwo kwifatira icyemezo mu gutanga umusanzu wanyu. Mufite ubushobozi bwo kuba mwahindura icyemezo cyanyu igihe icyo aricyo cyose ububushakashatsi buzaba bukorwa kandi ntangaruka bizagira kubufasha mwari musanzwe muhabwa kwa muganga.

Uwemeye kugira uruhari mu bushakashatsi.

Amazina yombi:……...……..
Itariki y'amavuko:…….…….
Umukono:……..Itariki:…….

Uwayoboye igikorwa cyo kugirana amasezerano:
Amazina yombi:……..
Umukono:……..Itariki:……..

Abashinzwe kugenzura imigendekere myiza y'ubushakashatsi mu bitaro bya kaminuza:

- Francois Xavier Sunday (secretary) 0788563311
- Prof. JB Gahutu (Vice Chairperson) 0783340040

8.1.2 English version

My name is MUCYO Willy. We are conducting a study in which we want to determine the factors associated with rapid kidney function decline among patients followed for hypertension at University of Rwanda Teaching Hospitals. The aim of our study is to try to understand why among hypertension patients some rapid loss of kidney function and others have don't. The results of our study may help prevent kidney complications in hypertension patients.

You are asked to participate in this study. In case you agree, you will sign a written informed consent form. It is completely voluntary to participate in this study.

Background

When hypertension is not well managed it can lead to serious complications. Among complications related with poor hypertension follow up there is decline of kidney function. There is lack of information on factors associated with rapid kidney function decline in Rwanda. The results of our study will contribute to the current understand of kidney function decline in hypertension patients in Rwanda.

Procedures

Study participants will be hypertension patients being followed for hypertension in outpatients' departments. We will ask you questions regarding relevant medical history and measure your blood pressure. The next step will be collecting blood and urine samples to assess your current kidney function and diabetes. We will keep measuring your blood pressure every month for twelve months. At the end of twelve months, we will measure your kidney function again to compare it to the first one.

Risks

If you accept to participate in this study the sample of blood will be taken using needle. From that needle you should have mild pain at site of puncture. But this will take some minutes and will resolve spontaneously.

Benefits

Information to be learned from this study may help in better follow up of hypertension patients, including yourself, and prevention of loss of kidney function.

If you have understood and are willing to take part in this study, then kindly sign below. You have the right to decide to participate or to withdraw at any point and this will not affect your medical care.

Participant:

Full name:……..
Date of Birth:…….
Signature:…….. Date……..

The person who conducted the informed consent discussion

Full name:…….
Signature:……..Date……

IRB contacts: Francois Xavier Sunday (secretary) 0788563311

Prof JB Gahutu (Vice Chairperson) 0783340040

8.2 Data collection sheet

Month 0.

ID	
Archive code	

Age	
Sex	☐ Female ☐ Male
Weight	
Height	
Baseline Blood Pressure	
Socio-economical status (*ubudehe* category)	☐ 1 ☐ 2 ☐ 3 ☐ 4
Education	☐ No formal education ☐ Primary ☐ Secondary ☐ Tertiary
Urine dipstick	☐ Neg☐ Trace ☐ 1+ ☐2+ ☐3+ ☐4+
Baseline creatinine	
HbA1C	

Extent of Nonadherence.

In order for blood pressure medicines to work best, people should take them according to the doctor's instructions. For one reason or another, people can't or don't always take all of their medicines as prescribed. We want to know how often you have missed your blood pressure

medicines over the past 7 days. You may be taking more than one medicine for your blood pressure. As you answer these questions, please think about all of your blood pressure medicines. Please rate your agreement with the following statements.

Over the past 7 days…

2. I took all doses of my blood pressure medication.	Strongly Disagree ○	Disagree ○	Neutral ○	Agree ○	Strongly Agree ○
3. I missed or skipped at least one dose of my blood pressure medication.	Strongly Disagree ○	Disagree ○	Neutral ○	Agree ○	Strongly Agree ○
5. I was not able to take all of my blood pressure medication.	Strongly Disagree ○	Disagree ○	Neutral ○	Agree ○	Strongly Agree ○

A total score reflectingnonadherence is calculated by averaging responses to items 1 (reverse-scored), 2, and 3.

(Extent of nonadherence) Kinyarwanda

Kugirangoimitiigabanyaumuvudukow'amarasoikoreneza, abantubagombagufataimitibakurikijeamabwirizayamuganga. Kuberaimpamvuzitandukanye, abantuntibafataimitiburigihenkukobikwiye. Turashakakumenyainshuroutashoboyegufataimiti mu minsiirindwiishize. Ushoborakubaurikumitiigabanyaumuvudukow'amarasoirenzeumwe. Ubwouribubeusubizaibibazobikurikira, utekerezeimitiyaweyoseigabanyaumuvudukow'amaraso. Usabwekugereranyaukowemeranyan'ibikikurikira. Mu minsi 7 ishize..

1. Nanyweyeibininibyosebigabanyaumuvudukow'amarasonkukonabyandiwenamuganga.	Ndabihakana cyane ○	Ndabihakana ○	Ntabwombyemera, ntanubwombihakana ○	Ndabyemera ○	Ndabyemera cyane ○

2. Ntabwonabashijekunywaibininibyosebigabanyaumuvudukow'amarasonkukonabyandikiwenamuganga.	Ndabihakana cyane ○	Ndabihakana ○	Ntabwombyemera, ntanubwombihakana ○	Ndabyemera ○	Ndabyemera cyane ○
3. Ntabwonigezenywaikininina kimwekigabanyaumvudukow'amaraso.	Ndabihakana cyane ○	Ndabihakana ○	Ntabwombyemera, ntanubwombihakana ○	Ndabyemera ○	Ndabyemera cyane ○

Access to antihypertensive medications

Over the previous 7 days, did you miss at least one dose of your antihypertensive medication (s) because:

1. You could not find the medication(s) in the hospital's pharmacy. ☐ Yes ☐ No
2. Medications were too expensive in pharmacies outside the hospital.☐ Yes ☐ No

Access to antihypertensive medications (Kinyarwanda)

Mu minsi 7 ishije, harubwowabautarafasheumutiugabanyaumuvudukow'amarasokuberako:

1. Wabuze iminti muri farumasi y'ibitaro. ☐Yego☐Oya
2. Imitiyariihenzecyanemurifarumasi zo hanzey'ibitaro. ☐Yego☐Oya

Month 12.

Systolic Blood Pressure recording.

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6

Month 7	Month 8	Month 9	Month 10	Month 11	Month 12

Creatinine at month 12:

8.3 Ethical Approval

UNIVERSITY OF RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 21st /08/2017

Dr Willy MUCYO
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 364 /CMHS IRB/2017

Your Project Title ***"A Prospective Cohort Study In Rwandan Referral Hospitals Of Factors Associated With Rapid GFR Decline In Patients With Hypertension"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS	X		
Prof Munyanshongore Cyprien	UR-CMHS		X	
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 17th August 2017, **Approval letter has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.
You are responsible for fulfilling the following requirements:

EMAIL: researchcenter@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: http://cmhs.ur.ac.rw/

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 21st August 2017
Expiration date: The 21st August 2018

Professor Kato J. NJUNWA
Chairperson Institutional Review Board
College of Medicine and Health Sciences, UR

Prof. JB Gahutu
Vice Chair

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR