



St. Paul's Hospital Millennium Medical college

Graduate study program

Prevalence of Apparent treatment resistant hypertension and associated factors among
hypertensive patients attending cardiology & nephrology follow up St. Paul Hospital Millennium
Medical Collage

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Acronyms and abbreviations

ABPM – Ambulatory Blood pressure measurement

ACC – American College of Cardiology

ACE – Angiotensin converting enzyme

AHA – American Heart Association

AOR – Adjusted odds ratio

ARB – Angiotensin receptor blocker

ASCVD – Atherosclerotic Cardiovascular Disease

aTRH – Apparent treatment Resistant hypertension

AV – Arteriovenous

BMI – Body mass index

BOO – Bladder outlet obstruction

BP – Blood Pressure

CCB – Calcium channel blocker

CHD – Coronary heart disease

CHF – Congestive heart failure

CKD – Chronic kidney disease

CMP – Cardiomyopathy

COR – Crude odds ratio

cRH – Controlled resistant hypertension

CV – Cardiovascular

CVA – Cerebrovascular accident

CVD – Cardiovascular Disease

DBP – Diastolic blood pressure

DENERHTN – Renal denervation for resistant hypertension

DM – Diabetes mellitus

EPO – Erythropoietin

ESC – European Society of Cardiology

ESH – European Society of Hypertension

ESRD – End stage renal disease

GFR – Glomerular filtration rate

HTN – Hypertension

IHD – Ischemic heart disease

IRB – Institutional review board

ISH – International Society of Hypertension

JHS – Jackson heart study

LVH – Left ventricular hypertrophy

MACE – Major adverse cardiovascular events

MASLD – Metabolic dysfunction associated steatotic liver disease

MI – Myocardial infraction

MMAS-8 – Morisky Green Levine adherence scale-8

MmHg – Millimeter of mercury

MUAC – Mid upper arm circumference

NICE – National Institute for Health and Care Excellence

NSAIDs – Nonsteroidal anti-inflammatory agents

OR – Odds ratio

OSA – Obstructive sleep apnea

PPI – Proton pump inhibitor

RCT – Randomized controlled trial

REGARDS - Reasons for geographic and racial differences in stroke

RH – Resistant Hypertension

SBP – Systolic blood pressure

SD – Standard deviation

SGLT2 – Sodium glucose cotransporter 2

SPHMMC – St Paul hospital millennium medical collage

SPSS – Statistical Package for the Social Sciences

T2DM – Type 2 diabetes mellitus

TIA – Transient ischemic attack

UAE – Urine albumin excretion

uRH – Uncontrolled resistant hypertension

VHD – Valvular heart disease

WHO – World Health Organization

Abstract

Background: Globally, around 10% of patients & 14.7% of patients with hypertension have true resistant hypertension and apparent treatment resistant hypertension (aTRH) respectively. Older age, black race, obesity, diabetes & CKD are common risk factors associated with RH.

Objective: The aim of this study was to measure the prevalence of apparent treatment resistant hypertension and assess socio demographic, lifestyle & medical related factors associated with apparent treatment resistant hypertension in hypertensive patients on follow up at cardiology & nephrology clinic of SPHMMC.

Methods: A cross sectional analytical study was conducted in cardiology & nephrology clinic of SPHMMC. Using systematic random sampling, 427 patients were selected and included in the study. The study was conducted from February 2023 - February 2024. Data was collected both from face-to-face interview & from medical records using data collection checklist which contains parameters on sociodemographic, lifestyle & medical related questions. Data analysis was conducted using SPSS version 27.0. Both bivariable & multivariable logistic regression models were carried out. p -value of < 0.05 in the multivariable logistic regression analysis was considered as statistically significant.

Result: A total of 427 adult hypertensive patients were enrolled in the study and more than half 227 (53.2%) were females. The average age of the patients was 54.2 ± 14.1 years & average duration of hypertension was 7.2 ± 7.8 years. Around 35% of the patients had family history of hypertension & 381 (93.8%) of patients had associated comorbidity. Out of the total patients enrolled, 249 (58.3%) had uncontrolled BP. 19 (4.4 %) of the enrolled hypertensive patients were found to have apparent treatment resistant hypertension & 2 (0.4%) had pseudo resistant hypertension due to adherence issues. Furthermore, patients that had CKD as a comorbidity (AOR 3.017; $p < 0.05$) were significantly associated with aTRH.

Conclusion: Apparent treatment resistant hypertension was found in 4.4% of hypertensive patients. Hypertensive patients with CKD were significantly associated with aTRH.

Keywords: Apparent treatment resistant hypertension, Resistant hypertension

1. Introduction

1.1. Background of study

Hypertension is the leading modifiable risk factor for cardiovascular disease and death (1,2). A large number of hypertensive adults still fail to achieve their blood pressure (BP) targets on 3 antihypertensive medications or require ≥ 4 medications to achieve their targets (1). Factors that may lead to inadequate control of BP are problems with adherence to treatment regimens (including lifestyle & dietary therapy), failure of physicians to intensify the treatment regimens (therapeutic inertia), white coat effect (elevated office BP but normal out-of-office BP), or true treatment-resistant hypertension (1,3).

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline defines hypertension as office based systolic BP ≥ 130 or diastolic BP ≥ 80 , which makes it different from the other guidelines (4). The European Society of Hypertension (ESH), the International Society of Hypertension (ISH), as well as the 2016 Ethiopian national guideline for non-communicable diseases define hypertension, using office-based BP, as a systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg (5–7).

Regarding treatment goals, AHA/ACC guideline, European Society of Cardiology and European Society of Hypertension (ESC/ESH) and the Ethiopian guideline slightly differ in their targets. According to the AHA/ACC 2017 guideline, the BP goal of treatment is $<130/80$ mm Hg for most individuals (independent of Clinical CVD or 10-year ASCVD risk & comorbidities) but for older adults the target is systolic < 130 (4). According to the European Society of Hypertension (ESH), it is recommended that the first objective of treatment should be to lower BP to $< 140/80$ mmHg in most patients and, provided that the treatment is well tolerated, treated BP values can be targeted to $130/80$ mmHg or lower in most patients up to 79 years old (7). In older patients (≥ 80 years), it is recommended that SBP should be targeted to a BP range of $140 - 150$ mmHg (7). The goal of treatment according to our Ethiopian guideline is to keep BP below $140/90$ & for elderly (>75 years of age) below $150/90$ (6). These differing thresholds for definition of hypertension and targets of treatment affect not only the prevalence of hypertension but also resistant hypertension in different countries.

RH (Resistant Hypertension) is defined as the BP of a hypertensive patient that remains elevated above goal despite the concurrent use of 3 antihypertensive agents of different classes,

commonly including a long-acting calcium channel blocker (CCB), a blocker of the renin angiotensin system (angiotensin converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]), and a diuretic. All agents should be administered at maximum or maximally tolerated doses and at the appropriate dosing frequency. RH also includes patients whose BP achieves target values on ≥ 4 antihypertensive medications, a condition that has been referred to as controlled RH. Thus, the term RH refers to hypertension with both uncontrolled and controlled BP, depending on the number of antihypertensive agents used (1,4).

True RH requires patient adherence to prescribed medications and that the uncontrolled subset has elevated BP outside the office setting (1). The term apparent treatment RH (aTRH) is used when ≥ 1 of the following data elements are missing: medication dose, adherence, or out-of-office BP; thus, pseudo resistance cannot be excluded (1,8).

1.2. Statement of the problem

Despite the widespread use of antihypertensive drugs and treatment strategies, many patients with hypertension still fail to achieve target BP on 3 antihypertensive medications or require ≥ 4 medications to achieve their targets (1,8). According to a meta-analysis done in 2018, the global prevalence of true resistant hypertension & apparent treatment resistant hypertension was estimated to be 10.3% and 14.7% respectively while the overall pooled prevalence of resistant hypertension in Africa was estimated to be 12.1% (9,10). Regarding our country Ethiopia, only one study was done in Mekelle hospital & the prevalence of apparent treatment resistant hypertension was estimated to be 8.6% (11).

Patients with resistant hypertension tend to have poor prognosis b/c they are at higher risk for CV morbidity & renal outcomes when compared with patients without resistant hypertension (12–14). And patients with RH are also at an increased CV mortality compared to patients without RH (13,15,16).

Common risk factors associated with resistant hypertension include older age, black race, longer duration of hypertension, obesity, chronic kidney disease (CKD), dyslipidemia and diabetes mellitus (DM). Patients with resistant hypertension are also more likely to have secondary causes of hypertension as well (1,17).

Prevalence of resistant hypertension and associated risk factors has been studied in different countries including Africa but data regarding this topic has not been extensively studied in our country Ethiopia. There is only one local study that was done in Ethiopia in 2020 in Mekelle hospital regarding resistant hypertension and associated risk factors & the limitation of their study was that the investigators used secondary data from the medical charts and so couldn't ensure that BP measurement was done with the necessary precautions and also the investigators couldn't assess certain variables like sociodemographic factors (employment status, educational status & monthly income), medical factors (adherence to antihypertensive medications, types of comorbidities associated with RH in detail), life style factors (physical exercise, alcohol intake, smoking history). With this study, we assessed these factors as well and ensured precautions for BP measurement since the data was retrieved both from the medical records and direct patient interview.

1.3. Significance of the study

For clinicians, knowing the prevalence and associated risk factors of resistant hypertension enhances their knowledge on the magnitude of the problem & its risk factors in our clinical context better. It will also help them screen these patients for the commonly associated factors with resistant hypertension and manage these patients accordingly.

For higher administrative bodies, knowing the prevalence of resistant hypertension will help them plan and design a system in which these patients can be treated with the specialized care they need according to their risk since providing better care for such patients will help enhance their survival and reduce the higher CV morbidity and mortality associated with resistant hypertension.

Future researchers can use this information as a basis for further research on studying the prevalence and risk factors associated with resistant hypertension and it also allows more researches to be done to further consolidate the causal relationship of resistant hypertension with its factors.

2. Literature review

2.1. Prevalence of resistant hypertension

2.1.1. Global prevalence of resistant hypertension

In 2018, a meta-analysis that included around 3.2 million patients globally with treated hypertension who participated in 91 studies between 1991 and 2017 reported the overall prevalence of true RH was 10.3%. The study also showed a high prevalence of aTRH and pseudo-RH, ~14.7% and 10.3%, respectively (9).

Prevalence of aTRH seems to be higher when an at risk group is selected compared to a population or clinic based samples. For example, a study that included 3367 hypertensive and nondialysis CKD patients showed that the prevalence of aTRH was 40.4% in CKD patients (18). Another cross sectional study that included 1,737 subjects with type 2 diabetes that visited an outpatient clinic in Japan showed that the prevalence of RH was 21.8% when treatment target of <140/90 was used (19).

2.1.2. Prevalence of resistant hypertension in Africa

In a systematic review & meta-analysis that included 5 studies from Cameroon, Nigeria, Burkina Faso, Lesotho and Algeria with a total population of 4,068 patients showed that the prevalence of resistant hypertension was respectively 11.7%, 4.9%, 14.6%, 14.3% and 19.0%, with an overall pooled prevalence of 12.1% but the definition of RH was not similar across the studies (10). Another cross-sectional study which involved 2912 participants with hypertension in five health facilities in Ghana found that 18.9% of study participants had aTRH (20).

2.1.3. Prevalence of resistant hypertension in Ethiopia

Only single study on resistant hypertension was conducted in our country Ethiopia which is hospital based cross sectional study which included 338 adult hypertensive patients on follow up in Mekelle Hospital hypertension clinic & found that prevalence of aTRH was calculated to be 8.6% (11). But the limitation of the study is that they used secondary data from medical registries and so couldn't ensure that BP measurement was done with necessary precautions and also the investigators couldn't assess certain variables like sociodemographic factors (employment status, educational status & monthly income), medical factors (adherence to antihypertensive medications, types of comorbidities associated with RH in detail), life style factors (physical exercise, alcohol intake, smoking history).

2.2. Prognosis of resistant hypertension

Individuals who are classified as having treatment-resistant hypertension (RH) are at an increased risk for target organ damage, morbidity, and mortality despite being on antihypertensive drug therapy (1).

Different retrospective and prospective cohort studies using either the 2008 or the 2018 AHA criteria showed that patients with RH are at higher risk for CV morbidity compared with patients without RH (12–14,21). In one retrospective cohort study which included 205,750 patients with incident hypertension showed that those with RH were almost 50% more likely to experience a CV event (defined as nonfatal MI, CHF, stroke, or CKD) over a median 3.8 years of follow-up compared to patients without RH but the differences in CV events in this study was largely caused by the development of CKD(14). In another study which included 470,386 patients, showed that patients with RH had a 32% increased risk of developing end stage renal disease, a 24% increased risk of an ischemic heart event, a 46% increased risk of heart failure, and 14% increased risk of stroke when compared to patients without RH (13). In another prospective study over a period of 3.9 years which included 1911 patients showed that persistent RH compared with never-having RH was associated with a 2.2-fold increased risk for CV morbidity (12).

RH is also associated with increased CV mortality compared to patients without RH (13,15,16). In a study that included 7455 hypertensive patients with symptomatic vascular disease, aTRH were at 27% increased risk of CV mortality (16). Another study that analyzed 6357 adult hypertensive participants, showed that aTRH was associated with a 47% higher risk of CVD mortality compared with the non-aTRH group (15).

Some studies have also shown that controlling the BP in patients with RH is associated with reduction of CV events (13,22,23). In a retrospective study which included 470,386 hypertensive patients, the uRH population compared cRH experienced over a 20% increased risk for CVD and ESRD, underscoring the importance of BP control (13). In the REGARDS study which included a total of over 14,000 patients, uncontrolled RH was associated with a 2 fold increased risk of CHD compared with controlled RH but not stroke or mortality (22). In another study that included 118,356 treated hypertensives, showed that BP control reduced the risk of incident stroke, coronary heart disease, or heart failure by 13% among those with RH (23).

2.3. Resistant hypertension & associated factors

2.3.1. Sociodemographic factors associated with RH

Two meta-analyses (one that was done globally that included 3.2 million patients & another in Africa that included 4068 patients) and also other cross-sectional studies have shown that RH is significantly associated with older age (9,10,24–26). Some metanalysis & cross sectional studies have also found an association with male sex while others have found significant associations with female sex (10,24,25). Apparent treatment RH is also significantly associated with black race (24).

A cross-sectional study that was done in Ghana showed significant association of periurban residence & secondary level education with aTRH relative to those residing in rural dwellings & those with tertiary level education but there was no significant association of aTRH with sex, employment status, & monthly income (20).

The prevalence of apparent RH did not seem to differ significantly across the various regions of the world, according to the setting or income, but income was assessed at a macroeconomic level rather than at an individual level (9).

2.3.2. Medical related factors associated with RH

2.3.2.1. Comorbidities

Patients with resistant hypertension are more likely to have an identifiable cause of hypertension (i.e. Secondary hypertension) (1). For example, the DENERHTN trial (renal denervation for resistant hypertension trial) which included 1,416 patients with resistant hypertension, 709 (50%) of patients were excluded from receiving denervation because a secondary cause for the hypertension was identified (27). The common causes of secondary hypertension are primary aldosteronism (Conn's syndrome), renal artery stenosis, CKD, pheochromocytoma, Cushing syndrome, coarctation of aorta & other less common causes include thyroid abnormalities, primary hyperparathyroidism, congenital adrenal hyperplasia, and acromegaly (1).

Multiple comorbidities also have been associated with RH like Obesity, diabetes, CKD, coronary artery disease, LVH, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, congestive heart failure and OSA which will be further discussed in the section below.

CKD can be the cause or the complication of poorly controlled hypertension. According to a metanalysis that included around 3.2 million patients globally, the prevalence of true RH was higher in patients with CKD (22.9%) & renal transplant (56.0%)(9). Cross sectional studies done in both Ghana and northern California also showed that there is a 73% more likelihood and 2 times more likelihood of having aTRH in patients with CKD respectively (20,28).

According to various cross-sectional studies, diabetes was found to be significantly associated with RH. Studies done in southern & northern California and in sri lanka showed diabetic patients were 58%, 20% and 67% more likely to have RH compared to those that are not diabetic (24,26,28). A higher prevalence of hyperlipidemia is also seen in RH patients (29).

In a cross-sectional study that was done in California (that included around 17,000 patients), RH was significantly associated with coronary artery disease, cerebrovascular accident /transient ischemic attack, peripheral vascular disease & CHF (OR, 1.3, 1.32, 1.29, 2.88 respectively; all $P < .05$) (28). Similar finding was seen in a metanalysis that was done in Africa & in cross-sectional studies that done in southern California and Italy (10,24,29).

An association of RH with higher BMI was seen in multiple cross-sectional studies done in Ethiopia & in western & Asian countries (3,11,28). The study done in mekelle hospital showed that patients with BMI of ≥ 30 were 12 times more likely to have RH & the study done in south india showed that patients with BMI of ≥ 25 were 4 times more likely to have RH (3,11).

2.3.2.2. Family history of hypertension

The genetics of BP & essential hypertension have been extensively investigated, but evidence on the genetic studies of aTRH are still limited. A cross sectional study that included 1,737 type 2 diabetes patients that visited the outpatient clinic of Jiyugaoka Internal Medicine in Japan found that family history of hypertension, which is linked to the genetic predisposition to hypertension, was identified as an independent factor associated with RH (19).

2.3.2.3. Duration of hypertension

Different studies have shown that, as the duration of hypertension increases, the prevalence of RH increased (3,11,20,26). According to these studies, patients with a duration of hypertension of > 6 years (study done in mekelle hospital) and > 10 years (study done in south India) were 4.1 times and 3.4 times more likely to have RH respectively (3,11).

2.3.2.4. Medication

Different classes of drugs can result in increment in BP, blunt the effect of antihypertensives and result in RH. A meta-analysis that included 38 randomized, placebo-controlled trials & 12 randomized but not placebo controlled trials showed that NSAIDs elevate supine mean BP by 5.0 mmHg & NSAIDs antagonized the antihypertensive effect of beta-blockers (BP elevation, 6.2 mm Hg) more than did vasodilators & diuretics (30).

Other medications (like steroids, erythropoietin, antidepressants & oral contraceptives) have not been directly linked to aTRH but have significant association with increment in BP in different studies (31).

2.3.3. Lifestyle related factors associated with RH

There is limitation of studies that show association between physical inactivity & resistant hypertension but an important clue to the importance of exercise comes from a systematic review & meta-analysis which included three RCT (144 participants) who were diagnosed with RH & underwent regular exercise, showed that exercise training intervention (8-12 weeks, 3 sessions/weeks) significantly reduced 24 hr BP (by -9.9 mmHg for systolic BP; and -5 mmHg for diastolic BP) and daytime ambulatory BP (-11.7 mmHg for systolic; and 7.4mmHg for diastolic BP) (32).

Different meta-analysis and cross-sectional studies have shown the association between alcohol intake, cigarette smoking and amphetamine use with increase in BP but there a limitation of studies highlighting the associations of these factors with aTRH (33–35).

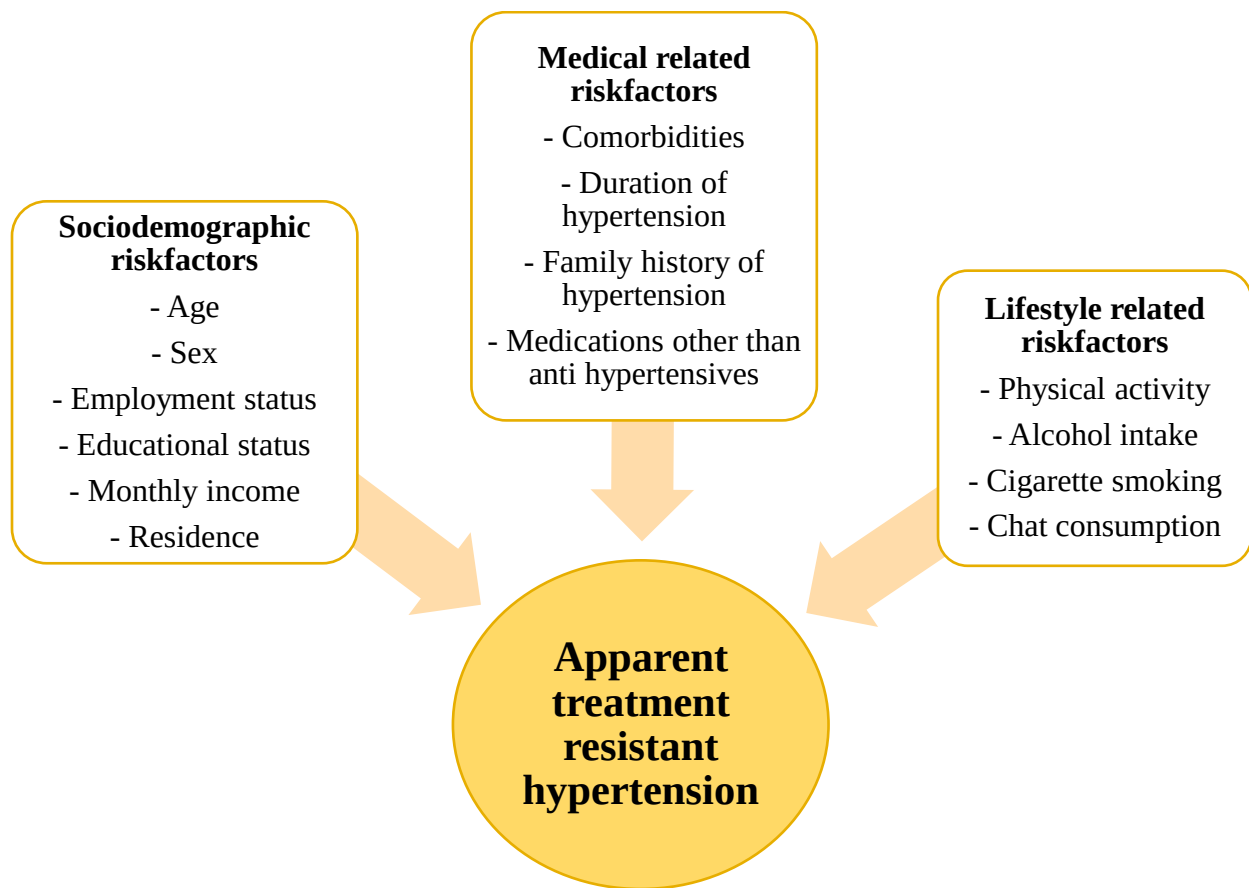


Figure 1. Conceptual frame work

3. Objective of the study

3.1. General objective

- To determine the prevalence of apparent treatment resistant hypertension (aTRH) and determine factors associated with aTRH among hypertensive patients attending cardiology and nephrology follow up at St Paul hospital millennium medical collage

3.2. Specific objective

- To determine the prevalence of apparent treatment resistant hypertension (aTRH) among hypertensive patients attending cardiology & nephrology follow up at St Paul hospital millennium medical collage
- To determine sociodemographic factors associated with apparent treatment resistant hypertension (aTRH)
- To determine medical related factors associated with apparent treatment resistant hypertension (aTRH)
- To determine lifestyle related factors associated with apparent treatment resistant hypertension (aTRH)

4. Methods

4.1. Study design

The study design was a cross-sectional, analytical study.

4.2. Study area & period

4.2.1. Study area

The study was conducted in cardiology & nephrology clinic of St Paul's hospital Millennium Medical College. SPHMMC was selected because it is one of the largest tertiary care centers in the country and it is one of the areas where high risk patients are referred. The cardiology and nephrology clinic were selected because hypertensive patients are usually referred to these clinics for their follow up at SPHMMC.

St Paul's Millennium Medical College is located in Addis Ababa, Ethiopia & it was established in 1968 by the late Emperor Haile Selassie. The college has more than 2800 clinical, academic and administrative and support staffs that provide medical specialty services to patients who are referred from all over the country, teaching medicine and nursing students and doing basic and applied researches. While the inpatient capacity is more than 700 beds, the College sees an average of 1200 emergency and outpatient clients daily (36).

The cardiology clinic runs from Monday to Wednesday (it is open both in the morning & afternoon) and the nephrology clinic runs on Monday, Wednesday and Friday (it is open in the morning only). The average number of hypertensive patients who came for follow-up per month on year 2022 at the cardiology and nephrology clinic was around 360 patients. Patients who have insurance are given available medications in the hospital for free during follow-up visits.

4.2.2. Study period

The study was conducted from October 2023 – January 2024.

4.3. Population

4.3.1. Source population

- Adult (>18 years of age) hypertensive patients having regular follow up at cardiology or nephrology clinic of St Paul hospital millennium medical collage

4.3.2. Study population

- Adult hypertensive patients who have regular follow-up at the cardiology or nephrology clinic of St Paul hospital millennium medical college and those who fulfill the inclusion criteria

4.4. Eligibility criteria

4.4.1. Inclusion criteria

- Adult (> 18 years of age) patients on follow up for hypertension at the cardiology or nephrology clinic of St Paul hospital millennium medical college and
- Patients on management for hypertension at SPHMMC for more than 3 months

4.4.2. Exclusion criteria

- Patients who are too ill/unable to answer the questionnaire
- Pregnant women
- Patients with mid arm circumference of < 22 cm or > 45 cm

4.5. Sample size determination & sampling technique

4.5.1. Sample size determination

Previous studies done either in Ethiopia or nearby African countries with a study design & operational definition for aTRH similar to this current study was not found. For this reason, the proportion of patients with apparent treatment resistant hypertension was assumed to be 50% with absolute precision of 5% and 95% confidence level, the calculated sample size was 384. Considering a non-response rate of 10%, we included 427 hypertensive patients for the study. Sample size was calculated using the formula depicted below:

The sample size for this study was calculated using the formula depicted below

$$n = Z^2 P(1-P) / d^2 = (1.96)^2 * 0.5 * 0.5 / (0.05)^2 = 384.1 \text{ approximated to } 384$$

Where n is the sample size, Z is the statistic corresponding to level of confidence, P is expected prevalence, and d is precision

Final sample size = Effective sample size / (1 - non response rate anticipated)

Non response rate expected was 10%

Final sample size = $384 / (1 - 0.1) = 426.6$ rounded off to 427

4.5.2. Sampling technique

In order to choose the sample for this study, systematic random sampling technique was used. The cardiology & nephrology clinics each run 3x/week and so we visited the clinics on those days. Data was collected from 215 patients on follow up at the cardiology clinic during the first 2 months of data collection and from 212 patients on follow up at the nephrology clinic for the last 2 months of the data collection period which gives a total of 427 patients included in the study.

After reviewing the monthly patient flow of the St Paul hospital from the registration books, the average number of hypertensive patients who came for cardiology or nephrology clinic follow-up per month on year 2022 was around 360. And so, the expected number of hypertensive patients on follow up for 4 months was 1,440 patients, from which 427 patients were included in the study. On each day of study, we first selected all the patients with hypertension from the daily clinic register. These patients were arranged in ascending order according to their clinic number. The first patient was chosen randomly from hypertensive patients and then every 3rd patient thereafter was invited for the study.

The sampling interval was calculated as follows

The interval for selecting the sample, $k = N_i/n_i$ (where N_i = expected number of hypertensive patients on follow up at cardiology clinic/ nephrology clinic for 4 months and n_i = the calculated sample size)

$$k = 1440/427 = 3.3 \text{ rounded off to } 3$$

4.6. Study variables

4.6.1. Independent variables

- Socio demographic factors - Age, Sex, Residence, Educational status, Employment status, Monthly income
- Lifestyle-related factors - Cigarette smoking, Alcohol intake, Chat consumption and Physical activity
- Medical related factors - Duration of hypertension, Family history of hypertension, Presence of comorbidities (including DM, IHD, CKD, dyslipidemia, CVA, other causes of secondary hypertension) and Medications (including number, doses of

antihypertensive medications, intake of other medications such as NSAIDs, steroids, antidepressants, erythropoietin, etc.) and adherence to medication.

4.6.2. Dependent variable

- Apparent treatment resistant hypertension (both controlled and uncontrolled

4.7. Operational Definitions

Uncontrolled hypertension was defined as office blood pressure measurement of SBP ≥ 140 and/or DBP ≥ 90 mm of Hg. Controlled hypertension was defined as office blood pressure measurement of SBP <140 and DBP <90 mm of Hg.

Uncontrolled resistant hypertension (RH) was defined as office blood pressure SBP ≥ 140 and/or DBP ≥ 90 mm of Hg on three or more antihypertensive drugs with maximal dose or maximally tolerated doses including a diuretic. Controlled resistant hypertension (RH) was defined as office blood pressure SBP <140 and DBP <90 mm of Hg on 4 or more antihypertensive drugs, provided that at least three of the antihypertensive drugs are at maximal dose or maximally tolerated doses including a diuretic.

Apparent treatment resistant hypertension is used when patients fulfill the definition of RH but either adherence to medication or AMBP measurement is unknown. Patients who fulfill the definition of RH but are either non adherent to their medication or for whom AMBP measurement was used to rule out resistance were considered to be pseudo resistant.

Adherence to antihypertensive medications was assessed using the Morisky Green Levine adherence scale 8 (37).

BMI was categorized according to WHO classification – below 18.5 as underweight, between 18.5 – 24.9 as normal weight, between 25 – 29.9 as pre obesity/ overweight, more than or equal to 30 as obesity.

Physical activity was defined as adequate if 30 minutes of aerobic exercise five times per week for a total of 150 minutes per week and considered inadequate if it doesn't fulfill these criteria.

Excess alcohol consumption was defined as >1 alcoholic drink per week for women and >2 alcoholic drink per week for men. A drink is defined as 14 gram of pure alcohol which is found in 12 ounces of regular beer which is usually about 5% of alcohol, 5 ounces of table wine which is

typically about 12 % of alcohol, 1.5 ounces of distilled spirits (gin, rum, tequila, vodka, whisky etc) which is about 40% of alcohol (4).

4.8. Data collection tool, methods & procedures

Data collection was done both from face-to-face interviews with patients & from patient chart by trained data collectors (6 internal medicine residents & 2 interns). Data was collected using pretested and structured questionnaire which was adopted from different kinds of literature of similar studies (3,11,20). And data regarding comorbidities and number and types of medication intake was taken from the patient's medical records.

BP was measured with a well calibrated Digital sphygmomanometer (oscillometric BP measurement). The instrument used for measurement in this study is the YuWell YE660D oscillometric upper-arm blood pressure (BP) with arm circumference of 22–45 cm (wide range) and has been validated for clinic and home BP measurements in adults after passing the requirements of the Advancement of medical instrumentation/European society of hypertension/International organization for standardization Universal Standard (ISO 81060-2 : 2018) and its Amendment 1. 2020 (38).

Regarding the measurement of BP, standard precautions were used. The dominant arm was used for BP recording. Adult cuff size was used for all patients with an arm circumference of 22 – 45 cm since the digital sphygmomanometer could only allow measurement for this specified range of arm circumference (MUAC was measured for all patients). Participants were advised to empty their bladder if needed. No smoking, food, exercise, or intake of caffeine within 30 minutes preceding the measurement was ensured. Participants were seated comfortably for 5 min before beginning the BP measurements. The BP cuff was positioned at the level of the heart, with the participant's back and arm supported, legs uncrossed and feet flat on the floor. No talking during measurement. BP was rechecked after 5 minutes. The second reading was taken as the actual blood pressure of the patient.

Adherence to antihypertensive medications was assessed using the Morisky Green Levine adherence scale 8. And response choices were “yes” or “no” for items 1 through 7 and Item 8 has a five-point Likert response scale. Each “no” response was rated as 1 and each “yes” response was rated as 0 except for item 5, in which each “yes” response was rated as 1 and each “no” response is rated as 0. For Item 8, the code (0-4) was standardized by dividing the result by 4 to calculate a

summated score. Total scores on the MMAS-8 ranged from 0 to 8, with scores of 8 taken as high adherence, 6 to < 8 taken as medium adherence, and <6 taken as low adherence (37).

Regarding the BMI, the weight and height of the participants was measured once by the data collectors after the interview.

4.9. Data quality control

The quality of the data was ensured through training of data collectors and supervisors, close supervision and prompt feedback. The training consisted of instruction on interview techniques as per the prepared tool. Data was checked for completeness, consistency, clarity and appropriate corrections were made by the two supervisors and principal investigator on a daily basis.

4.10. Data processing & analysis

Data entry and Data analysis was conducted using statistical package for the social sciences (SPSS) version 27.0. Simple frequency, percentage, mean, and standard deviations were calculated as descriptive statistical analyses.

A binary logistic regression model was used to identify the factors associated with aTRH. Both bivariable and multivariable logistic regression models were carried out. Variables with a p-value of < 0.2 in the bivariable analysis were entered into the multivariable analysis. Both the crude odds ratio (COR) and adjusted odds ratio (AOR) with 95% Confidence interval were estimated to show the strength of associations. Finally, a p-value of < 0.05 in the multivariable logistic regression analysis was used.

4.11. Ethical considerations

Ethical clearance was obtained from the SPHMMC institutional review board (IRB) prior to conducting the research. Permission was sought from the school of administration to carry out the research.

Participants were informed about the purpose, objectives, and their right to participate and not to participate in the study. Eligible patients were enrolled in the study after taking verbal informed consent and each patient's name & other identification revealing information was kept confidential.

4.12. Result dissemination

The results of this study will be submitted to the department of Internal medicine & Public health, SPHMMC in partial fulfillment of the requirement for the specialty certificate in internal medicine. It will also be presented to the Cardiology unit. In addition, the findings will be distributed to major tertiary care centers in the country. The results will be published in peer reviewed journals.

5. Result

5.1. Sociodemographic characteristics of the studied population

In this study, we included 215 hypertensive patients from the cardiac clinic & 213 hypertensive patients from the nephrology clinic which is a total of 427 adult hypertensive patients. From the total patients enrolled, 227(53.2%) were females and 200(46.8%) were males. The average age (mean $\pm$ SD) of the patients was 54.2 ± 14.1 years. 81 (19%) of the hypertensive patients were classified in the age category of 39 years old or less while 171(40%) were in the age of 40–59 years old & the rest 175(41%) were age 60 & above. Of the total patients enrolled, 80% had income of ≤ 4999 birr and 59% were unemployed. Around 90% of the patients had urban residence (Table 1).

Table 1- Sociodemographic characteristics of hypertensive patients

Sociodemographic factors		aTRH			
		Yes		No	
		Count	%	Count	%
Age	≤ 39	3	0.7%	78	18.3%
	40 – 59	6	1.4%	165	38.6%
	≥ 60	10	2.3%	165	38.6%
Sex	Male	13	3.0%	187	43.8%
	Female	6	1.4%	221	51.8%
Educational status	Primary education	7	1.6%	117	27.4%
	Secondary education	3	0.7%	106	24.8%
	Tertiary education	7	1.6%	110	25.8%
	No education	2	0.5%	75	17.6%
Residence	Urban	15	3.5%	367	85.9%
	Rural	4	0.9%	41	9.6%
employment status	Governmental	2	0.5%	64	15.0%
	Non-governmental	0	0.0%	3	0.7%
	Self employed	5	1.2%	101	23.7%
	Unemployed	12	2.8%	240	56.2%
Monthly Income	≤ 4999	16	3.7%	326	76.3%
	5000 – 14999	2	0.5%	65	15.2%
	≥ 15000	1	0.2%	17	4.0%

5.2. Medical characteristics of the studied population

Around 35% of the patients had family history of hypertension and duration of hypertension was ≥ 6 years in 43.8% of the patients. The average duration of hypertension since diagnosis was 7.2 ± 7.8 years which ranged from a minimum of 3 months to a maximum of 40 years. Almost half, 207 (48.5%) of the enrolled patients had a normal BMI ($18.5 - 24.9 \text{ kg/m}^2$) and around 195 (45.2%) were above the normal BMI. The average BMI (Mean $\pm$ SD) of the analyzed patients was $25 \pm 4.9 \text{ kg/m}^2$ (table 2).

Concerning the frequency of antihypertensive medications prescribed, Calcium channel blocker was the most frequently prescribed medication accounting for 36.3% followed by ACE inhibitor (23.5%) and diuretic (23%) (Figure 2, table 2). And most hypertensive patients were taking single antihypertensive medication (37.5%) or dual antihypertensive medications (38.9%) while patients receiving three or more medications were 23.7%. And around 20.8% of patients with uncontrolled BP were on single antihypertensive medication and 23.4% of patients with uncontrolled BP were on dual antihypertensive medications (Figure 3).

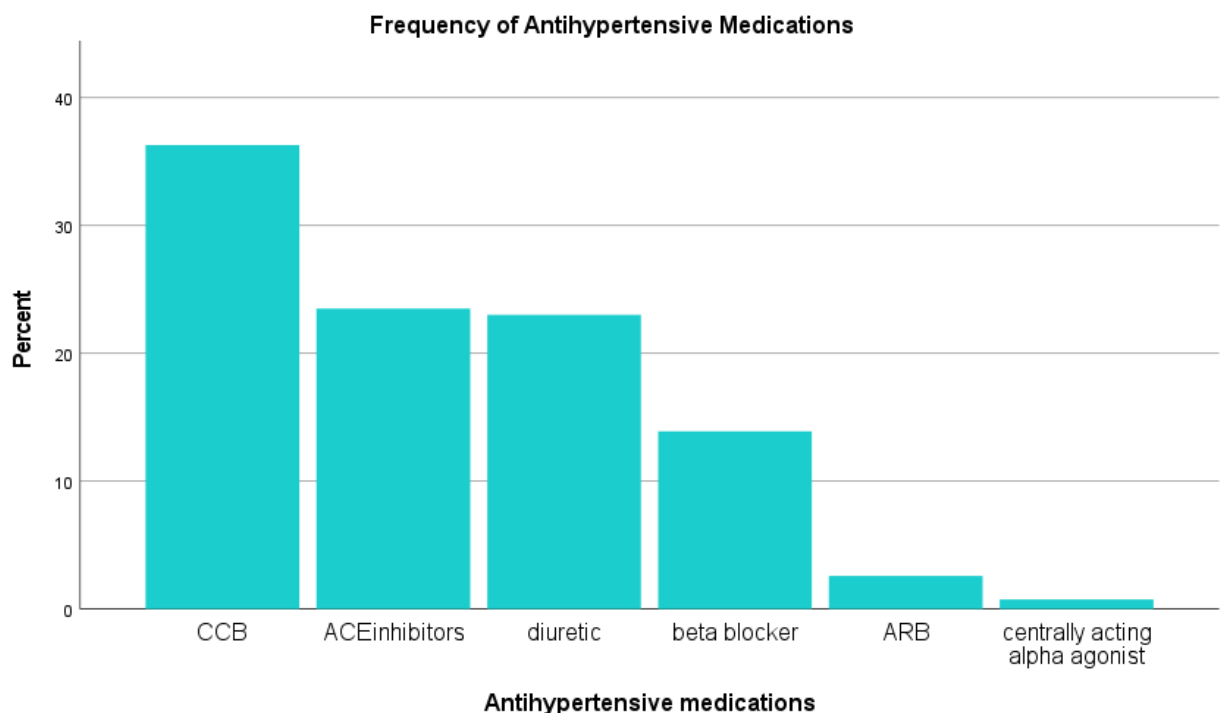


Figure 2 – Frequency of antihypertensive medications prescribed to patients

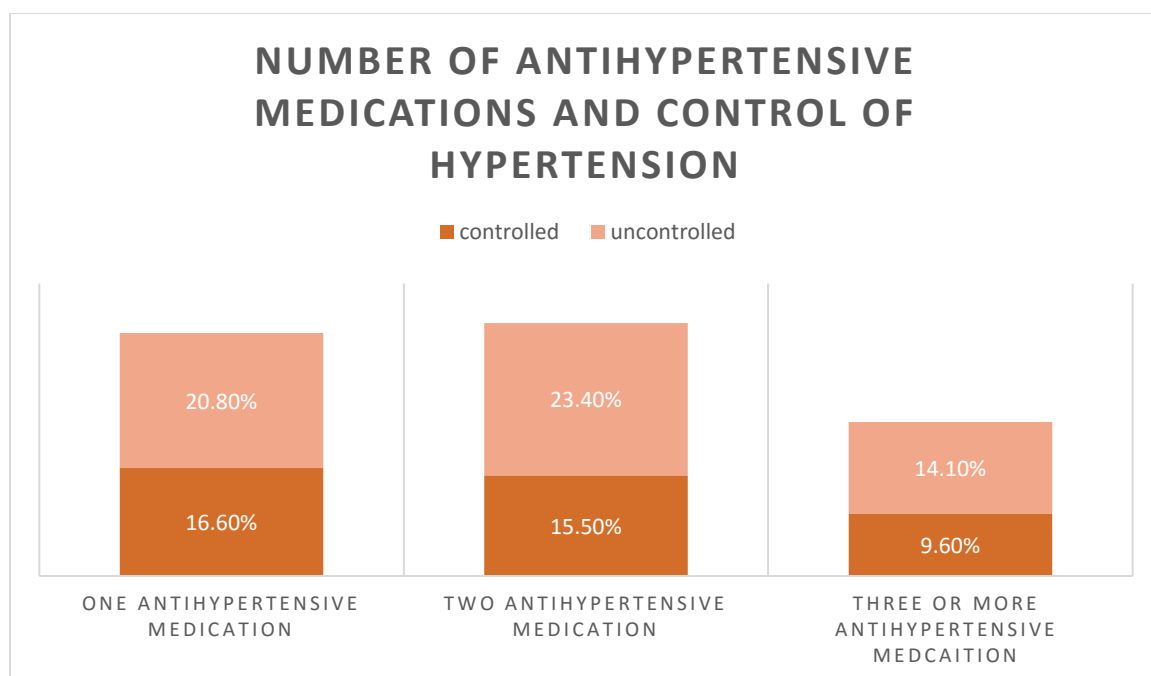


Figure 3 – Number of antihypertensive medications & control of hypertension

From the total patients enrolled in the study, 381(93.8%) of patients had associated comorbidity & 46 (6.2%) of the patients had no associated comorbidity. 20.8% of the patients had associated CKD as comorbidity and 14.4% of patients had diabetes mellitus (table 2).

Regarding medications other than antihypertensives, 75.5% of patients enrolled on the study had medications other than antihypertensive while 24.5% of patients had no medication prescribed other than antihypertensive. 11.9% of the patients were taking NSAID in addition to their antihypertensive medications (table 2).

Table 2 – Medical characteristics of hypertensive patients

Medical factors		aTRH			
		Yes		No	
		Count	%	Count	%
Family history of hypertension	Yes	5	1.2%	147	34.4%
	No	14	3.3%	261	61.1%
Duration of hypertension	<=5.9	11	2.6%	229	53.6%
	>=6	8	1.9%	179	41.9%
BMI	<=18.4	1	0.2%	26	6.1%
	18.5 - 24.9	10	2.3%	197	46.1%

	25 - 29.9	6	1.4%	125	29.3%
	>= 30	2	0.5%	60	14.1%
Comorbidities	Diabetes	10	1.4%	96	13.0%
	Thyrotoxicosis	0	0.0%	10	1.4%
	Pheochromocytoma	0	0.0%	1	0.1%
	IHD	2	0.3%	29	3.9%
	Heart failure	0	0.0%	6	0.8%
	HHD	3	0.4%	35	4.7%
	PAD	0	0.0%	5	0.7%
	CKD	13	1.8%	140	19.0%
	AKI	1	0.1%	28	3.8%
	Dyslipidemia	1	0.1%	50	6.8%
	CVA/TIA	1	0.1%	24	3.3%
	Other comorbidities ^	14	1.9%	222	30.1%
	No comorbidities	0	0.0%	46	6.2%
Antihypertensive Medication	ACE inhibitors	12	1.5%	179	22.0%
	ARB	2	0.2%	19	2.3%
	Beta blocker	17	2.1%	96	11.8%
	CCB	16	2.0%	279	34.3%
	Diuretic	19	2.3%	168	20.7%
	Centrally acting alpha agonist	1	0.1%	5	0.6%
Other medications	Steroid	2	0.4%	23	4.4%
	NSAID	5	1.0%	57	10.9%
	Erythropoietin	1	0.2%	6	1.1%
	Antidepressants	1	0.2%	27	5.2%
	Other non-antihypertensive medications *	16	3.1%	257	49.1%
	No other medication other than antihypertensive	2	0.4%	126	24.1%

aTRH – apparent treatment resistant hypertension

^ **Other comorbidity** – benign and malignant tumors, BOO, obstructive lung diseases, infection, arthritis, brady and tachyarrhythmia & conduction abnormalities, cystic diseases, electrolyte abnormalities, hypothyroidism, neuropathies, VHD, viral hepatitis, MASLD, movement disorders, seizure disorders, ophthalmologic disorders, hematologic disorders, nephrotic and nephritic syndrome, intervertebral disc abnormalities, psychiatric disorders, esophageal abnormalities, thrombosis, uremia, vitamin deficiencies, dermatitis, metabolic bone disorders, CMP, nephrolithiasis, cholelithiasis, hernia, varicose vein

* **Other medications** – statin, antiviral, antibiotics, SGLT2 inhibitors, oral and injectable hypoglycemic agents, antiepileptics, phosphodiesterase 5 inhibitors, PPI, anticoagulants, antiplatelet, vitamin supplements, calcium & iron supplements, xanthine oxidase inhibitors, alpha blocker, antihistamine, antithyroid agent, antipsychotic medications, thyroxine supplement, immunomodulators, folate supplement, digitalis glycosides, bronchodilator, potassium binder, antiparkinsonian agents, expectorant, anti inflammatory agents

From the total patients enrolled, 300 (70.3%) of the patients had high adherence to their antihypertensive medications and the rest 127 (29.8%) had medium to low adherence to medication (Figure 4).

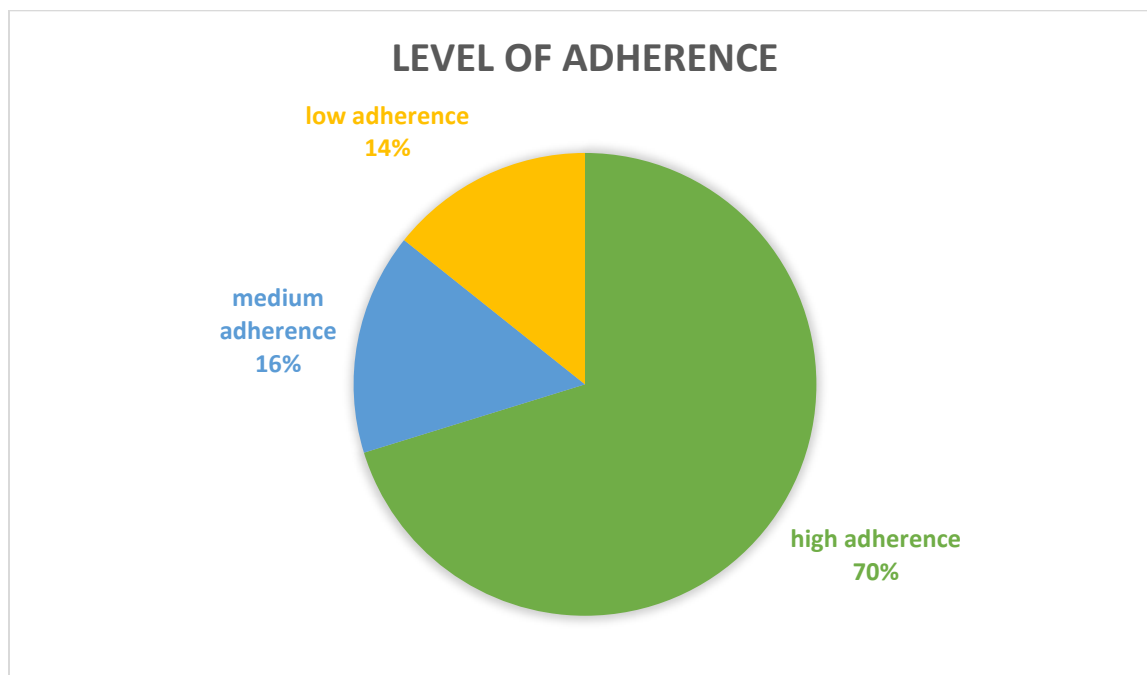


Figure 4- level of Adherence to antihypertensive medication among hypertensive patient

5.3. Life style characteristics of the studied population

Regarding life style factors, 60.7% of the total enrolled patents had adequate physical activity and >90% of the patients have never used cigarette, were not using chat at the time of the study period and were not having excess alcohol consumption (table 3).

Table 3- Lifestyle characteristics of hypertensive patients

Lifestyle factors		aTRH			
		Yes		No	
		Count	%	Count	%
Physical activity	Adequate	11	2.6%	248	58.1%
	Not adequate	8	1.9%	160	37.5%
Cigarette use	Current use	0	0.0%	4	0.9%
	Former use	1	0.2%	21	4.9%
	Never used	18	4.2%	383	89.7%
Excessive Alcohol consumption	Yes	1	0.2%	5	1.2%
	No	18	4.2%	403	94.4%
Current chat consumption	Yes	0	0.0%	7	1.6%
	No	19	4.4%	401	93.9%

5.4. Prevalence of apparent treatment resistant hypertension (controlled and uncontrolled aTRH)

Patients that fulfilled the operational definition for resistant RH (controlled or uncontrolled) were 21(4.9%) out of the total enrolled patients. And 2(0.4%) out of 21(4.9%) of patients had medium to low adherence to antihypertensive medication whereas 19(4.4%) of patients had high adherence. And so only patients with high adherence were finally included into the apparent treatment resistant hypertension 19(4.4%) & those with medium to low adherence 2(0.4%) were regarded as pseudo resistant due to adherence issues (Figure 5).

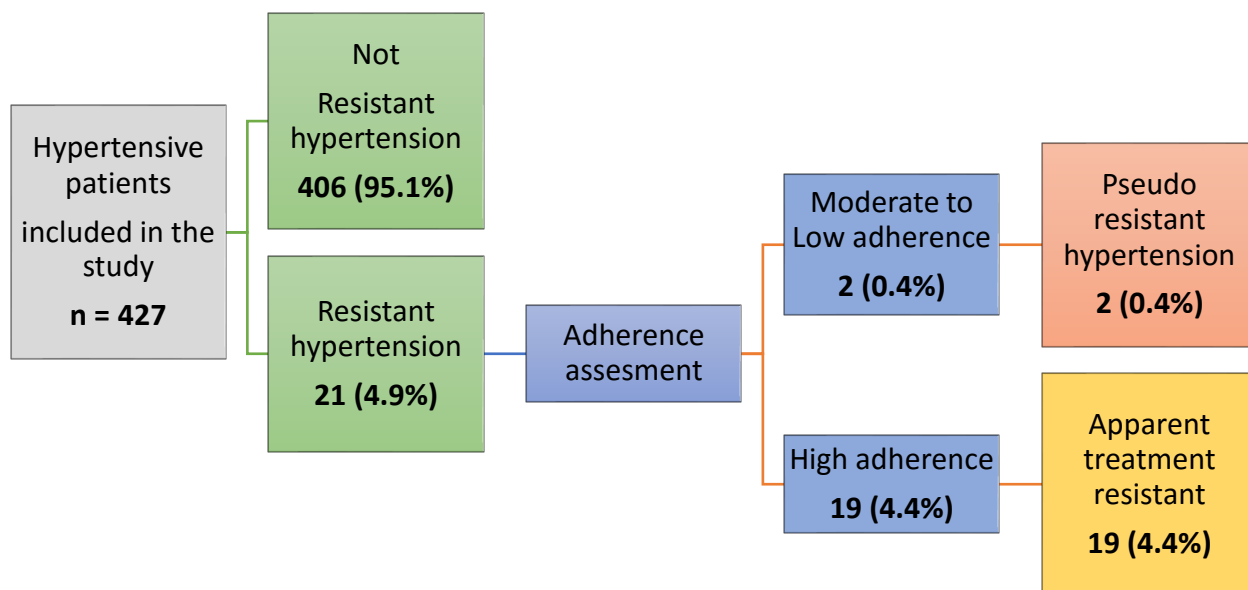


Figure 5 – Prevalence of aTRH and pseudo resistant hypertension

The average SBP of the patients in the entire follow up was 141.5 ± 20.8 mmHg and the average DBP of was 84.7 ± 11.8 mmHg.

Overall, 249 (58.3%) of the patients studied had uncontrolled BP and 178 (41.7%) had controlled BP. In regards to hypertension control among aTRH and non aTRH, 241 (56.4%) of the non treatment resistant patients had uncontrolled BP while 8 (1.9%) of the apparent treatment resistant patients had uncontrolled BP (Table 4).

Table 4 – Hypertension control in apparent treatment resistant hypertension (aTRH) & non apparent treatment resistant hypertension

			aTRH		Total
			Yes	no	
Hypertension control	Controlled	Count & %	11 (2.6%)	167 (39.1%)	178 (41.7%)
	Uncontrolled	Count & %	8 (1.9%)	241 (56.4%)	249 (58.3%)
Total		Count & %	19 (4.4%)	408 (95.6%)	427 (100.0%)

5.5. Factors associated with aTRH

Bivariable logistic regression was done and 6 factors were found to have p value of < 0.2 (these are gender, residence, diabetes mellitus, CKD, NSAID use and excessive alcohol use) (table 4). These variables were then entered into multivariable logistic regression. In the multivariable logistic regression, the presence of CKD as a comorbidity in hypertensive patients was found to be significantly associated with presence of apparent treatment resistant hypertension (P value of <0.05) (table 5).

There was no significant association between other comorbidities (other than CKD) and apparent treatment resistant hypertension. The study also did not find a significant association between aTRH and sociodemographic factors (age, educational status, gender, employment status, monthly income), life style factors (physical activity, smoking cigarette, chat use and excessive alcohol intake), other medical factors (like duration of hypertension, family history of hypertension, use of medications like steroid, antidepressants, NSAIDS or erythropoietin)

Table 5 – Bivariable and Multivariable logistic regression result of factors associated with apparent treatment resistant hypertension

Variable	Category	aTRH		Bivariable logistic regression		Multivariable logistic regression	
		Yes	No	COR	P value	AOR	P value
Gender	Male	13 (6.5%)	187 (93.5%)	2.561(0.955-6.869)	0.062	1.709(0.599-4.879)	0.317
	Female	6(2.6%)	221(97.4%)	1		1	
Residence	Urban	15(3.9%)	367(96.1%)	0.419(0.133-1.322)	0.138	0.442(0.133-1.469)	0.183
	Rural	4(8.9%)	41(91.1%)	1		1	
Diabetes mellitus	Yes	10(9.4%)	96(90.6%)	3.611(1.426-9.145)	0.007	2.154(0.788-5.886)	0.135
	No	9(2.8%)	312(97.2%)	1		1	
CKD	Yes	13(8.5%)	140(91.5%)	4.148(1.543-11.148)	0.005	3.017(1.044-8.717)	0.041*
	No	6(2.2%)	268(97.8%)	1		1	
NSAID use	Yes	5(8.1%)	57(91.9%)	2.199(0.763-6.340)	0.145	1.913(0.622-5.886)	0.258
	No	14(3.8%)	351(96.2%)	1		1	
Excessive Alcohol use	Yes	1(6.7%)	5(83.3%)	4.478(0.497-40.345)	0.181	3.106(0.309-31.252)	0.336
	No	18(4.3%)	403(95.7%)	1		1	

* Indicates p value of <0.05, AOR – adjusted odds ratio, COR – crude odds ratio

1 indicates the reference used

6. Discussion

Even though antihypertensive drugs are being widely used and different treatment strategies are available, patients with hypertension still fail to achieve target BP on 3 antihypertensive medications or require ≥ 4 medications to achieve their BP targets (1,8). According to different studies, Individuals who are classified as having treatment-resistant hypertension (RH) are at an increased risk for target organ damage, morbidity, and mortality despite receiving antihypertensive drug therapy (1). This research is assumed to be the second research done regarding treatment resistant hypertension in this country. According to this study, 19(4.4 %) of the enrolled hypertensive patients were found to have apparent treatment resistant hypertension and 2(0.4%) of patients were found to have pseudo resistance due to adherence problems. Out of the 4.4% of patients found to have aTRH, 8(1.9%) were found to have uncontrolled aTRH and 11(2.6%) were found to have controlled aTRH. Furthermore, the presence of chronic kidney disease as a comorbidity was significantly associated with apparent treatment resistant hypertension.

This study found aTRH on 19 hypertensive patients on follow up at the cardiac and renal clinic, which made the prevalence of apparent treatment resistant hypertension to be 4.4%. This finding is quite lower when compared to the prevalence of RH in another study done in Ethiopia, Mekelle hospital which illustrated aTRH prevalence of 8.6%(11). This difference might have occurred due to several reasons. The first being the study from Mekelle hospital used secondary data from medical registries and couldn't ensure whether BP measurement was done with necessary precautions whereas in this study direct interview with patients at the clinic during their follow up was used and BP measurement precautions were ensured. The second reason is the study done in Mekelle didn't assess adherence using validated scales in the enrolled patients so was not able to exclude patients who had pseudo resistance due to adherence issues. The third reason is study done in Mekelle university used secondary data so did not specify which method was commonly used to measure BP whereas this study used well calibrated Digital sphygmomanometer (oscillometric BP measurement) for BP measurement.

The prevalence of aTRH in this study is also lower when compared to a systematic review & meta-analysis that included 5 studies from Cameroon, Nigeria, Burkina Faso, Lesotho and Algeria which had an overall pooled prevalence of aTRH to be 12.1% and another cross-sectional

study done in five health facilities in Ghana that also found a prevalence of aTRH to be 18.9% (10,20). The reason for this maybe the operational definition of RH used in these African countries was different compared to this study in regards to the BP thresholds used, the number & dose of medications required and whether the presence of diuretic was required to define RH or not. The systematic review and metanalysis done in 5 countries in Africa also included studies that had retrospective study design and adherence to antihypertensive medications was not assessed.

In contrast, the prevalence of aTRH done in this study is higher when compared to a study done in Israel (included around 170, 000 patients), which showed that prevalence of aTRH to be 2.2% but the study only assessed the prevalence of uncontrolled resistant hypertension not controlled RH (39). When considering studies done on a global scale, the prevalence for aTRH in this study is lower when compared to meta-analysis (included 3.2 million patients globally) that found the prevalence of true RH to be 10.3% (9). The reason for this difference may be due to the underrepresentation of Africa (since the number of studies that were included from Africa were 5 out of the total 91 studies) and some of the studies that were included in the metanalysis were retrospective studies and methods of BP measurement as well as the definition of RH used were different among the studies included.

The lower prevalence of aTRH in this study may also be due to failure to escalate the antihypertensive medications in timely manner by physicians since 20.8% of patients with uncontrolled BP were on single antihypertensive medication and 23.4% of patients with uncontrolled BP were on dual antihypertensive medications.

CKD can be the cause or the complication of poorly controlled hypertension. In this study, patients who had CKD as a comorbidity were 3 times more likely to have apparent treatment resistant hypertension (aTRH) than patients without CKD (AOR 3.017, p value <0.05). There are many studies advocating this finding. In a metanalysis that included around 3.2 million patients globally, the prevalence of true RH was higher in patients with CKD (22.9%) & renal transplant (56.0%) (9). Similar finding was also seen in a cross sectional study done in Ghana, which showed there is a 73% higher adjusted risk of aTRH in patients with CKD (20). Two cross-sectional studies, one that were done in northern California (that included 17,466 patients) and the other in southern California (that included 470,386 patients) also showed that CKD patients were 2.1 times and 1.8 times more likely to have resistant hypertension (24,28). These findings show that more

focus should be put on CKD patients treated for Hypertension since they are at an increased risk for CV morbidity and mortality both due to CKD itself and concomitant higher likelihood of resistant hypertension in these patients.

7. Strength of the study

- The study has included adequate sample size of 427 hypertensive patients attending the cardiac and renal clinics
- BP for all patients was measured using well calibrated Digital sphygmomanometer (oscillometric BP measurement) and since the data collection was also made by direct interview it was possible to measure BP using the standard precautions needed
- The study was able to assess adherence using the Morisky Green Levine adherence scale 8 and was able to find patients with pseudo resistance.
- The study was also able to collect sociodemographic data and life style related factors since the mode of data collection for the study was both from direct interviews and medical records
- To my knowledge, this is the second study on the subject of resistant hypertension among our country Ethiopia. And so, it can contribute to the global efforts that are being made to determine the prevalence of resistant hypertension and identify factors associated with it.

8. Limitation of the study

- The prevalence of resistant hypertension might be an over estimation since the study was not able to rule out white coat effect using 24 hr ambulatory BP measurement. 24 hr Ambulatory BP measurement was not done because the sample size of the study was large which resulted in inadequate time left in the study period to filter out patients with resistant hypertension and then appoint them for ambulatory BP measurement (AMBP).
- The study did not include other clinics like endocrine clinics and it did not include other tertiary care centers other than SPHMMC which might have under estimated prevalence of apparent treatment resistant hypertension
- The study design was cross sectional and so it is unable to affirm the causal relationship between the variables and treatment resistant hypertension
- Since the study was conducted in a tertiary care center the results may not be representative of the general population, primary or secondary health care centers
- This study did not assess association between diet (salt intake, fruit and vegetable intake) and resistant hypertension in an objective manner and these factors may have effect on blood pressure

- The mode of BP measurement was digital sphygmomanometer and the BP cuff size for the device allows only arm circumference of 22 to 45 to be measured and due to this reason patients with arm circumference of < 22 and > 45 cm were excluded from the study.
- Even though BP measurement precautions were adhered to there were patients in whom we could not use the dominant arm especially in the renal clinic since those patients had AV fistula created for dialysis purposes or injury to their dominant arm.

9. Conclusion

Prevalence of apparent treatment-resistant hypertension and pseudo resistant hypertension among hypertensive patients on follow up at cardiac and renal clinic in SPHMMC is 4.4% and 0.4% respectively. Hypertensive patients that had chronic kidney disease as a comorbidity were more likely to have apparent treatment resistant hypertension compared to those patients that did not have CKD (P value of <0.05).

10. Recommendation

Apparent treatment resistant hypertension is not uncommon and patients with resistant hypertension should be worked up for comorbidities (especially associated renal abnormalities) and timely measures should be taken to control their blood pressure to target levels. And more emphasis should be put for future studies to estimate the prevalence of true resistant hypertension.

Regular reminders by physicians to patients regarding the benefit of adherence to antihypertensive medications and adequate physical activity as well as timely escalation of medications in patients who have uncontrolled BP may help reduce the high number of patients with uncontrolled hypertension.

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Annex

1. Consent form (verbal)

1.1. Consent form in English

This questionnaire is prepared for collection of data on the prevalence of apparent treatment resistant hypertension and associated risk factors among hypertensive patients on follow up at cardiology and nephrology clinic of SPHMMC. This research is conducted by Dr. Haimanot Behailu who is a third-year Internal medicine resident in SPHMMC.

Participation in this study will involve an interview regarding your sociodemographic status, lifestyle related and medical related questions and the interview will take about 15 minutes. There are no known or anticipated risks to you for participating. Although this study will not benefit you personally, we hope that our results will add to the knowledge about prevalence and factors associated with resistant hypertension.

The information that you provide during this study will be kept confidential and all of your responses will be held anonymous. Only the researchers will have access to the questionnaires and the information that you provide.

Your participation in this study is voluntary and you have the right to refuse to participate, the right to withdraw at any time for any reason & the right to refuse to answer any individual question without penalty.

If you have any question, you can contact the investigator at any time that is convenient for you using the following address:

Principal investigator

Name - Dr Haimanot Behailu

Phone number - +251-9-00 64 56 84

Address - Addis Ababa, Ethiopia

E-mail - wond.haimi@gmail.com

Do you agree to participate in this study?

A. yes

B. No

The participant has received sufficient information about the study from the information sheet above by the explanation provided by _____ and has agreed to voluntarily participate in this study.

Signature of investigator: _____ Date: _____

1.2. Consent form in Amharic

ይህ መጠይቅ የተዘጋጀው በጳውሎስ ሆስፒታል የልብ እና የኩላሊት ህክምና ክሊኒክ ለደም ግፊት በሽታ ክትትል የሚያደርጉ ታካሚዎች ውስጥ፣ ሶስት እና ከዚያ በላይ የደም ግፊት መደሃኒት የሚያስፈልጋቸውን የታካሚዎች መጠን እና ተያያዥ ምክንያቶች ላይ መረጃ ለመስጠት ነው። ይህ ጥናት የሚደረገው በጳውሎስ ሆስፒታል የሶስተኛ ዓመት የውስጥ ደዌ ተማሪ በሆነችው በዶ/ር ሀይማኖት በኃይሉ ነው።

ቃለ መጠይቁ ስለእርስዎ የስነ ሕዝብ አወቃቀር ሁኔታ፣ የአኗኗር ዘይቤ እና ከሕክምና ጋር የተያያዙ ጥያቄዎችን ያካትታል እና ቃለ መጠይቁ 15 ደቂቃ ያህል ይወስዳል። በመሳተፍዎ በእርስዎ ላይ ምንም የሚታወቁ ወይም የሚጠበቁ አደጋዎች የሉም። ምንም እንኳን ይህ ጥናት እርስዎን በግል ባይጠቅምም የጥናቱ ውጤት በበሽታው ላይ ያለንን እውቀት ይጨምራል ብለን ተስፋ እናደርጋለን።

በዚህ ጥናት ወቅት የሚያቀርቡት መረጃ በሚስጥር ይጠበቃል ፣ ለጥያቄዎቹ የሚሰጡን መልስዎችም የዕርስዎን ማንነት የሚገልጹ አይሆኑም። መጠይቆቹን እና እርስዎ የሚሰጡትን መረጃ ማግኘት የሚችሉት ተመራማሪዎቹ ብቻ ናቸው።

በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ በፈቃደኝነት ነው እናም ለመሳተፍ ፈቃደኛ አለመሆን፣ በማንኛውም ጊዜ እና በማንኛውም ምክንያት ከቃለ መጠይቁ የመውጣት መብት እና ማንኛውንም ጥያቄ ያለ ምንም ቅጣት መልስ ያለመስጠት መብት አለዎት።

ማንኛውም አይነት ጥያቄ ካለዎት በሚከተለው አድራሻ እና በሚመችዎት ጊዜ መርማሪዎን ማነጋገር ይችላሉ።

ዋና መርማሪ

ስም - ዶ/ር ሀይማኖት በኃይሉ

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በዚህ ጥናት ለመሳተፍ ተስማምተዋል?

ሀ. አዎ

ለ. አይ

ተሳታፊው ስለ ጥናቱ ከላይ ካለው የመረጃ ወረቀት በ_____ በተሰጠው ማብራሪያ መሰረት በቂ መረጃ አግኝተዋል እናም በዚህ ጥናት ውስጥ በፈቃደኝነት ለመሳተፍ ተስማምቷል።

የመርማሪው ፊርማ _____ ቀን _____

2. Blood pressure measurement instructions

- a. BP should be measured with a well calibrated Digital sphygmomanometer (oscillometric BP measurement).
- b. The dominant arm should be used for BP recording.
- c. Adult cuff size should be used for all patients.
- d. Participants should be advised to empty their bladder if needed.
- e. No smoking, food, exercise, or intake of caffeine within 30 minutes preceding the measurement should be ensured.
- f. Participants should be seated comfortably preferably in quiet environment for 5 min before beginning the BP measurements.
- g. The BP cuff should be positioned at the level of the heart, with the participant's back and arm supported, legs uncrossed and feet flat on the floor.
- h. No talking during measurement.
- i. BP will be rechecked after 5 minutes.

3. Data collection checklist

3.1. Data collection checklist in English

Chart no.		
Socio demographic factors related questions		
Age		
Sex	Male	Female
Educational status	Tertiary Secondary Primary None	
Location of residence	Urban	Rural
Occupation	Governmental Nongovernmental Self employed Unemployed	
Monthly Income		
Medical related questions		
Family history of hypertension	Yes	No
Duration of hypertension (in terms of years)		

Comorbidities	Diabetes mellitus Ischemic heart disease (IHD) Chronic kidney disease Dyslipidemia Stroke Other, specify		
BMI		Weight	Height
Arm circumference (in cm)			
Current BP of patient			
Repeat BP of patient (after 5 min rest)			
List the antihypertensive drugs the patient is on and dose and frequency			
Is the patient on 3 or more antihypertensives with one of them being diuretic?	Yes	No	
If the answer to the above question is yes, are 3 of the antihypertensive medications (including the diuretic) at maximum dose or at optimally tolerated dose for the patient?	Yes	No	

Other medications the patient is on other than antihypertensives	Steroid NSAID Antidepressants Erythropoietin Others, specify	
Adherence assessment		
1. Do you sometimes forget to take your medication?	Yes	No
2. People sometimes miss taking their medication for reasons other than forgetting. Over the past 2 weeks were there any days when you did not take your medication?	Yes	No
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	Yes	No
4. When you travel or leave home do you	Yes	No

sometimes forget to bring your medication?		
5. Did you take all your medication yesterday?	Yes	No
6. When your symptoms are under control, do you sometimes stop taking your medication?	Yes	No
7. Taking medication every day is real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	Yes	No
8. How often do you have difficulty remembering to take all your medication?	Never/ rarely Once in a while Sometimes Usually All the time	
Lifestyle related questions		
Physical activity	Adequate	Not adequate
Cigarette use	Current use Former use Never used	

Excess alcohol consumption	Yes	No
Chat consumption (current)	Yes	No

3.2. Data collection checklist in Amharic

ቁጥር		
ከስነ ሕዝብ አወቃቀር ጋር የተያያዙ ጥያቄዎች		
እድሜ		
ጾታ	ወንድ	ሴት
የትምህርት ደረጃ	ሶስተኛ ደረጃ ሁለተኛ ደረጃ አንደኛ ደረጃ ምንም	
የመኖሪያ ቦታ	ከተማ	ገጠር
የሥራ ዓይነት	የመንግስት የመንግስት ያልሆነ የግል ስራ ምንም	
ወርሃዊ የገቢ መጠን		
ከህክምና ጋር የተያያዙ ጥያቄዎች		
በቤተሰብ ውስጥ የደም ግፊት በሽታ ያለበት ሰው አለ ወይንስ የለም	አለ	የለም

የደም ግፊት በሽታ አለብዎት ከተባሉ ምን ያህል ጊዜ ሆነ (በአመታት)			
የተጓዳኝ በሽታዎች ዝርዝር	የስኳር በሽታ የልብ በሽታ (ዲስኬሚክ ሀርት ዲዚዝ) የኩላሊት በሽታ (ክሮኒክ ኪድኒ ዲዚዝ) ዲስሊፒዲሚያ ስትሮክ ሌሎች _____		
የሰውነት ብዛት መረጃ ጠቋሚ (ቦዲ ማስ ዲጋይዝስ)		ክብደት	ቁመት
የክንድ ዙሪያ በ ሳንቲ ሜትር			
የታካሚው የአሁን የደም ግፊት መጠን			
ሁለተኛ የታካሚው የደም ግፊት መጠን (ከ 5 ደቂቃ እረፍት በኋላ)			
በሽተኛው የሚወሰደውን የደም ግፊት መድሃኒቶችን ዝርዝር፣ መጠን እና የአወሳሰድ ሁኔታ			
በሽተኛው ሶስት እና ከዚያ በላይ የደም ግፊት መድሃኒቶችን (ከሶስቱ አንዱ ዳዩሬቲክ የሆነ) እየወሰደ ነው?	አዎ	አይደለም	
ከላይ ላለው ጥያቄ መልሱ አዎ ከሆነ፣ ሶስቱ የደም ግፊት መድሃኒቶች (ከሶስቱ አንዱ ዳዩሬቲክ የሆነ) የመጨረሻ ከፍተኛ መጠናቸው ላይ	አዎ	አይደለም	

ናቸው ወይም ለታካሚው መሰጠት በሚችለው መጠን ላይ ናቸው ?		
በሽተኛው ከደም ግፊት መድሃኒቶች ውጪ የሚወስዳቸው መድሃኒቶች ስም ዝርዝር	ስቴሮይድ ስቴሮይድ ያልሆነ አንታይ ዒንፍላማቶሪ መድሃኒት አንታይ ዲፕሪሳንት ዒሪትሮፖፔቲን ሌሎች _____	
የመድሃኒትን ወሳሰድ ሁኔታ		
1. አንዳንድ ጊዜ መድሃኒትዎን መውሰድ ይረሳሉ?	አዎ	አይ
2. ሰዎች አንዳንድ ጊዜ መድሃኒቶቻቸውን በመርሳት ሳይሆን በሌሎች ምክንያቶች ላይወስዱ ይችላሉ። ባለፉት 2 ሳምንታት መድሃኒትዎን ያልወሰዱባቸው ቀናት ነበሩ?	አዎ	አይ
3. መድሃኒትዎን ሲወስዱ ስላልተስማማዎት፣ ለሐኪምዎ ሳይናገሩ መጠኑን ቀንሰው ወይም ሙሉ-ለሙሉ ሳይወስዱ ቀርተው ያውቃሉ?	አዎ	አይ
4. ሲጓዙ ወይም ከቤት ሲወጡ አንዳንድ ጊዜ መድሃኒትዎን ይዘው መሄድ ይረሳሉ?	አዎ	አይ
5. ትላንትና ሁሉንም መድሃኒቶችን ወስደዋል?	አዎ	አይ
6. የሕመም ምልክቶችዎ ሲቀንሱ፣ አንዳንድ ጊዜ	አዎ	አይ

መድሃኒትዎን መውሰድ ያቆማሉ?		
7. በየቀኑ መድሃኒት መውሰድ ለአንዳንድ ሰዎች ምችት ሊያሳጣ ይችላል፤ የህክምና እቅድዎ ለመከተል ተቸግረው ያውቃሉ?	አዎ	አይ
8. ሁሉንም መድሃኒቶችዎን አስታውሰው ለመውሰድ ምን ያህል ጊዜ ተቸግረው ያውቃሉ?	በጭራሽ/አልፎ አልፎ ከስንት አንዴ አንዳንዴ አብዛኛውን ጊዜ ሁልጊዜ	
ከአኗኗር ዘይቤ ጋር የተያያዙ ጥያቄዎች		
አካላዊ እንቅስቃሴ	በቂ ነው	በቂ አይደለም
የሲጋራ አጠቃቀም	አሁን ይጠቀማሉ በፊት ይጠቀሙ ነበረ መቼም ተጠቅመው አያውቁም	
የአልኮል አጠቃቀም (ከመጠን በላይ)	ይጠቀማሉ	አይጠቀሙም
የጫት አጠቃቀም (አሁን ላይ)	ይጠቀማሉ	አይጠቀሙም

4. Information sheet

Research title: Prevalence of apparent treatment resistant hypertension and associated risk factors among hypertensive patients attending cardiology and nephrology follow up at St Paul hospital millennium medical collage

Principal investigator: Dr Haimanot Behailu (Internal Medicine Resident)

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Advisors: Dr Fetene Adamu (Consultant Internist, Cardiologist)

: Mr Hailemichael Bizuneh (BSc, MPH)

Sponsor: St. Paul's Hospital Millennium Medical Collage

5. Assurance of investigator

I the undersigned resident agree to accept all responsibilities for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Research and Publication Directorate and /or Department of Public Health of St. Paul's Hospital Millennium Medical College.

Name of the Resident: _____

Signature: _____

Date: _____

Approval of Advisors

Name of Public Health Advisor: _____

Signature: _____

Date: _____

Name of Clinical Advisor: _____

Signature: _____

Date: _____