Prevalence of uncontrolled hypertension and the pharmacogenomics of enalapril-induced adverse effects among patients in the Vhembe district

By

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Abstract

Introduction:

Controlling blood pressure (BP) among individuals with hypertension is important in the prevention of cardiovascular diseases (CVDs). However, maintaining optimal BP levels in individuals who are prone to drug-induced adverse reactions remains a challenge. Nonetheless, the magnitude of uncontrolled hypertension and drug-induced adverse reactions as well as contributing risk factors remain elusive, particularly among individuals residing in the rural areas of South Africa. Thus, establishing the magnitude of uncontrolled hypertension and understanding the complexity of drug-induced adverse reactions as well as associated risk factors, is important in determining appropriate intervention strategies. This study aims to:

(1) To investigate the prevalence and factors associated with uncontrolled hypertension among individuals receiving chronic care in facilities located in the Vhembe district of the Limpopo Province.

(2) To determine factors associated with non-adherence and adverse drug reactions among adult patients clinically diagnosed with hypertension.

(3) To investigate the association between 12 selected genetic markers and enalapril-induced adverse reactions (dry cough and hyponatremia) among patients with hypertension.

Methods: A total of 402 patients with hypertension were recruited from four healthcare facilities in the Vhembe municipality of the Limpopo province. Participants with Systolic arterial Pressure (SAP) ≥ 140 Millimetre mercury (mmHg) and diastolic blood pressure (DBP) ≥ 90mmHg were characterised as uncontrolled, as per the South African Hypertension Society guidelines. Adherence to prescribed drugs and adverse drug reactions (ADRs) including dry cough were self-report. At the same time, hyponatremia was determined by reviewing blood chemistry results from

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each patient's medical records. The 12 selected single nucleotide polymorphisms (SNPs) were genotyped using a Mass-Array system. Logistic regression (adjusted and unadjusted) and chi-square models were used to determine factors associated with uncontrolled hypertension and non-adherence. In addition, the methods were also used to further determine the association between selected SNPs and enalapril-induced ADRs (Dry cough and hyponatremia).

Results

Study one: A total of 402 participants were recruited, of whom 344 (85.57%) were female and 58 (14.43%) were male. About 49.0% of the study participants were ≥66 years of age and 90.05% belonged to the Venda ethnic group. The prevalence of uncontrolled hypertension was estimated at 38.56% (n=155). The Unadjusted logistic regression model analysis showed that participants taking three anti-hypertensive drugs (COR =0.18, 95%CI 0.03-0.95) were less likely to exhibit uncontrolled hypertension. After adjusting for confounding factors, the adjusted logistic regression model analysis showed that participants who were taking 2 (AOR=0.13, 95%CI 0.02-0.75), 3 (AOR=0.13; 95%CI 0.02-0.74), 4 (AOR=0.17; 95%CI 0.03-0.97) drugs, participants who did not experience ADRs (AOR=0.54; 95%CI 0.29-0.99), along with those who did not have diabetes mellitus (AOR=0.57; 95%CI 0.34-0.93) were less likely to exhibit uncontrolled hypertension.

Study two: Out of 407 participants, 77 (19.15%) reported the incidence of ADRs. Furthermore, the prevalence of non-adherence was estimated at 14.43% (n=58). The chi-square analysis showed significant relationships (P< 0.05) between the number of drugs, ADRs and non-adherence. The logistic regression model analysis showed that participants who experienced ADRs [(COR=0.38, 95%CI 0.21-0.70); (AOR=0.47, 95%CI 0.24-0.92)], and participants who were taking more than three drugs (AOR=0.20, 95%CI 0.07-1.80) were less likely to adhere to their prescribed medication.

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Study three: One hundred individuals on enalapril therapy were recruited; of whom, 85% were female, 66% (n=50) were over the age of 50 years, and 76% had been living with hypertension for more than 5 years. About 18% (n=18) of the study cohort reported an incidence of enalapril-induced dry cough, while 19% (n=19) exhibited hyponatremia. No significant associations were detected between an enalapril-induced dry cough and the 12 selected SNPs. On the other hand, the adjusted logistic regression model analysis showed that carriers of the TT genotype (AOR=10.95, 95%CI 1.35-88.77) and T allele (AOR=2.80, 95%CI 1.18-6.70) SNP rs6749447 were more likely to exhibit hyponatremia.

Conclusion: This investigation revealed a high prevalence of uncontrolled hypertension that may be associated with the presence of DM, ADRs and the number of prescribed anti-hypertensive drugs. The study also demonstrated a high prevalence of ADRs and non-adherence that may be attributed to the number of prescribed drugs and ADRs. Furthermore, the study found no association between the selected SNPs and enalapril induces Dry cough. However, an association was observed between the TT genotype, T allele of rs6749447 and enalapril-induced hyponatremia. These results indicate that medical practitioners should pay close attention to ADRs, prescription patterns of antihypertensive drugs, adherence, and comorbidities to improve hypertension control and prevent resource misuse in the Vhembe district and other settings. Although no association was observed between an enalapril-induced dry cough and the selected SNPs, the study provided first-time evidence of the association of genetic polymorphisms with enalapril-induced hyponatremia. Furthermore, the current study has laid a foundation for more pharmacogenomics studies in Africa, particularly those focusing on drug-induced ADRs.

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Keywords

Hypertension South Africa

Vhembe district

Enalapril

Drug adverse reaction

Pharmacogenetics

Single nucleotide polymorphism

Genetics

Enalapril-induced dry cough.

Enalapril-induced hyponatremia.

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Declaration

I, Rendani Musoliwa, declare that "***Prevalence of uncontrolled hypertension and the pharmacogenomics of enalapril induced adverse effects among patients in Vhembe district***" is my work, that it has not been submitted before for any degree or examination in any other university and that all the sources I have used or quoted have been indicated and acknowledged as complete references.

Full name...Musoliwa Rendani..... Date.....26/07/2022.....

Signed..... .....

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Dedication

This work is dedicated to my wonderful parents,

Musoliwa Phelemon Fhambanani and Nekhumbe Elisah Naledzani.

Thank you so much for the invaluable life lessons that will forever be imprinted on my heart.

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Abbreviations

ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ADRB2	Beta-2 adrenergic receptors
ADRs	Adverse drug reactions
AOR	Adjusted odds ratio
BDKRB2	Bradykinin receptor B2
BP	Blood pressure
CCB	Calcium channel blockers
COR	Crude odds ratio
CVDs	Cardiovascular diseases
DBP	Diastolic blood pressure
DFGC	Donald Fraser gateway clinic
DM	Diabetes mellitus
HCTZ	Hydrochlorothiazide
KKS	Kallikrein-kinin system
mmHg	Millimetre mercury
Mmol/L	Millimoles per litre
NOS3	Nitric oxide synthase 3
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system

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SAP	Systolic arterial Pressure
SSA	Sub-Saharan Africa
SLCO1B1	Solute carrier transporter O1B1
SNP	Single nucleotide polymorphisms
STK39	Serine/Threonine Kinase 39
WECHC	William Eddie Community health centre
WHO	World health organisation

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Chapter 1: Introduction

The prevalence of non-communicable diseases such as hypertension, diabetes mellitus (DM) and obesity is increasing at an alarming rate worldwide (1). Hypertension alone accounts for 7.5 million global deaths (2). In Africa, it is estimated that hypertension contributed to approximately 900 000 deaths in 2016, making up 10% of all deaths in the continent (3). Furthermore, studies have shown that people with hypertension are most likely to develop stroke and coronary artery disease (4, 5). At the same time, others have shown that hypertension accelerates the progression of diabetic nephropathy, retinopathy, and neuropathy (6, 7). Thus, hypertension should be managed and controlled to limit the risk of developing associated complications and premature death (8). Nonetheless, the world has seen an increasing prevalence of uncontrolled hypertension even with the availability of various effective therapeutic drugs (9-13). It has been estimated that less than 35% of patients undergoing treatment achieve optimum Systolic arterial Pressure (SAP) >140 Millimetre mercury (mmHg) and or diastolic blood pressure (DBP) >90 mmHg) (Zhou et al., 2021). On the other hand, only 7% of patients in sub-Saharan Africa (SSA) achieve blood pressure (BP) control (14). Different antihypertension drugs such as angiotensin-converting enzyme inhibitors (ACEi), thiazide diuretics, calcium channel blockers (CCBs), beta-blockers, long-acting and angiotensin II receptor Blockers have demonstrated benefits in controlling hypertension (15, 16). However, several factors often hinder their effectiveness, including non-adherence and adverse drug reactions (ADRs) (17). The determinants of non-adherence include lack of knowledge, polypharmacy, and ADRs (18). While ADRs have been associated with similar factors, including genetics (19-21). The implication of genetic factors with response therapeutic drugs has led to a new branch of science known as precision medicine (22). Precision medicine is informed by pharmacogenomics studies, which have demonstrated that single nucleotide

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polymorphisms (SNPs) occur in genes that are directly or indirectly associated with hypertension and the pathways of anti-hypertensive drugs were associated with drug response (23). This leads to the aim of this branch of sciences which is to use an individual's unique clinical, molecular and lifestyle information to guide the treatment and prevention of diseases and ADRs. However, the potential limitations of precision medicine are the underrepresentation of African populations in genomics research, especially in research that concerns anti-hypertensive drugs, as well as the lack of public health data quantifying the extent of uncontrolled hypertension as well as related factors such as non-adherence and ADRs.

To bridge this knowledge gap, we designed a cross-sectional study to evaluate the extent of uncontrolled hypertension and the associated factors in the rural district of Vhembe (**Chapter 3**). We further evaluated the prevalence and factors associated with adherence as well as ADRs (**Chapter 4**). Numerous research suggests that dry cough and hyponatremia are among the most prominent ADRs experienced by patients undergoing antihypertensive therapy and are associated with the use of ACEi. Thus, the study was extended to investigate the association between SNPs and the occurrence of enalapril-induced adverse reactions (**Chapter 5**). The main conclusions of the study and prospects are summarised in **Chapter 6.**

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Chapter 2: Literature review

2.1 Prevalence of hypertension

Hypertension is a non-communicable disease with a significant health burden, affecting more than 1 billion individuals globally (24-26). Studies have shown that the prevalence of hypertension is progressively growing in low and middle-income nations (27, 28). According to Gómez-Olivé, Ali (29), South Africa has the highest prevalence of hypertension. It was further demonstrated that 44% of South African men and 46% of women had hypertension in the year 2016 (30). If left unattended, these figures are expected to double in the next few years (31).

2.2 Pathophysiology and Clinical Features of Hypertension

The pathophysiology of hypertension is related to the cardiovascular system, which results from the system's failure to normalize BP (32). Thus, hypertension is defined as the force or pressure exerted on the blood vessels (33). The peak pressure created against arterial walls when the heart pumps out is SAP, and it is considered normal when it is below 120 mmHg (34). SAP is directly proportional to the amount of blood released by the heart (stroke volume); as the volume increases, SAP also increases (35). At the same time, the lowest pressure in the artery at the beginning of the cardiac cycle when the ventricles are at rest and refilling is called DBP and is typically regarded as normal when it is below 80 mmHg (34).

Various physiological changes play an important role in the development of hypertension, (36) including an irreversible rise of peripheral resistance resulting from prolonged smooth muscle constriction likely mediated by angiotensin. This leads to calcium influx that causes the thickening of the arteriolar vessel walls (37). Overexpression of vasoconstrictor angiotensin II has also been demonstrated to induce elevated BP (38). Furthermore, angiotensin II also stimulates the release

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of the steroid hormone aldosterone, which causes an increase in sodium reabsorption, thus leading to increased BP (39). Other physiological changes involve the constant release of catecholamine by the sympathetic nervous system in response to stress, leading to increased heart rate, cardiac output, and BP (40). The increase in BP alters the balance between vasopressor and vasodilator processes in the cardiovascular system (41), thus posing a severe risk for other Cardiovascular diseases (CVDs) such as arrhythmias and myocardial-or cerebral infarction (42).

2.3 Uncontrolled hypertension

Despite the availability of hypertension treatments, many people who suffer from the disease remain uncontrolled (43). Uncontrolled hypertension is characterised BP of ≥ 140/90 mmHg, which persists despite administering antihypertensive medication (44). Trends of uncontrolled hypertension have been documented in countries such as the United Kingdom (38.1%) (45), China (43.5%) (46) and Switzerland (59.2%). In SAA, countries such as Botswana, Zimbabwe, Nigeria and South Africa reported a prevalence of up to 60% (47-50). These numbers are a clear indication that uncontrolled hypertension is a significant public health challenge among hypertensive patients in low-income countries (51).

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2.3.1 Risk factors associated with uncontrolled hypertension.

Uncontrolled hypertension is multifactorial and is mediated by various factors such as age, sex, body mass index, un-recommended, lack of physical exercise, alcohol consumption, number of medications, salt intake, comorbidities, smoking nicotine-containing substances, and non-adherence to antihypertensive drugs.

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2.3.1.1 Age

Uncontrolled hypertension is common among older adults, and they account for a larger portion of all hypertension-related morbidities and mortalities (52-55). Hypertension among the elderly is associated with changes affecting haemostatic balances, including sodium levels (56). Furthermore, hypertension control in the elderly might further be affected by physiological function decline and decreased stress tolerance (53). Hormones in women before menopause have been shown to protect them against hypertension and CVDs (57). Thus, young women tend to have better hypertension control in comparison to older women (58), (59, 60).

2.3.1.2 Body mass index

Body Mass Index is a simple calculation that takes into consideration a person's height and weight. Increased obesity determined by body mass index categories >30 kg/m^2 was associated with the risk of hypertension as well as a poor control (61). It was further demonstrated that obese individuals with uncontrolled hypertension have a high risk of cardiovascular mortality in comparison to patients of normal weight (62). This may be attributed to the lipolysis of fat cells, which tend to produce large quantities of inflammatory cytokines, thus increasing BP above acceptable levels (63). Furthermore, obesity was associated with elevated expression of vasoconstrictor angiotensin II and aldosterone related, which are known triggers of BP elevation (64).

2.3.1.3 Diet and Physical Exercise

Consumption of high-BP-promoting foods and beverages, such as salt and caffeine, contributes to uncontrolled hypertension (65, 66). A high salt diet plays a significant role in water retention that builds up in the system, resulting in high BP (67). Physical exercise benefits BP control (68-70).

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Furthermore, physical inactivity has associated with uncontrolled hypertension and the risk of developing CVDs (71-74).

2.3.1.4 Alcohol and Smoking Status

Taking the medication with substances such as alcohol and other drugs interferes with the mechanism of drugs (75). For instance, nicotine elevates pulse rate, plasma-free fatty acids, hyperglycaemia, and increased catecholamine in the blood, which may affect BP control (76). While alcohol consumption causes hemodynamic changes, such as increased heart rate, and left ventricular function (77). Additionally, long-term alcohol use has been associated with metabolic changes that cause obesity and may affect BP control (78). Studies have demonstrated that reducing the intake of these substances is essential for hypertension control (79-81).

2.3.1.5 Non-adherence

Other factors associated with uncontrolled hypertension include not adhering to medication (82, 83). Between 20%–60% of patients on anti-hypertensive therapy do not adhere to their medication (84-86). Medication adherence can be defined as the degree to which a person's behaviour corresponds with the recommended dosing regimen, including time, dosing, and interval of medication intake (87-89). There are several ways in which patients may not adhere to medication including fulfilment non-adherence, also known as primary non-adherence, where medication has been prescribed, but the patient never initiates it or uses it (90). Patients may also stop the medication they have initiated intentionally or unintentionally, this non-adherence is called non-persistence (90, 91). Furthermore, another type of non-adherence is called non-conforming, where patients may take medication incorrectly, such as taking medication at the wrong times, taking small or more doses than prescribed, or even kipping doses at times (92).

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2.4 Factors Associated with Non-adherence to Medication.

Various factors influence patients' decision to stop adhering to a prescribed drug (93). Amongst those factors is polypharmacy, as some patients feel overwhelmed by taking too many drugs and decide to quit (94). While some patients stop adhering because they believe they do not need medication if BP readings are normal (17). Furthermore, patients who feel that medications worsen their condition by having adverse effects are likely to stop adhering to that medication (18, 95) 2019). Besides contributing to poor adherence, ADR negatively impacts an individual's health (96).

2.4.1 Age and Sex

The association between non-adherence to medication association, age and sex is complicated and needs better interpretation as some studies have reported different findings (97). Several studies found that young people are less adherent to medication (98-101), while others showed that older patients are less likely to adhere to their medication (102, 103). Young individuals are considered less concerned about their health than the elderly (104). While non-adherence in the elderly is influenced by a widespread misconception regarding the efficiency and safety of modern drugs (84). Furthermore, health factors in old age such as arthritis, visual impairment, and hearing, may also interfere with their capacity to take medication. On the other hand, some studies found that women were more likely than men to not adhere to prescribed drugs (105, 106), while others found that this is not the case (107, 108). Different perceptions of health issues may be the leading factors influencing gender-specific non-adherence. Men who believe their medication may not work tend to stop adhering to treatment. In contrast, women are more likely to consult and renew their prescriptions (109), (110).

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2.4.2 Polypharmacy

Polypharmacy is treating one or more coexisting conditions or diseases with different drugs (111). For example, most studies and guidelines recommend using different anti-hypertensive drugs to manage hypertension (44, 112-114). However, antihypertensive drug combinations have been linked

to more adverse drug reactions when compared to monotherapy (115). Furthermore, hypertension is a risk factor for other conditions, such as DM and cardiovascular conditions, requiring drug treatment; thus, most hypertensive patients end up using multiple drugs (116). Consequently, polypharmacy may lead to ADRs, extended hospital admission and readmissions (117), which might discourage patients from adhering to multiple drugs.

2.4.3 ADRs

The World health organization (WHO) defines ADRs as a noxious, unintended effect of a drug that occurs in doses typically used in humans for the diagnosis, prophylaxis, and treatment of disease (118). ADRs are difficult to predict and may not be picked up during animal models and human trials (119). ADRs may develop a negative perception of patients' physical and mental health, leading them to negatively perceive prescribed drugs (120). Furthermore, in South Africa, ADRs are known to cause adult deaths and hospital admissions (121). Due to these reasons, patients may become reluctant to take their medications if they notice ADRs. Therefore, there is a need for proper reporting and systematic surveillance of ADRs to boost patient confidence and save lives (122). This can also be achieved by knowing the different antihypertensive drugs, mechanisms and possible ADRs (Alomar, 2014)

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2.5 Antihypertensive drugs mechanism and ADRs.

Different antihypertensive drugs with different modes of action have been produced, and are commercially available (65, 123, 124). However, the South African hypertension guidelines recommend hydrochlorothiazide (HCTZ), enalapril, and amlodipine as first-line drugs (44).

2.5.1 Therapeutic Effects of HCTZ and Associated ADRs

Hydrochlorothiazide is a thiazide diuretic that remains one of the most prescribed drugs in South Africa (72). This drug reduces BP by blocking the transport of sodium and chloride ions (125). However, despite its high prescription status, this drug has been reported to have several ADRs, such as hypokalaemia, impaired glucose tolerance and increased serum cholesterol and uric acid levels (126). Susceptibility to these adverse reactions may be associated with the inter-individual variation, age, gender, and ethnicity (127).

2.5.2 Therapeutic Effects of Amlodipine and Associated ADRs

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Another class of drug that is highly prescribed is amlodipine (128) Amlodipine alleviate BP by blocking the influx of calcium ions into vascular smooth muscles, cardiac myocytes, and cardiac nodal tissues (129), resulting in vasodilation of vascular smooth muscles, and reduction in heart rate (129). Most ADRs induced by amlodipine occur during treatment initiation and they include headaches, heart palpitation, oedema, and constipation (130).

2.5.3 Therapeutic Effects of Enalapril and Mechanisms Associated with ADRs

Enalapril is an angiotensin enzyme inhibitor recommended as a first-line drug (131). This drug elicits its antihypertensive activity by inhibiting the production of angiotensin-II, which plays a significant role in vessel constriction (132). In addition, inhibition of angiotensin-II also elevates the concentrations of bradykinin, a vasodilator molecule (133). This indicates that this drug has

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two modes of action through which BP can be lowered (134). However, even with these benefits, studies have reported common ADRs associated with the drug and they include dry cough, reduced sodium level, increased blood creatinine, headache, angioedema, dizziness, and weakness (135-137).

2.5.3.1 Dry cough

Dry cough is the most prominent enalapril-induced ADR (138-141). Enalapril-induced dry cough is characterized by an irritating sensation in the throat (142). The most commonly accepted theory is that dry cough is stimulated by the accumulation of bradykinin and substance P in the respiratory tracts, which leads to bronchoconstriction (143). Furthermore, it has been suggested that enalapril-induced ADRs may be associated with its long T half-life (11 hours), which leads to the prolonged suppression of angiotensin II and the accumulation of bradykinin and substance P (143). The prevalence of enalapril-induced dry cough is reportedly between 5 and 35% (144). Previous studies have shown that enalapril-induced dry cough is not dose-dependent, and it is most common in non-smokers than smokers (145-147). At the same time, other studies demonstrated that it is more common in women than in men (148).

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2.5.3.2 Decreased Sodium (Hyponatremia)

Hyponatremia is the most common electrolyte abnormality that lands patients in hospitals and is associated with increased morbidity and mortality (149, 150). Hyponatremia is defined as a serum sodium concentration below 135 millimoles per litre (mmol/L) and may be associated with low (275 to 290 mmol/kg) or high osmolality (151). The mechanism by which enalapril induces hyponatremia is not entirely understood (152). However, it is believed that unconverted angiotensin I in peripheral cells enters the brain and gets converted into angiotensin II, which

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promotes the stimulation of thirst and the release of antidiuretic hormone (153) leading to the blockage of aldosterone-induced renal tubular sodium reabsorption and potassium secretion and lowering serum sodium. Most hyponatremia cases are attributed to therapeutic drugs such as antibiotics and antidepressants (154). However, enalapril-induced hyponatremia has been documented (135, 155, 156). It was further demonstrated that nearly 60% of hyponatremia are associated with enalapril (135). Furthermore, literature suggests that men are more susceptible to developing enalapril-induced hyponatremia than women (151).

2.6 Factors associated with ADRs

Individual-specific ADRs occurrence is complex and attributed to many different factors such as gender (157, 158), polypharmacy (159) and environmental influences such as smoking and drinking (Daly, 2013). In addition, pathological factors include kidney failure (160) and ageing (161).

2.6.1 Age

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ADRs are most likely to affect elderly and paediatric patients since drug trials are less likely to be conducted among these age groups (162). Moreover, drug absorption and metabolism are highly variable and less predictable in these groups (163). Elderly patients with multiple medical problems taking various drugs and those with a reduced capacity to eliminate drugs are at high risk for ADRs (164). Body fat stores rise with ageing, whereas total body water levels fall (165). These significant alterations may affect therapeutic drug levels, causing higher concentrations of water-soluble drugs and longer half-lives for fat-soluble drugs. Furthermore, the risk of adverse consequences is significantly higher due to lowered renal and hepatic function, lower lean body mass and deteriorating hearing, vision, cognition, and mobility in older patients (117).

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2.6.2 Gender

Women are 1.5 to 1.7 times more at risk of ADR than men (166). It was further demonstrated that women were more likely than men to use more than one drug simultaneously, potentially contributing to ADRs (167). Furthermore, sex differences in the physiological, hormonal, and genetic factors that affect a medication's pharmacokinetics and pharmacodynamics could account for the differential frequency of ADRs in men and women (168, 169). Women also take longer to excrete drugs in comparison to men, thus increasing their chances of developing ADRs (170). Other biological differences exist between males and females that may contribute to their susceptibility to ADRs, including body mass (171). Body mass may influence a drug's pharmacokinetics and pharmacodynamics, including drug absorption, distribution, metabolism, and elimination (127).

2.6.3 Kidney failure and blood plasma.

The efficacy of a drug is determined by its concentration in the blood plasma (172). Furthermore, drug bioavailability is significant in maintaining drug plasma concentration within the therapeutic range (173). Thus, alteration in the renal profile can alter the plasma level of drugs (174). For instance, kidney failure can result in decreased renal clearance, resulting in an electrolyte imbalance (175). If this is left unmonitored, it might result in over-accumulation of the drug in the system (176). Additionally, kidney failure may alter the rate at which creatinine is cleared from the body, which could negatively impact drug therapy (177).

2.6.4 Body Weight and Fat distribution

Different drugs penetrate cells at different rates depending on the drug's ability to cross membrane bilayers (178). Some drugs penetrate slowly and accumulate in adipose tissue, thus, prolonging

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the drug's effect on the body, thus leading to ADRs. This indicates that the distribution of a drug varies based on body size and fat distribution (98). For example, obese people may store large amounts of fat-soluble drugs, whereas thin people may store relatively small amounts (179).

2.6.5 Smoking and Alcohol

Smoking can decrease the pharmacological effects of some drugs, such as those metabolized by hepatic Cytochrome P450 1A2 (CYP1A2) (180-182). Moreover, nicotine mimics some medications by stimulating the sympathetic nervous system (180). While alcohol can intensify the action of many drugs (183). These actions can lead to ADRs such as nausea, vomiting, headaches, drowsiness, fainting, and loss of coordination.

2.6.6 Immunological Predisposition to ADRs

The immune system has evolved in both cognitive breadth and specificity to protect the body from various infectious and carcinogenic challenges (184). Unfortunately, this perception can also extend to some treatments that cause drug hypersensitivity in individuals (185). The mechanism by which a drug can cause side effects includes an idiosyncratic response to the drug (119, 186). Thus, immune antibodies can cross-react with a drug as an antigen and induce sensitisations, manifesting as a drug allergic reaction (187). Immune-mediated inflammatory reactions account for 5-10% of all drug reactions and represent true drug hypersensitivity (188).

2.6.7 Genetic variation

Genetic factors account for 20 to 90 inter-individual variations in drug disposition and responses (119, 189). Drug mechanisms involve diverse proteins, such as drug-metabolizing and transporting enzymes (190). Understanding drug mechanism and elimination pathways are essential in understanding the factors determining genetic predisposition to ADRs (191, 192) since genetic

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variation influences the pharmacokinetics and pharmacodynamics of drugs (193). Furthermore, it is well-recognised that patients' altered medication responses have a significant hereditary component (194-196). African populations are more genetically diverse than others, with more than 2,000 ethnolinguistic groups (197). This high genetic diversity makes this region vulnerable to excessive ADRs (119). For instance, African descents are the most affected by enalapril-induced ADRs (127, 198, 199).

2.7 Single-Nucleotide Polymorphisms

Single Nucleotide Polymorphisms are single base mutations that occur in the human genome once per 1000 base pairs (200). Thus, different individuals may inherit different base pairs at the same position from their parents. These polymorphisms enable the classification of SNPs as either transition (C/T or G/A) or trans-versions (C/G, A/T, C/A, or T/G) (201). SNPs make up the majority of inter-individual diversity in the human genome, accounting for 90% of all polymorphisms (202). They also provide the highest degree of molecular genetic markers (200). These markers might occur in a population at various frequencies (203) and can be used to assess disease phenotypes in population groups (204).

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Figure 2. 1: Example of individual base pair variation in a population (picture adapted from: https://www.genome.gov/genetics-glossary/Single-Nucleotide-Polymorphism).

2.7.1 SNPs Associated with Enalapril Response and ADRs

SNPs found in the genes that encode for the RAAS components have been shown to impact the pharmacogenomics of ACEi, including the effects of vasodilation associated with nitric oxide and bradykinin (205-207). Single nucleotide polymorphisms located in the nitric oxide synthase 3 (NOS3) genes including rs2070744, were predominantly detected among people who had poor responses to enalapril. Genotype and allele (205). Another gene that is important for enalapril response is bradykinin receptor B2 (BDKRB2). It was revealed that individuals with the CC genotype of BDKRB2 rs1799722 were more likely to respond favourably to enalapril in comparison to carriers of the TT genotype. (208). This may be useful because bradykinin and nitric oxide are two substances thought to be responsible for enalapril-induced dry cough (142). Furthermore, SNPs in transporter genes such as solute carrier transporter O1B1 (SLCO1B1) rsrs4149056 and the ABO rs495828 gene were implicated in enalapril-induced dry cough (21, 209). While Serine/Threonine Kinase 39 (STK39) rs6749447 and Beta-2 adrenergic receptors (ADRB2) rs1042714 have been associated with sodium-sensitive hypertension (62, 210). Enalapril has been

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shown to actively normalize BP among individuals with sodium-sensitive hypertension (211). Individuals with sodium-sensitive hypertension may have adverse effects from enalapril, such as hypotension (caused by hyponatremia) (212). Having any of the specific genotypes for the aforementioned SNPs may potentially exaggerate or reduce the effects of the drug and lead to the development of ADRs.

2.8 The role of precision medicine in adverse reactions

Precision medicine is complemented by pharmacogenomics, a concept that was unknown until recently. Pharmacogenetics is the study of how a person's genes respond to a drug. This branch is associated with genetic-level studies, functional studies and pharmacology (includes pharmacokinetics and pharmacodynamics). All these branches together aid in the development of safe, and effective medications along with doses which are probably tailored to an individual persona's genetic makeup. This fits into the aim of precision medicine, which is to target the right treatments to the right patients at the right time, thus eliminating the occurrence of ADRs. (Patil, 2015, León-Cachón et al., 2012). The causes of ADRs are still poorly understood due to their clinical heterogeneity and complexity. However, the role of genetic mutations in the ADRs pathogenesis has been shown either for dose-dependent or dose-independent reactions. This potentiates a revolution in drug therapy and could significantly expand the therapy outcomes and drug uses (213). Also, clinicians may be able to minimize possible adverse effects with the aid of genetic information for matching suitable drugs to a suitable patient at an appropriate dose. The scientific community has made advances in the field of precision medicine and this has allowed for the establishment of SNP databases such as the Pharmacogenetics Implementation Consortium and Pharmacogenomics Knowledgebase (214). These databases accelerate the translation of test results into actionable prescribing decisions using SNP information that correlates with individual

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drug responses (215). For example, the Food and drug administration has included the recommendation for genetic tests for some drugs before prescribing (216). In addition, the advances in biochemical genetics and biotechnological tools such as microarrays allowed the search for more genes and their expression to determine how they affect drug responses (217). Different collaborations have since been formed between various organisations and this has led to the development of a library of 300000 SNPs (218, 219). However, the potential limitations of precision medicine are the underrepresentation of African populations in genomics research, especially in research that concerns anti-hypertensive drugs, as well as the lack of public health data quantifying the extent of uncontrolled hypertension as well as related factors such as non-adherence and ADRs.

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Chapter 3: Prevalence and Determinants of Uncontrolled Hypertension among Adult Patients Receiving Chronic Care in Government Facilities Serving Vhembe district: A Cross-sectional Study

Abstract

Introduction: Uncontrolled hypertension is the leading risk factor for CVDs and premature mortality. However, only a few studies have assessed the prevalence of uncontrolled hypertension and its determining factors among individuals residing in rural areas of South Africa. **Aim:** This study investigates the prevalence and factors associated with uncontrolled hypertension among adult patients dwelling in the Vhembe district. **Methods:** This was a community-based cross-sectional study composed of 402 participants with a known diagnosis of hypertension. Blood pressure (BP) was measured in triplicates. Patients with SAP of ≥ 140 mmHg and/ or DBP ≥90 mmHg were defined as uncontrolled. Logistic regression odds ratios and their 95% confidence interval were used to identify factors associated with uncontrolled hypertension. **Results:** About 49.00% of the study participants were ≥66 years of age and 90.05% belonged to the Venda ethnic group. The prevalence of uncontrolled hypertension was estimated at 38.56%. The logistic regression model analysis showed that participants who were taking 2 (AOR=0.13, 95%CI 0.020.75), 3 (AOR=0.13; 95%CI 0.02-0.74) and four drugs (AOR=0.17; 95%CI 0.03-0.97) were less likely to exhibit uncontrolled hypertension. Furthermore, participants who did not experience ADRs (AOR=0.54; 95%CI 0.29-0.99), along with those who did not have DM (AOR=0.57; 95%CI 0.34-0.93) were less likely to exhibit uncontrolled hypertension. **Conclusion:** This study reports a high prevalence of uncontrolled hypertension among patients receiving chronic care in government facilities serving the Vhembe district. The study further demonstrated that DM, ADRs and the number of anti-hypertensive drugs prescribed were associated with hypertension control.

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Keywords: Uncontrolled Hypertension, South Africa, Adverse drug reactions, Vhembe district municipality

3.1 Introduction

Hypertension is the leading risk factor for CVDs and premature mortality (220), accounting for approximately 45% of all CVDs associated deaths (221). The distribution of hypertension varies from region to region. However, a surge in the prevalence of the disease has been observed in SSA (43). The estimated pooled prevalence of hypertension was estimated at 30.0-31.1% in SAA. While countries such as South Africa have reported an estimated prevalence of 27.4% in men and 26.1% in women (222). These figures are likely an underestimation, as our current knowledge of the prevalence of hypertension is limited by studies with small sample sizes and the lack of data from rural communities. As such, the magnitude, and the speed at which the disease has evolved in rural communities remains unknown. Therefore, this study investigates the prevalence and factors associated with uncontrolled hypertension among adult patients dwelling in the Vhembe district.

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Hypertension is characterised by elevated SAP ≥140 mmHg and/or DBP ≥90 mmHg (29). The pathogenesis of hypertension is not entirely understood, however; activation of neuro-hormonal systems such as the sympathetic nervous system and RAAS as well as increased dietary salt intake is linked to the onset of the disease (72, 223, 224). Furthermore, other factors, such as insulin resistance and obesity, were associated with the pathophysiology of hypertension.

Compelling evidence suggests that achieving and maintaining the recommended BP levels requires the use of oral anti-hypertensive therapy (159, 225-227). There most prescribed anti-hypertensive drug classes include Diuretics, ACEi, and CCBs (44). Diuretics reduce BP by increasing the

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amount of water and salt expelled from the body through urine. While ACEi blocks the formation of a natural vaso-constricting ACE, allowing vessels to relax (131). On the other hand, CCBs work by preventing calcium from entering the cells of the heart and arteries (228).

There is no official record of the statistics and prescription patterns of anti-hypertensive medication among South Africans. However, literature suggests that most South African adult patients with hypertension fail to achieve and maintain adequate BP even with the aid of antihypertensive drugs (6, 50). Nonetheless, only a few studies have assessed the prevalence of uncontrolled hypertension and its determining factors among individuals residing in rural areas of South Africa. Therefore, the current study aims to assess the factors of uncontrolled hypertension among patients receiving health care in government facilities serving the Vhembe district in the Limpopo province, South Africa.

3.2 Materials and Methods

3.2.1 Study setting and design.

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The present study was a community-based cross-sectional study conducted in four public health facilities serving the Vhembe district, Limpopo. Ethical clearance for this study was obtained from the Senate Research Committee of the University of the Western Cape (Ethics clearance number BM/16/5/19) (See appendix 1 and 2). Permission to implement the study protocol was granted by the clinical governance of the Vhembe district (See Appendix 4) and the Department of Health of the Limpopo Province (See appendix 3). All participants received information on the purpose and procedure of the study in their home language (Tsonga and Venda) before signing an informed consent form (See Appendix 5).

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For this study, 402 participants were selected through convenience sampling. The study included individuals aged ≥18 years who had been diagnosed with hypertension and initiated on anti-hypertensive medication at least a year prior to the study. Individuals who were bedridden, mentally compromised, pregnant or unable to consent were excluded from the study.

3.2.2 Data Collection

Participants underwent face-to-face interviews using a standardized questionnaire encompassing three major items: demographic, lifestyle behaviour, and clinical data. A trained research nurse conducted the interviews and performed anthropometric measurements (weight and height) according to standard protocols. Clinical data were extracted from the medical records of each participant. The following clinical data were obtained from the medical records: duration of hypertension, the number of anti-hypertensive drugs, drug combinations and comorbidities. Adverse drug reactions were self-reported. BP was measured in triplicates; patients with SAP of ≥ 140 mmHg and/ or DBP ≥90 mmHg were defined as uncontrolled BP.

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3.2.3 Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, New York, USA. Categorical variables were reported as frequency and percentage. The relationships between the selected variables and uncontrolled hypertension were examined using chi-square analysis. Multivariate logistic regression analysis using crude (COR) and adjusted (AOR) logistic regression model analysis fitted with their 95% confidence intervals were used to identify the independent determinants of uncontrolled hypertension. A p-value of less than 0.05 was considered statistically significant.

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3.3 Results

3.3.1 Description of the study cohort

This study included 402 patients with a known diagnosis of hypertension; 344 (85.57%) of the patients were female and 58 (14.43%) were male. About 49.00% of the study participants were ≥66 years of age, 90.05% belonged to the Venda ethnic group, 72.64% had been diagnosed with hypertension for ≥ 5 years and 21,64% had a positive hypertension family history. In addition, 2.24% were active tobacco smokers/consumers, 94.28% consumed moderate-high salt, and 26.37% had a known diagnosis of DM (Table 3. 1).

Table 3.1: General characteristics of the study cohort (n=402)

Variable	**Total (n; %)**	**Male (n; %)**	**Female (n; %)**
All	402 (100.00)	58 (14.43)	344 (85.57)
Ethnicity			
Venda	362 (90.05)	19 (5.25)	343 (94.75)
Tsonga	40 (9.95)	39 (97.50)	1 (2.50)
Age			
18-25 years			
26-35 years	2 (0.49)	1 (50.00)	1 (50.00)
36-45 years	19 (4.73)	0 (0.000)	19 (100.00)
46-55 years	67 (16.67)	9 (13.43)	58 (86.57)
56-65 years	117 (29.10)	18 (15.38)	99 (84.62)
≥66 years	197 (49.00)	30 (15.22)	167 (84.77)
Tobacco use			
No	393 (97.76)	54 (13.74)	339 (86.26)
Yes	9 (2.24)	4 (44.44)	5 (55.56)
Salt Intake			
Low	23 (5.72)	2 (8.70)	21 (91.30)
Moderate-High	379 (94.28)	56 (14.78)	323 (85.22)
Duration of diagnosis			
< 5 years	110 (27.36)	15 (13.64)	95 (86.36)

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≥ 5 years	292 (72.64)	43 (14.73)	249 (85.27)
Presence of DM			
Yes	106 (26.37)	19 (17.92)	87 (82.08)
No	297 (73.88)	39 (13.13)	257 (86.53)
Adherence			
Yes	344 (85,57)	47 (13.66)	297 (86.34)
No	58 (14.43)	11 (18.97)	47 (81.03)
Number of drugs			
1	106 (26.37)	21 (19.81)	85 (80.19)
2	195 (48.51)	22 (11.28)	173 (88.72)
3	94 (23.38)	14 (14.89)	80 (85.11)
4	7 (1.74)	1 (14.29)	6 (85.71)
BP ≤140/90			
Yes	265 (65.92)	48 (18.11)	217 (81.87)
No	137 (34.08)	10 (7.30)	127 (92.70)
ADR			
Yes	77 (19.15)	10 (12.99)	67 (87.01)
No	325 (80.85)	48 (14.77)	277 (85.23)
Positive Family history			
No	315 (78.36)	47 (14.92)	268 (85.08)
Yes	87 (21,64)	11 (12.64)	76 (87.36)

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3.3.2 Distribution of uncontrolled hypertension within chronic facilities

Out of the 402 participants, 155 (38.56%) exhibited uncontrolled hypertension. A large portion of participants with uncontrolled hypertension was recorded at Donald Fraser gateway clinic (DFGC) (n=93), followed by William Eddie Community health centre (WECHC) (n=37) and Mphambo clinic (n=19) **(Figure 3.1**).

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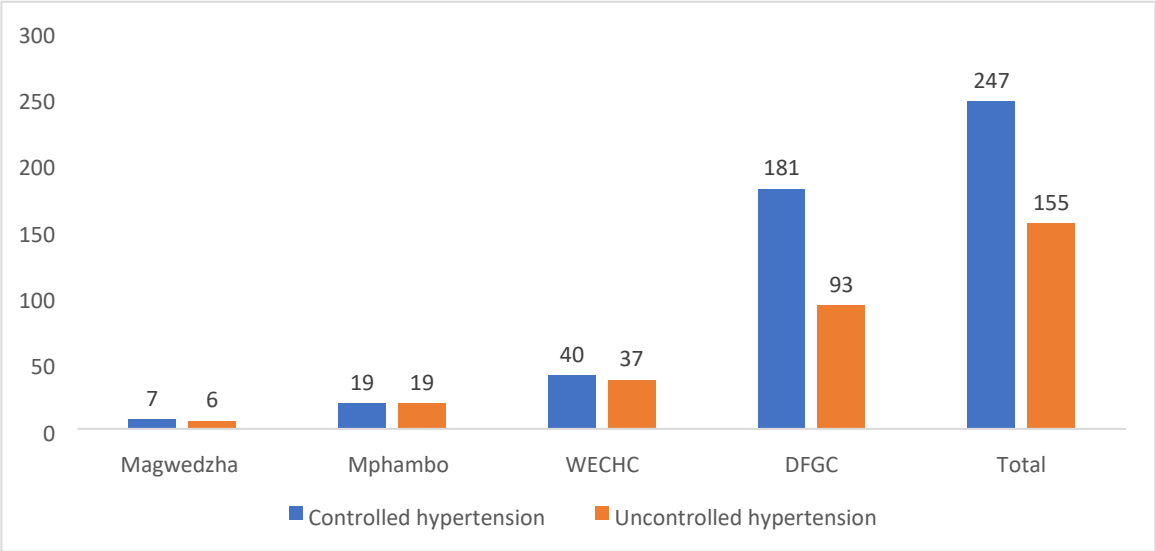

Figure 3.1: Distribution of hypertension control vs uncontrolled with respective clinics.

3.3.3 Factors associated with uncontrolled hypertension

The Chi-square analysis established no significant relationships between uncontrolled hypertension and the selected variables (**Table 3.2**).

Table 3.2: Chi-square analysis showing factors associated with uncontrolled hypertension (n=402)

Variable	**Total (n; %)**	**Controlled Hypertension (n; %)**	**Uncontrolled Hypertension (n; %)**	**P-values**
All	402 (100)	247 (61.44)	155 (38.56)	.
Sex				
Male	58 (14.43)	32 (55.17)	26 (44.83)	
Female	344 (85.57)	215 (62.50)	129 (37.50)	0.29
Age				
<55 years	78 (19.40)	52 (66.67)	26 (33.33)	
≥55 year	324 (80. 60)	195 (60.19)	129 (39.81)	0.29
Tobacco use				
No	393 (97.76)	241 (61.32)	152 (38.68)	
Yes	9 (2.24)	6 (66.67)	3 (33.33)	0.74
Salt Intake				
Low	23 (5.72)	16 (69.57)	7 (30.43)	
Moderate-High	379 (94.27)	231 (60.95)	148 (39.05)	0.41
Duration of diagnosis				

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< 5 years	110 (27.36)	64 (58.18)	46 (29.67)	
≥ 5 years	292 (72.64)	183 (62.67)	109 (37.33)	0.41
Number of anti-hypertensive drugs prescribed				
1	106 (26.37)	65 (61.32)	41 (38.68)	
2	195 (48.51)	126 (64.62)	69 (35.38)	
3	94 (23.38)	54 (57.45)	40 (42.55)	
4	7 (1.74)	2 (28.57)	5 (71.43)	0.19
Adherence to medication				
Non-adherent	58 (14.43)	30 (51.72)	28 (48.28)	
Adherent	344 (85.57)	217 (63.08)	127 (36.92)	0.10
Adverse drug reactions				
No	77 (19.15)	52 (67.53)	25 (32.46)	
Yes	325 (80.85)	195 (60.00)	130 (40.00)	0.22
Presence of DM				
No	106 (26.37)	58 (54.72)	48 (45.28)	
Yes	296 (73.63)	189 (63.85)	107 (36.45)	0.97
Positive Family history				
No	315 (78.36)	195 (61.90)	120 (38.10)	
Yes	87 (21.64)	52 (59.77)	35 (40.23)	0.72

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The Multivariate logistic regression model analysis (Unadjusted) showed that participants who were taking three anti-hypertensive drugs (COR=0.18, 95%CI 0.03-0.95) were less likely to exhibit uncontrolled hypertension.

After adjusting with Age, Sex and duration of diagnosis, the multivariate logistic regression model analysis showed that participants who were taking two drugs (AOR=0.13, 95%CI 0.02-0.75), 3 (AOR=0.13; 95%CI 0.02-0.74) and 4 (AOR=0.17; 95%CI 0.03-0.97) were less likely to have uncontrolled hypertension. Furthermore, participants who had experienced adverse effects from anti-hypertensive drugs (AOR=0.54; 95%CI 0.29-0.99), along with those who have DM (AOR=0.57; 95%CI 0.34-0.93) were less likely to exhibit uncontrolled hypertension (**Table 3.3**).

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Table 3.3: Adjusted and unadjusted logistic regression model analysis showing the factors associated with uncontrolled hypertension.

Variable	**Unadjusted odds ratios (95%CI)**	**Adjusted odds ratios (95%CI)**
Sex		
Male	**Ref**	**Ref**
Female	0.89 (0.50-1.60)	0.86 (0.464-1.61)
Age		
<55 years	**Ref**	**Ref**
≥56 year	0.80 (0.48-1.33)	0.78 (0.46-1.34)
Tobacco use		
No	**Ref**	**Ref**
Yes	1.85 (0.59-5.74)	2.39 (0.72-7.90)
Salt Intake		
Low	**Ref**	**Ref**
Moderate-High	0.55 (0.26-1.16)	0.51 (0.23-1.12)
Duration of diagnosis		
< 5 years	**Ref**	**Ref**
≥ 5 years	1.281 (0.81-2.02)	1.55 (0.95-2.53)
Number of anti-hypertensive drugs prescribed		
1	**Ref**	**Ref**
2	0.21 (0.03-1.14)	**0.13 (0.02-0.75) ****
3	**0.18 (0.03-0.95) ***	**0.13 (0.02-0.74) ****
4	0.23 (0.04-1.26)	**0.17 (0.03-0.97) ****
Adherence to medication		
Non-adherent	**Ref**	**Ref**
Adherent	0.69 (0.39-1.22)	0.64 (0.34-1.20)

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ADRs		
Yes	**Ref**	**Ref**
No	0.62 (0.35-1.08)	**0.54 (0.29-0.99) ***
Presence of DM		
Yes	**Ref**	**Ref**
No	0.68 (0.43-1.07)	**0.57 (0.34-0.93) ** **
Positive Family history		
No	**Ref**	**Ref**
Yes	1.11 (0.67-1.85)	1.08 (0.63-1.56)

3.4 Discussion

The present study examined the prevalence and determinants of uncontrolled hypertension among patients receiving chronic care in four primary healthcare care facilities serving the Vhembe districts of the Limpopo province. The prevalence of uncontrolled hypertension was estimated at 38.55%. The figure reported in the current study was comparable to figures reported in Israel. (35.9%) and Ethiopia (37%) (229, 230). However, lower than the figure reported in various parts of South Africa, including KwaZulu-Na (51%), Mpumalanga (56.8%), and the Eastern Cape (75.5%) (6, 72, 231). The Low prevalence of uncontrolled hypertension that was observed in this study may result from social behaviour, including adherence to medication, physical activity, and a healthy diet. Although physical activity and diet were not assessed in this study, it is important to note that as a rural province, Limpopo benefits from a government initiative in South Africa that makes use of community health workers (CHWs). Under facility-based nurses' supervision, they provide health education, promote healthy behaviour and assess community health needs (232).

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Studies have shown that hypertension is often accompanied by DM (233-235) and that the presence of DM adds a significant burden to overall morbidity and mortality (236, 237). In the current study, we observed a high (26.37%) proportion of individuals with co-existing DM and hypertension. Furthermore, the participants with no known diagnosis of DM were less likely to have uncontrolled hypertension. Similar observations were made in Spain (238), China (239), and Ghana (240). These findings suggest that treatment for hypertension should be individualized according to concomitant risk factors, including DM.

In this study, participants on combination therapy of three anti-hypertensive drugs were less likely to have uncontrolled hypertension. Though single-drug treatment may be effective in some patients, the literature suggests that more than 50% will require more than one drug to control their BP appropriately (241) as drug combinations allow for action on different hypertensive mechanisms (242). As such, it is recommended that two or more antihypertensive medications be prescribed to achieve BP reduction goals (243).

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In addition, the current study showed that participants who experienced adverse reactions were less likely to exhibit uncontrolled hypertension. We found no record of the association of adverse reactions with uncontrolled hypertension. However, it is well known that patients who experience ADRs tend to lose confidence in their treatment and are more likely to stop adhering to their medication (18, 244, 245). To improve hypertension control and avoidable resource misuse, clinicians should pay close attention to ADRs, and adjust dosages to eliminate their occurrence and improve treatment outcomes.

3.5 Study limitations

Given the study's small sample size and cross-sectional design, the identified determinants should not be considered as causation. Notwithstanding the small sample size, this study was conducted

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in four primary healthcare centres serving the predominantly rural communities of the Vhembe district. As a result, the findings are applicable to the district's hypertensive population and similar settings throughout the country. Nonetheless, this is the first study to find a link between ADRs and uncontrolled hypertension in a South African population.

3.6 Conclusion

This study reports a high prevalence of uncontrolled hypertension among patients receiving chronic care in government facilities serving the Vhembe district. The study further demonstrated that DM, ADRs and the number of anti-hypertensive drugs prescribed were associated with hypertension control. These determinants should be addressed decisively through the collaborative efforts of clinicians and health authorities. Such collaboration would facilitate achieving treatment targets for BP among residents of the Vhembe district.

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Chapter 4: Adverse effects and non-adherence to antihypertensive medications among patients receiving chronic care in government facilities serving Vhembe district.

Abstract

Introduction: Non-adherence to anti-hypertensive treatment is increasingly recognised as a contributor to the high prevalence of uncontrolled hypertension. Thus, investigating factors that predict non-adherence to medication and ADRs is necessary for improving BP control among South Africans. **Aim:** To investigate the prevalence and factors associated with non-adherence and adverse reactions to anti-hypertensive medication among South African adults receiving chronic healthcare in government facilities serving the Vhembe district. **Methods:** A total of 402 individuals with hypertension were recruited for this study. Chi-square and Logistic regression (adjusted and unadjusted) model analysis were used to determine factors associated with non-adherence and ADRs. A P value < 0.05 was considered statistically significant. **Results**: Most of the study participants were female (85.57%) and ≥55 years of age (80.60%). Nearly 60% of the study participants did not adhere to their anti-hypertensive medication, while 77 (19.15%) reported ADR incidences. The logistic regression model analysis showed that participants taking more than three drugs (AOR=0.20, 95%CI 0.07-1.80) and those who had experienced ADRs (AOR=0.47, 95%CI 0.24-0.92) were less likely to adhere to their prescribed medication. While participants belonging to the Venda ethnic group (AOR=20.9, 95%CI 6.52-6.79) were more likely to adhere to their antihypertensive medication. **Conclusion**: This study found a high prevalence of non-adherence to anti-hypertensive drugs, which could be attributed to ADRs, the number of drugs and ethnic background. The study also found a high prevalence of ADRs, which we mostly observed among patients on ACEi therapy.

Keywords: hypertension, non-adherence, ADRs

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4.1 Introduction

The number of adult patients living with hypertension is increasing at an alarming rate. According to global estimates, the prevalence of hypertension is expected to increase by 30% in the year 2025 (246, 247). It was further demonstrated that hypertension drives the global burden of cardiovascular morbidity and CVD-associated mortality (43). In the past few decades, anti-hypertensive medications served as the cornerstone for hypertension management and the prevention of associated complications (18). Despite the documented evidence of their effectiveness, only 40-50% of patients achieve optimal BP control (44). As such non-adherence to anti-hypertensive treatment has been recognised as a contributor to the high prevalence of uncontrolled hypertension (248). Furthermore, it has been suggested that ADRs influence non-adherence to prescribed medication (95). Thus, understanding the complexity of ADRs, non-adherence to medication and their associated factors is essential in determining intervention strategies (92).

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Medication adherence is the extent to which patients can follow the recommendations for prescribed treatments (87, 89). Contrarily, medication non-adherence is described as not following the recommendations for prescribed treatments; however, it is a multifaceted, complex phenomenon that can take many different forms including non-fulfilment, non-conforming and non-persistence adherence (90). Nonconforming adherence occurs when a patient fails to adjust to the recommended doses or times. Furthermore, non-persistence adherence occurs when a patient decides on their own, without the advice of a health care professional, to discontinue a medication that they have begun. (92). It was recently demonstrated that more than 40% of patients do not adhere to their prescribed medication (249, 250). The factors associated with non-adherence

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include not understanding the treatment plan, limited supply of medication, personal constraints, the severity of the disease, cost, and ADRs (251).

Non-adherence to medication due to adverse reactions is known as rational non-adherence (252). ADRs are described as harmful or unpleasant reactions resulting from an intervention related to medication use. ADRs occur in 6-15% of hospitalised patients (253), while 25% of out-patients have also reported to have experienced ADRs (254). Furthermore, ADRs can have a significant impact on a patient's health. As such, patients tend to lose confidence in the healthcare system and stop adhering to their medication or opt to self-medicate (255, 256). Poor adherence to prescribed medication diminishes the aim of treatment, leading to poor outcomes, including poor BP control among individuals with hypertension (95).

The cost of treating lifestyle diseases such as hypertension is very high (257). Thus, systematic surveillance of ADRs perceived to be induced by anti-hypertensive medication, as well as monitoring adherence, could benefit South Africa by minimising government expenditures on drugs that could be harmful and that patients fail to adhere to. Also, investigating factors that predict non-adherence to medication and ADRs is necessary to improve BP control among South Africans. The current study investigates the prevalence and factors associated with non-adherence and adverse reactions to anti-hypertensive medication among South African adults receiving chronic healthcare in government facilities serving the Vhembe district.

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4.2 Materials and methods

4.2.1 Study design and settings

This was a community-based cross-sectional study conducted in Magwedzha, Donald Fraser gateway clinic, William Eddie Community health centre and Mphambo clinic. These healthcare facilities provide chronic care services for the residents of Vhembe Municipality, in the Limpopo Province. Vhembe District municipality is located at the north-western tip of South Africa in the Limpopo Province, with a population of approximately 1,294,722. Most people who occupy the area are of the Venda ethnic group (67.2%), followed by the Tsonga ethnic group, which accounts for about 24.8 % of the population.

4.2.2 Data collection

Eligible participants were recruited sequentially in the study settings over the study period. Trained research assistants conducted face-to-face interviews with consenting participants by using a standardised questionnaire. Data regarding ADRs, adherence to medication, smoking status and other lifestyle factors were self-reported. The following clinical data were obtained from the medical records: duration of hypertension diagnosis, presence of DM and the number of drugs administered. A trained research nurse conducted measurements of BP using a validated automated digital BP monitor (Macro-life BP A 100 Plus model) in accordance with standard protocols.

4.2.3 Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, New York, USA). Categorical variables were reported as frequency and percentages. The associations between selected variables and non-adherence were determined using chi-square analysis. Multivariate odd ratios (crude and adjusted) using logistic regression model analysis,

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were estimated with their 95% confidence intervals (95% CIs) to identify the independent and significant determinants of non-adherence. A P value < 0.05 was considered for statistical significance.

4.3 Results

4.3.1 General characteristics

For the current study, 402 patients with hypertension were enrolled, of whom 344 (85.57%) were female and 58 (14.43%) were male. About 324 (80.60%) of the participants were under the age of 55, 68.16% were drawn from the DFGC, 72.64% had been given a diagnosis with hypertension for more than five years, and 247 (61.44%) had blood pressure readings higher than 140/90 mm/hg. Additionally, only 26.37% of patients received antihypertensive monotherapy, and 2.24% were active smokers or consumers of tobacco. Other characteristics are shown in Table **4**.

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Table 4.1: Basic characteristics of the cohort (n=402).

Variable	**Frequency (%)**
Age	
18-25 years	
26-35 years	2 (0.49)
36-45 years	9 (2.24)
46-55 years	67 (16.67)
56-65 years	117 (29.10)
≥66 years	197 (49.00)
Sex	
Male	58 (14.43)
Female	344 (85.57)

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Ethnicity	
Tsonga	40 (9.95)
Venda	362 (90.05)
Salt Intake	
Low	23 (5.72)
Moderate-High	379 (94.28)
Chronic care facility	
Magwedzha	13 (3.23)
Mphambo	38 (9.45)
Tshidimbini	77 (19.15)
Tshitereke	274 (68.16)
Duration of Hypertension	
<5 years	110 (27.36)
≥ 5 years	292 (72.64)
Number of anti-hypertensive drugs	
1	106 (26.37)
2	195 (48.51)
3	94 (23.38)
4	7 (1.74)
BP ≤140/90	
Yes	155 (38.56)
No	247 (61.44)
Smoking status	
Yes	9 (2.24)
No	393 (97.76)

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4.3.2 Distribution of non-adherence

In addition, the overall prevalence of non-adherence to antihypertensive medication was estimated at 14.43% (n=58), while 85.57% (n=344) of the study participants were adherent (**Figure 4.1**).

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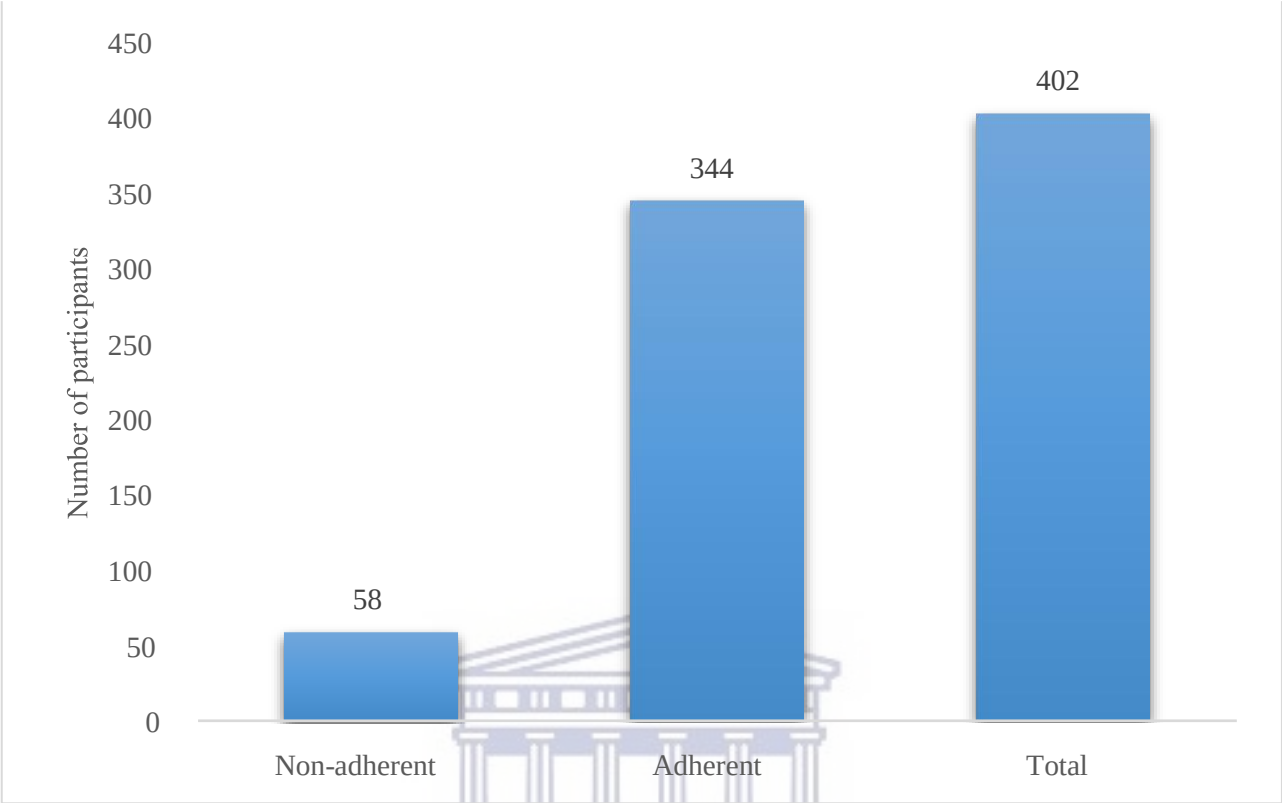

Figure 4.1: Overall prevalence of non-adherence in the study population (n=402).

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4.3.3 Factors associated with non-adherence

The Chi-square analysis showed that there were no relationships between ADRs, the number of antihypertensive, salt intake and the presence of DM (P>0.05). Other factors are shown in **Table 4.2**

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Table 4.2: Predictors of non-adherence by chi-square (n=402).

Variable	**All Participants (n; %)**	**Controlled Hypertension (n; %)**	**Uncontrolled Hypertension (n; %)**	**P-values**
All	402 (100)	247 (61.44)	155 (38.56)	.
Sex				
Male	58 (14.43)	32 (55.17)	26 (44.83)	
Female	344 (85.57)	215 (62.50)	129 (37.50)	0.29
Age				
<55 years	78 (19.40)	52 (66.67)	26 (33.33)	
≥55 year	324 (80. 60)	195 (60.19)	129 (39.81)	0.29
Tobacco use				
No	393 (97.76)	241 (61.32)	152 (38.68)	
Yes	9 (2.24)	6 (66.67)	3 (33.33)	0.74
Salt Intake				
Low	23 (5.72)	16 (69.56)	7 (30.43)	
Moderate-High	379 (94.27)	231 (60.95)	148 (39.05)	0.41
Duration of diagnosis				
< 5 years	110 (27.36)	64 (58.18)	46 (41.81)	
≥ 5 years	292 (72.24)	183 (62.67)	109 (37.33)	0.41
Number of anti-hypertensive drugs prescribed				
1	106 (26.37)	65 (61.32)	41 (38.68)	
2	195 (48.51)	126 (64.62)	69 (35.38)	
3	94 (23.38)	54 (57.45)	40 (42.55)	
4	7 (1.74)	2 (28.57)	5 (71.43)	0.19
Adherence to medication				
Non-adherent	58 (14.43)	30 (51.72)	28 (48.28)	

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Adherent	344 (85.57)	217 (63.08)	127 (63.08)	0.10
Adverse drug reactions				
No	77 (19.15)	52 (67.53)	25 (32.47)	
Yes	325 (80.85)	195 (60.00)	130 (40.00)	0.22
Presence of DM				
No	106 (26.37)	58 (54.72)	48 (45.28)	
Yes	296 (73.63)	189 (70.26)	107 (39.78)	0.97
Positive Family history				
No	315 (78.36)	195 (61.90)	120 (38.10)	
Yes	87 (21.64)	52 (59.77)	35 (40.23)	0.72

The multivariate logistic regression (unadjusted) analysis showed that participants in William Eddie Community health centre (COR=2.45, 95%CI 1.01-5.97) were more likely to adhere to medication, while participants taking more than three drugs (COR=0.16, 95%CI 0.66-0.38 and those who experienced ADRs (COR=0.38, 95%CI 0.21-0.70) were less likely to adhere to their prescribed medication.

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After adjusting with Age, Sex and duration of diagnosis, the multivariate logistic regression model analysis showed that participants who took more than three drugs (AOR=0.20, 95%CI 0.071.80) and those who had ADRs (AOR=0.47, 95%CI 0.24-0.92) were less likely to adhere to medication. Moreover, participants belonging to Venda ethnic group (AOR=20.9, 95%CI 6.526.79) were found to be more likely to adhere to antihypertensive medication (**Table 4.2**).

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Table 4.3: Adjusted and unadjusted logistic regression models showing the predictors of non-adherence (n=402).

Variable	**Unadjusted odds ratios (95%CI)**	**Adjusted odds ratios (95%CI)**
Sex		
Male	**Ref**	**Ref**
Female	1.48 (0.72-3.05)	1.43 (0.65-3.16)
Age		
<55 years	**Ref**	**Ref**
≥55 year	0.54 (0.23-1.24)	0.64 (0.26-1.53)
Ethnicity		
Tsonga	**Ref**	**Ref**
Venda	0.63 (0.22-1.85)	**20.9 (6.52-6.79)*** **
Chronic care facility		
Tshitereke	**Ref**	**Ref**
Magwedzha	2.49 (0.32-19.57)	1.64 (0.18-14.89)
Tshidimbini	**2.45 (1.01-5.97)***	1.92 (0.73-5.02)
Mphambo	1.76 (0.60-5.20)	2.19 (2.19-2.19)
Tobacco use		
No	**Ref**	**Ref**
Yes	0.33 (0.79-1.34)	0.42 (0.90-1.94)
Salt Intake		
Low	**Ref**	**Ref**
Moderate-High	1.27 (0.42-3.87)	1.38 (0.41-4.64)
Duration of diagnosis		
< 5 years	**Ref**	**Ref**
≥ 5 years	0.51 (0.25-1.04)	0.59 (0.27- 1.31)
Number of anti-hypertensive drugs prescribed		

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1	**Ref**	**Ref**
2	0.62 (0.25-1.52)	0.70 (0.27-1.80)
3	**0.16 (0.66-0.38)*** **	**0.20 (0.07-1.80)** **
4	0.18(0.29-1.08)	0.26(0.05-2.27)
BP		
≤140/90	**Ref**	**Ref**
>140/90	0.69 (0.39-1.22)	0.62 (0.32-1.19)
Adverse drug reactions		
No	**Ref**	**Ref**
Yes	**0.38 (0.21-0.70)** **	**0.47 (0.24-0.92)* **
Presence of DM		
No	**Ref**	**Ref**
Yes	0.93 (0.50-1.74)	0.98 (0.48-2.01)

4.3.4 Distribution of ADRs

Out of 402 participants, 77 (19.15%) reported to have experienced ADRs, of whom 67 were female and only 10 were male.

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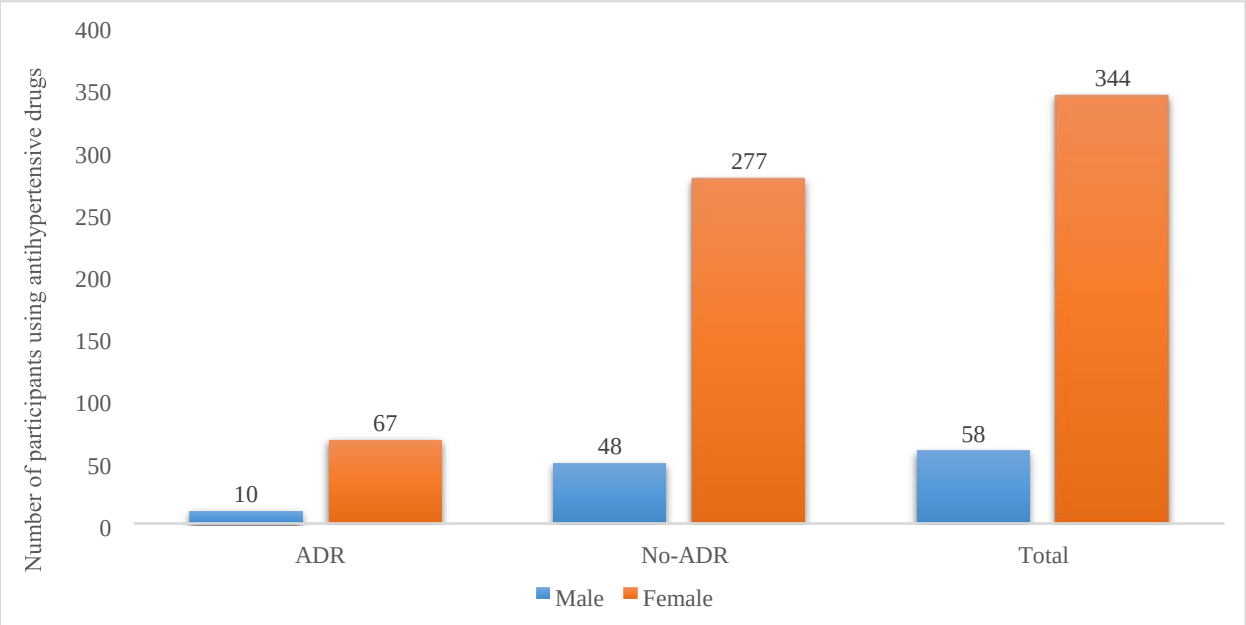

Figure 4.2: Prevalence of ADRs among patients undergoing anti-hypertensive therapy.

Among the 77 participants who reported to have experienced ADRs, 41 (53.25%) were on enalapril therapy, while 14 (18.18%) were on HCTZ (**Figure 4.3**). In addition, enalapril-induced dry cough was the most prominent adverse reaction reported (42.86%), followed by HCTZ-induced drowsiness (16.88%)

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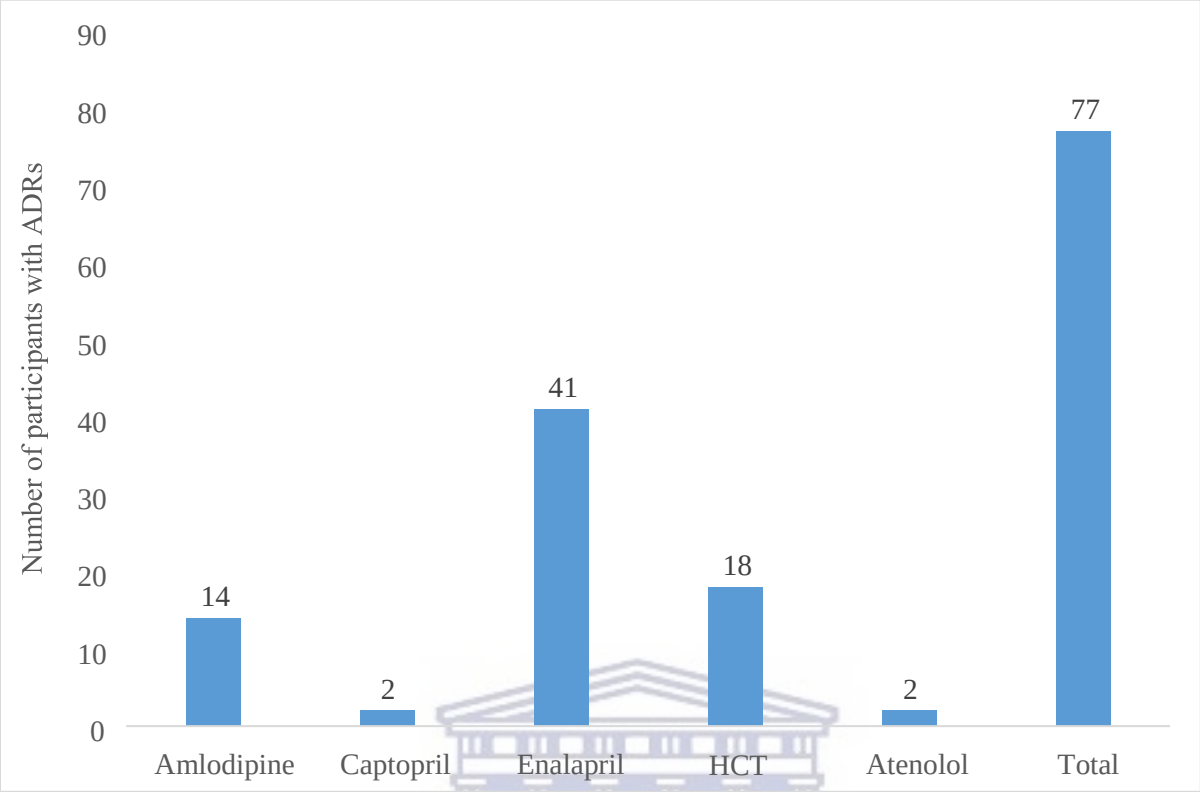

Figure 4.3: Distribution of antihypertensive drugs among patients who experienced ADR (n=77).

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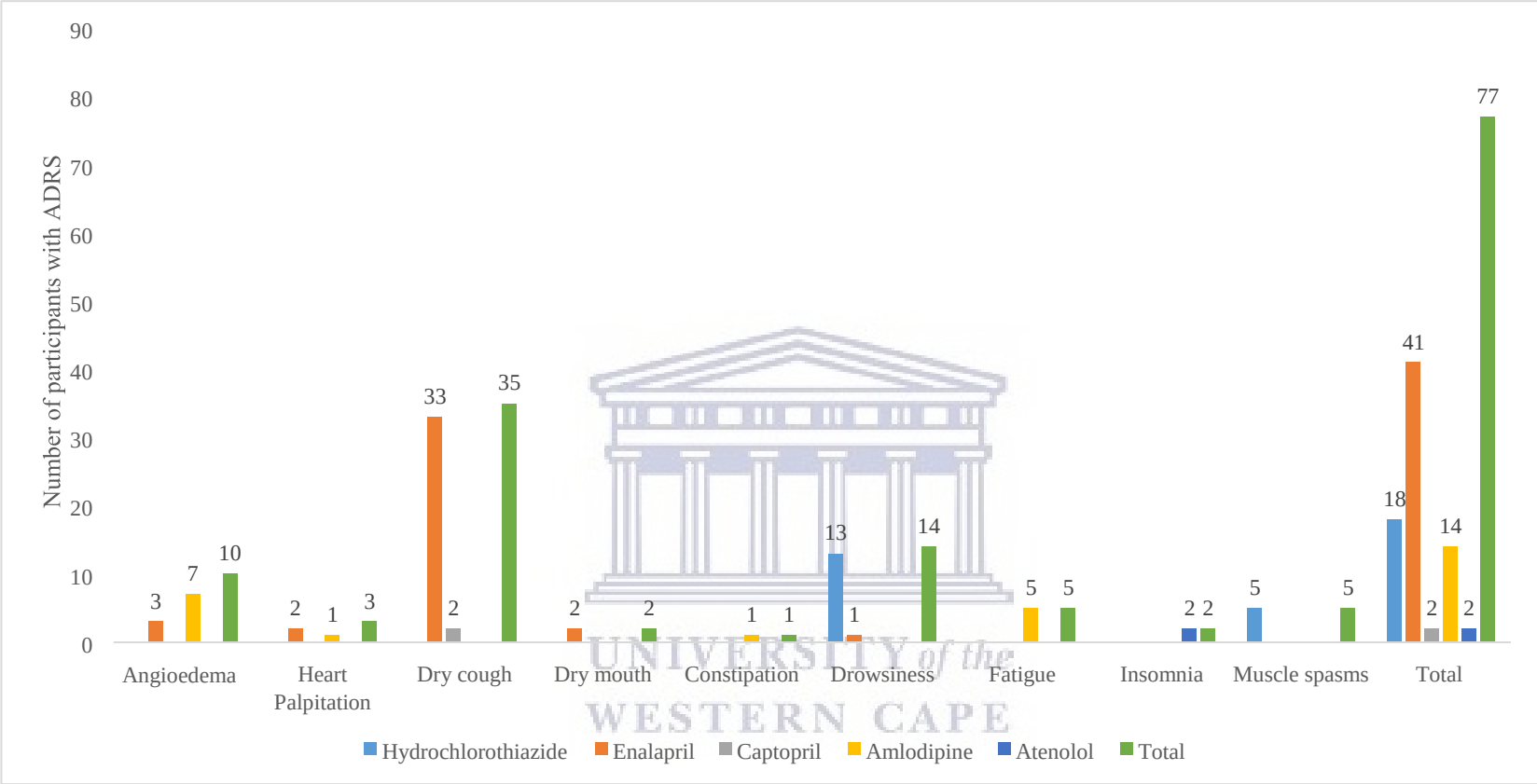

Figure 4.4: Distribution of adverse reactions according to different anti-hypertensive drugs prescribed to the study cohort (n=77).

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4.4 Discussion

The present study examined the prevalence and factors associated with non-adherence and ADRs among a South African cohort. The rate of non-adherence to anti-hypertensive medication was 14.43%. This figure was lower than the numbers reported in the United States of America (32.4%), Pakistan (23%), Korea (18%) and Tshwane, South Africa (19%). However, higher than that reported in Ethiopia (11.4%). The rate of non-adherence observed across the different countries may be due to factors such as religion, cultural beliefs and access to health care which were not assessed in this study. Future studies are expected to assess the factors mentioned above to establish the causality of non-adherence.

The study population was composed of two populations (Venda and Tsonga). Our result showed that participants of Venda origin were more likely to adhere to their anti-hypertensive medication. We found no record of adherence patterns among these two ethnic groups; however, other studies have shown that drug adherence varies among different population groups (258, 259). For instance, a study on cultural and non-cultural Arab Americans found that cultural differences and behaviour play a role in antihypertensive drug adherence (260). It should be noted that only a small number of participants with Tsonga ancestry were included in the current study; as a result, future research should ensure that a larger number of this ethnic group is included among studies to produce epidemiological data that is representative of the Vhembe district's population.

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Polypharmacy is defined as the use of multiple medicines. However, other studies have defined this phenomenon using numerical counts for a given duration of therapy or setting (117, 261). Polypharmacy is of particular concern since it may impact adherence to medication (262). The present study showed that patients who were taking three (3) Drugs were less likely to adhere to their medication. Our findings are similar to what has been reported in the literature (85, 263, 264),

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where it was shown that polypharmacy could lead to non-adherence. These studies examined non-adherence alongside confounding factors such as patient, health system, and provider factors. They further suggested that these factors should not be considered in isolation; rather, they should be viewed as interacting with many other factors, and clinicians must evaluate each patient individually to assess their unique barriers as they change over time. Although the present study did not assess the aforementioned confounding factors, we found that patients who experienced ADRs were less likely to adhere to medication. Other studies demonstrated that patients who experience ADRs tend to lose confidence in their medication and the healthcare system, leading to poor treatment outcomes (18, 255). Research has shown that monitoring ADRs among patients on antihypertensive medication is critical for improving treatment outcomes. In addition, our study has laid a foundation for future studies that will comprehensively assess the relationship between polypharmacy, medication adherence and the occurrence of ADRs in South Africa and other similar settings.

Additionally, we observed a high prevalence of ADRs (19.15%) and many patients who reported ADRs were on enalapril therapy, and dry cough was prominent. The prevalence of ADRs that was observed in this study is comparable to figures reported in central Nepal (18%) and Nigeria (18.1%) (265, 266). Literature also suggests that ACEi account for 26.8% of ADRs observed among patients with hypertension, and dry cough represents between 5-30% of the reported ADRs (144, 267). We found no record of the quantification of ADRs associated with anti-hypertensive drugs in SA. However, the observations made in this study indicate that South Africa would benefit from well-structured pharmacovigilance programs aimed at monitoring ADRs associated with antihypertensive drugs, particularly in rural communities.

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4.5 Conclusion

This study found a high prevalence of non-adherence to anti-hypertensive drugs, which could be attributed to reported ADRs, polypharmacy and ethnic background. The study also found a high prevalence of ADRs, which we mostly observed among patients on ACEi therapy. Furthermore, enalapril-associated dry cough was the most prominent ADR observed. The observations made in this study indicate that there is an urgent need for South Africa to implement pharmacovigilance programmes aimed at monitoring adherence and ADRs, particularly among patients on ant-hypertensive therapy.

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Chapter 5: SNPs associated with enalapril-induced dry cough and Hyponatremia among South African Adults with Hypertension

Abstract

Introduction: One of the more popular anti-hypertensive medications is enalapril, which is also known to cause several adverse side effects. However, it is unclear to what extent a person's genetics, especially those of African descent, affect their susceptibility to ADRs. **Aim**: This study investigates the association of selected SNPs with enalapril-induced ADRs (dry cough and hyponatremia) among adult patients with hypertension residing in the rural areas of the Limpopo province, South Africa. **Methods:** 100 eligible participants were enrolled in the present study. A total of 12 SNPs previously associated with enalapril were selected and genotyped using the Mass Array genotyping system. Data were analysed using IBM SPSS Statistics Version 25.0. Multivariate logistic regression analysis fitted with 95% confidence intervals was used to determine the relationship between the selected SNPs and enalapril-induced ADRs. **Results:** About 18% (n=18) and 19% (n=19) of the study cohort reported enalapril-induced dry cough and hyponatremia incidence, respectively. No significant association was found between an enalapril-induced dry cough and the 12 selected SNPs. The multivariate logistic regression analysis showed carriers of TT (AOR=10.95, 95%CI 1.35-88.77) genotype and the T (AOR=2.80, 95%CI1.18-6.70) allele were more likely to exhibit enalapril-induced hyponatremia. **Conclusion** The present study reports a high prevalence of enalapril-induced dry cough and hyponatremia among patients in the Vhembe district. The study further demonstrated that hyponatremia was associated with rs6749447.

Keywords: Hypertension; ADRs; dry cough; hyponatremia

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5.1 Introduction

Controlling and maintaining adequate BP levels among individuals with hypertension is essential in preventing cardiovascular and kidney diseases (268). Despite the availability of anti-hypertensive drugs and increasing awareness of the disease, the rate of hypertension control and adherence to anti-hypertensive therapies remains low (43). It has been shown that about 50% of patients stop adhering to their hypertension medication, in less than a year of their initial prescription (89). In addition, adverse reactions to anti-hypertensive drugs were shown to have a negative influence on adherence and BP control (18, 269). Furthermore, SNPs within the transporter and coding region have been associated with developing ADRs in patients taking hypertension drugs (21, 209). However, there is currently insufficient evidence of the specific SNPs that predict ADRs in response to antihypertensive therapies among populations of African origin.

Enalapril has been a cornerstone in managing hypertension, heart failure, left ventricular dysfunction, and chronic kidney failure for many decades (270-272). This drug exerts its anti-hypertensive effect by inducing vasodilation and improving endothelial function. The safety and efficacy of enalapril are well documented in the literature; however, ADRs associated with the drug were also reported (136, 138). The most common side effect associated with enalapril is a dry cough. Enalapril is thought to cause dry cough by stimulating the production of bradykinin in the lungs; this happens due to angiotensin II inhibition. (138, 141, 209, 273, 274).

Other known enalapril-induced ADRs include hyponatremia (275), defined as a serum sodium concentration of less than 136 mmol/L (276). Hyponatremia is one of the most common electrolyte abnormalities observed in a hospital setting (277). The condition and its treatment can be

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associated with significant morbidity and mortality (278). Administering enalapril inhibits the conversion of angiotensin I to angiotensin II which halts the production of sodium (279).

Several polymorphisms have been associated with enalapril-induced ADRs, such as dry cough and hyponatremia. For instance, SLCO1B1 rs4149056 and rs495828 of the ABO gene were associated with enalapril-induced dry cough among the Asian population (21, 209). While rs2070744 and rs1799722 of NOS3 and BDKRB2 genes were associated with hypotension (208). Furthermore, the T allele of BDKRB2 rs1799722 was linked to increased transcription of BDKRB2, a gene responsible for the production of bradykinin in the lungs (280). In contrast, rs6749447 of the STK39 gene was associated with variable responses to enalapril treatment among patients with hypertension. (281).

It is clear that ADRs could profoundly affect a patient's quality of life and burden the healthcare system significantly (159). Nonetheless, there is no record of the prevalence of enalapril-induced adverse reactions among South Africans. Furthermore, there is currently insufficient evidence on the specific SNPs that could predict ADRs in response to antihypertensive therapies. Therefore, this study investigates the association of genetic polymorphisms with enalapril-induced dry cough and hyponatremia among adult patients with hypertension residing in the rural areas of the Limpopo province, South Africa.

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5.2 Materials and Methods

5.2.1 Study setting and design

The study was conducted in four healthcare facilities within the Vhembe district, Limpopo. Ethical clearance for this study was obtained from the Senate Research Committee of the University of

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the Western Cape (Ethics clearance number BM/16/5/19). Permission to conduct the current study within the health care facilities was granted by the clinical governance of Vhembe district and the Department of Health of the Limpopo Province. All participants received information on the purpose and procedure of the study in their home language (Tsonga and Venda) before signing an informed consent form.

5.2.2 Data Collection

To be eligible for the current study, participants had to be over 18 years old and have been taking the antihypertensive drug enalapril for at least a year. The patient's medical records were used to obtain information about the participant's medical history, such as BP readings for the previous three months and blood chemistry readings, such as serum sodium, potassium, chloride, urea, and total body cholesterol. Serum sodium was considered normal if it ranged between 136 and 145 millimoles per litre (mmol/L), with less than 136 mmol/L being less than normal and more than 145 mmol/L being above normal. Whereas serum potassium was considered normal between 3.5 and 5.0 mmol/L, anything less than 3.5 mmol/L was considered less than normal, and anything more than 5.0 mmol/L was considered above normal. Normal serum chloride ranges were 98-106 mmol/L, with less than 98 mmol/L considered less than normal and 106 mmol/L considered above normal. Participants with levels ranging between 2.1 to 8.5 mmol/L were classified as having normal serum urea levels. Furthermore, serum creatinine was classified as normal when it ranged between 61.9 and 114.9 µmol/L, while 61.9 µmol/L serum creatinine levels were classified as less than normal, and 114.9 µmol/L levels were above normal. Lastly, serum cholesterol levels were considered normal when the reading was equal to or less than 4.9 mmol/L and high when it was above 5 mmol/L.

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The patient's family medical history of hypertension, duration of the condition, adherence to medication, salt intake, smoking/ tobacco intake status, ethnicity and ADR experiences were self-reported. Genetic samples were collected as buccal swabs and temporarily stored in a freezer at the University of Venda before being transported to the University of the Western Cape for further processing.

5.2.3 DNA extraction

DNA was extracted using the salt lysis technique described by Leat et al. (2004). DNA was precipitated by adding 6M NaCl and vigorously shaken for 15s. Cell debris was pelleted by centrifugation at 5000 rpm for 15 min, and the supernatant was collected. DNA was aggregated by adding cold isopropanol and placed in a -80°C freezer for 30 minutes. DNA was pelleted by centrifuging at 14 000 rpm for 30 minutes. The pellet was washed with 70% alcohol to remove any remaining salts before centrifuging for 8 minutes at 14000 RPM. The pellet was heat dried for 30 minutes with a heating block at 650 degrees Celsius before re-suspending in SABAX water. The concentration of DNA was measured using a Nanodrop ND 1000 UV-Vis Spectrophotometer (Thermo Fisher Scientific, Inc., USA). Samples were immediately stored at -20°C for future use.

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5.2.4 SNP selection

A total of 12 SNPs that were previously associated with enalapril or other antihypertensive drugs outcomes were selected from the Pharmacogenomics Knowledge Base database and were genotyped using the Mass Array system that was designed at Agena BioscienceTM and optimised by Inqaba Biotechnical Industries (Pretoria, South Africa) in 2017. Mass Array chemistry utilised the matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry as a detection method. Briefly, PCR assays and extension primers were designed using Mass-Array

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software. Reactions were performed with a concentration of 3 ng of genomic DNA, one pmol of each amplification primer, 0.2 mM of each dNTP, 2.5 mM MgCl2, and 0.2 U of HotStarTaq DNA Polymerase. Reactions were heated at 95°C for 15 minutes and then subjected to 45 cycles of amplification (20 sec at 94°C, 30 sec at 60°C, and 30 sec at 72°C). The final extension was 7 min at 72°C. Extension reactions were conducted with different allele-specific extension primers, along with the Mass EXTEND Reagents Kit, before being cleaned using Spectro CLEANER on a MULTIMEK 96 automated 96-channel robot.

Table 5.1: General description of twelve selected SNPs.

SNP	Gene	Ancestral allele	Alleles	Location in a gene
rs10267099	ABCB1	A	G/A/C/T	intron variant
rs1042714	ADRB2	G	G/A/C/T	stop gained
rs149711321	PPARA	T	T/C	intron variant
rs2070744	NOS3	C	C/G/T|	intron variant
rs4149056	SLCO1B1	T	T/C	missense variant
rs4648287	PTGS2	A	A/G	intron variant
rs6749447	STK39	T	T/C/G	intron variant
rs495828	ABO	G	T/G	upstream gene variant
rs1799722	BDKRB2	C	C/G/T	5 prime UTR variant
rs7297610	YEATS4	C	C/T	intergenic variant
rs1104514	NONE	A	A/G	intergenic variant
rs699947	VEGFA	A	A/C/T	upstream gene variant

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5.2.5 Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, New York, USA). The general characteristics of the participants were reported as

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frequency and percentages. The associations between the selected ADRs (dry cough and hyponatremia) and the 12 genetic variants were examined using a chi-square analysis. The presence of dry cough and serum sodium levels were used as dependent variables in the multivariate logistic regression model analysis, and the 12 genotypes were used as fixed factors. a p-value of less than 0.05 was considered statistically significant.

5.3 Results

5.3.1 General characteristics of the cohort

Hundred (100) individuals with hypertension and on enalapril therapy were recruited for the current study. About 15% of the participants were Male, while 85% were female. Most of the study participants were over 50 years old (66%), 76% had been living with hypertension for more than five years and 92% did not have a positive family history of hypertension. In addition, 32% of the participants had DM and 85% were adherent to their medication. Approximately 18% of the participants reported enalapril-induced dry cough, 19% had serum sodium levels lower than the normal range (35 mmol/L) and 88 (88%) had normal potassium levels. Other characteristics of the study cohort are shown in **Table 5.2**.

Table 5.2: General characteristics of the cohort (n=100).

Variable	**Total (n; %)**	**Female (n; %)**	**Male (n; %)**
All	**100 (100.00)**	**85 (85.00)**	**15 (15.00)**
Age			
> 60	34 (34.00)	32 (94.12)	2 (5.88)
≤ 60	66 (66.00)	53 (80.30)	13 (19.70)
Duration of HPT			
> 5 years	24 (24.00)	22 (91.67)	2 (8.33)
≤ 5 years	76 (76.00)	63 (82.89)	13 (17.11)

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Family history of hypertension			
Yes	15 (15.00)	12 (80.00)	3 (20.00)
No	85 (85.00)	73 (85.88)	12 (14.12
Smoker			
Yes	8 (8.00)	4 (50.00)	4 (50.00)
No	92 (92.00)	81 (88.04)	11 (11.96)
Salt intake status			
Moderate/ high salt intake	92 (92.00)	78 (84.78)	14 (15.22)
No salt intake	8 (8.00)	7 (87.50)	1 (12.50)
DM			
Yes	32 (32.00)	27 (84.38)	5 (15.63)
No	68 (68.00)	58 (85.29)	10 (14.71)
Adherence to medication			
Yes	85 (85.00)	73 (85.88)	12 (14.12)
No	15 (15.00)	12 (80.00)	3 (20.00)
Cough			
Yes	18 (18.00)	17 (20.00)	1 (6.67)
No	82 (82.00)	68 (85.00)	14 (93.33)
Sodium level (mmol/L)			
> 136	19 (19.00)	15 (17.65)	4 (26.67)
136 – 145	77 (77.00)	67 (78.82)	10 (66.67)
< 145	4 (4.00)	3 (3.53)	1 (6.67)
Potassium level (mmol/L)			
> 3.5	9 (9.00)	7 (8.24)	2 (13.33)
3.5 - 5.0	88 (88.00)	75 (88.24)	13 (86.67)
< 5.0	3 (3.00)	3 (3.53)	0 (0.00)
Chloride level (mmol/L)			
> 98	23 (23.00)	18 (21.18)	5 (3.33)

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98-106	73 (73.00)	63 (74.12)	10 (66.67)
< 106	4 (4.00)	4 (4.71)	0 (0.00)
Urea level (mmol/L)			
2.1 - 8.5	100 (100.00)	85 (100.00)	15 (100.00)
Creatinine level µmol/L			
> 61.9	33 (33.00)	31 (36.47)	2 (13.33)
61.9 - 114.9	63 (63.00)	53 (62.35)	10 (66.67)
< 114.9	4 (4.00)	1 (1.18)	3 (20.00)
Cholesterol level mmol/L			
≥ 4.9	83 (83.00)	70 (82.35)	13 (86.67)
< 5.0	17 (17.00)	15 (17.65)	2 (13.33)

5.3.2 Distribution of ADRs

About 18% (n=18) of the study cohort reported an incidence of enalapril-induced dry cough. Furthermore, 19% (n=19) of the study cohort had hyponatremia (**Figure 5.1**).

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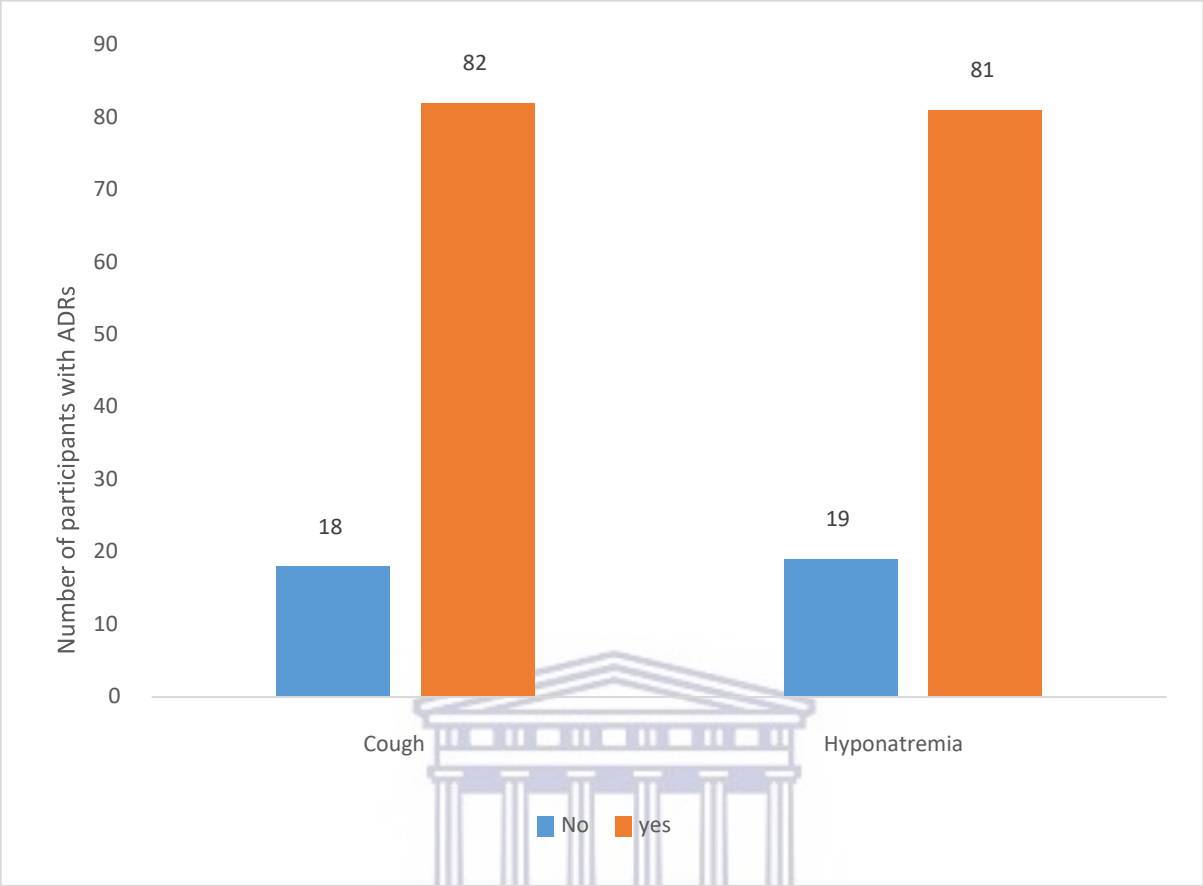

Figure 5.1: Distribution of ADRs in the study cohort.

5.3.3 Analysis of SNPs frequency

The minor allele frequencies of the selected SNPs were compared to other populations worldwide. The minor allele C of rs149711321 was not detected in the current study, however; it was detected in high proportions in other African populations, such as African Caribbean in Barbados (ACB) (19%), African ancestry in the southwest of the US (ASW) (16%) and Esan in Nigeria (ESN) (17%). Furthermore, the minor allele frequency of SNPs rs4648287 and rs7297610 was only dominant in the present study and other African populations. In contrast, SNP rs1799722 was observed in high proportions in populations of European, East Asian and south Asian origin. More details on the minor allele frequencies of the selected SNPs are shown in **Table 5.3**.

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Table 5.3: Comparison of Venda minor allele Percentages with other populations**.**

		Minor allele frequency (%)											
		African				**American**		**European**		**East Asian**		**South Asian**	
SNPs identifier	**Nucleotide**	**VEN**	**ACB**	**ASW**	**ESN**	**CLM**	**MXL**	**GBR**	**IBS**	**CBH**	**JPT**	**GIH**	**PJL**
rs10267099	A	9	18	17	18	16	10	31	25	0	5	14	15
rs1042714	G	11	16	12	12	23	14	43	43	11	6	23	23
rs1104514	G	29	38	42	31	75	77	76	69	68	68	73	69
rs149711321	C	0	19	16	17	0	0	0	0	0	0	0	0
rs2070744	C	15	12	16	8	30	46	11	10	46	50	24	26
rs4149056	C	1	2	7	0	18	8	14	8	14	12	2	4
rs4648287	G	23,5	17	13	16	2	0	0	0	0	0	0	0
rs6749447	T	37	52	53	38	67	50	74	75	27	29	61	59
rs699947	A	35	19	22	17	35	42	50	47	27	34	33	41
rs7297610	T	37,5	32	23	29	9	5	6	8	0	0	3	2
rs495828	T	6,5	12	15	15	13	14	2	20	17	24	14	15
rs1799722	T	35,5	27	39	23	40	41	44	43	53	54	41	36

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VEN- Venda**; ACB**- African Caribbean in Barbados**; ASW**- African ancestry in the south-west of the US; **ESN**- Esan in Nigeria; **CLM**- Colombian in Medellin; **MXL**- Mexican ancestry in Los Angeles; **CHB**- Han Chinese in Beijing; **JPT**- Japanese in Tokyo; **GBR**- British in England and Scotland; **IBS**- Iberian population in Spain; **GIH**- Gujarat Indian Huston; **PJL**- Punjabi in Lahore, Pakistan

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5.3.4 Association between SNPs and enalapril-induced dry cough

The chi-square analysis showed no significant relationships between an enalapril-induced dry cough and 12 SNPs (**Table 5.4**).

Table 5.4: Chi-square analysis of examination between an enalapril-induced dry cough and SNPs.

Variables	Total (n; %)	Dry cough (n; %)	No dry cough (n; %)	P-value
All	100 (100.00)	18 (18.00)	82 (82.00)	
rs10267099				
Genotype				
GA	18 (18.00)	2 (11.11)	16 (88.98)	
AA	82 (82.00)	16 (19.51)	66 (80.49)	0.4
Allele				
G	18 (9.00)	2 (11.11)	16 (88.98)	
A	182 (91.00)	34 (18.68)	148 (81.32)	0.54
rs1042714				
Genotype				
GC	22 (22.00)	3 (13.64)	19 (86.36)	
CC	78 (78.00)	15 (19.23)	63 (80.77)	0.56
Allele				
G	22 (11.00)	3 (13.64)	19 (86.36)	
C	178 (89.00)	33 (18.44)	145 (81.46)	0.77
rs1104514				
Genotype				
GG	5 (5.00)	1 (20.00)	4 (80.00)	
AG	48 (48.00)	6 (12.50)	42 (87.50)	
AA	47 (47.00)	11 (23.40)	36 (76.59)	0.38
Allele				
G	58 (29.00)	8 (13.79)	50 (86.21)	
A	142 (71.00)	28 (19.72)	114 (80.28)	0.42

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rs149711321				
Genotype				
TT	100 (100.00)	18 (100.00)	82 (100.00)	-
Allele				
T	200 (100.00)	36 (100.00)	164 (100.00)	-
rs2070744				
Genotype				
CC	6 (6.00)	1 (16.66)	5 (83.33)	
CT	18 (18.00)	3 (16.67)	15 (83.33)	
TT	76 (76.00)	14 (18.42)	62 (81.58)	0.98
Allele				
C	30 (15.00)	5 (16.66)	25 (83.33)	
T	170 (85.00)	31 (18.24)	139 (81.76)	1.00
rs4149056				
Genotype				
CT	2 (2.00)	0 (0.00)	2 (100.00)	
TT	98 (98.00)	18 (18.37)	80 (81.63)	0.50
Allele				
C	2 (1.00)	0 (0.00)	2 (100.00)	
T	198 (99.00)	36 (18.18)	162 (81.81)	1.00
rs4648287				
Genotype				
GG	6 (6.00)	1 (16.67)	5 (83.33)	
AG	35 (35.00)	5 (14.29)	30 (85.71)	
AA	59 (59.00)	12 (20.33)	47 (79.66)	0.76
Allele				
G	47 (23.50)	7 (14.89)	40 (85.10)	
A	153 (75.50)	29 (18.95)	124 (81.05)	0.67
rs6749447				
Genotype				

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TT	12 (12.00)	3 (25.00)	9 (75.00)	
GT	50 (50.00)	9 (18.00)	41 (82.00)	
GG	38 (38.00)	6 (15.79)	32 (84.21)	0.77
Allele				
T	74 (37.00)	15 (20.27)	59 (79.72)	
G	126 (63.00)	21 (16.67)	105 (83.33)	0.57
rs699947				
Genotype				
AA	2 (2.00)	0 (0.00)	2 (100.00)	
CA	32 (32.00)	7 (21.88)	25 (78.13)	
CC	66 (66.00)	11 (16.67)	55 (83.33)	0.66
Allele				
A	35 (17.50)	7 (20.00)	28 (80.00)	
C	165 (82.50	29 (17.58)	136 (82.83)	0.81
rs7297610				
Genotype				
TT	15 (15.00)	3 (20.00)	12 (80.00)	
CT	45 (45.00)	6 (13.33)	39 (86.67)	
CC	40 (40.00)	9 (22.50)	31 (77.50)	0.53
Allele				
T	75 (37.5)	12 (16.00)	63 (84.00)	
C	125 (62.5)	24 (19.20)	101 (80.80)	0.70
rs495828				
Genotype				
GT	13 (13.00)	0 (0.00)	13 (100.00)	
GG	87 (87.00)	18 (20.69)	69 (79.31)	0.07
Allele				
T	13 (6.50)	0 (0.00)	13 (100.00)	
G	187 (93.50)	36 (19.25)	151 (80.75)	0.13
rs1799722				

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Genotype				
TT	20 (20.00)	5 (25.00)	15 (75.00)	
CT	31 (31.00)	7 (22.58)	24 (77.42)	
CC	49 (49.00)	6 (12.24)	43 (87.76)	0.33
Allele				
T	71 (35.50)	17 (23.94)	54 (76.06)	
C	129 (64.50)	19 (14.73)	110 (85.27)	0.13

Furthermore, the multivariate logistic regression model (unadjusted and adjusted) also showed that none genotypes and alleles of the selected SNPs were significantly associated with enalapril-induced dry cough (Table 5.5).

Table 5.5: Adjusted and unadjusted logistic regression model analysis showing the association between SNPs and enalapril-induced dry cough

Variables	**Unadjusted odds ratios (95%CI)**	**Adjusted odds ratios (95%CI)**
rs10267099		
Genotype		
AA	**Ref**	**Ref**
GA	1.94 (0.40-9.31)	0.41 (0.06-2.66)
Allele		
A	**Ref**	**Ref**
G	1.84 (0.40-8.37)	0.40 (0.08-1.98)
rs1042714		
Genotype		
CC	**Ref**	**Ref**
GC	1.43 (0.37-5.49)	0.82 (0.17-4.09)
Allele		
C	**Ref**	**Ref**

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G	1.54 (0.40-5.16)	0.96 (0.25-3.73)
rs1104514		
Genotype		
AA	**Ref**	**Ref**
AG	2.14 (0.72-6.36)	0.38 (0.11-1.40)
GG	1.22 (0.12-12.11)	0.69 (0.06-8.44)
Allele		
A	**Ref**	**Ref**
G	1.54 (0.65-3.60)	0.51 (0.20-1.33)
rs149711321		
Genotype		
TT	-	-
Allele		
T	-	-
rs2070744		
Genotype		
TT	**Ref.**	**Ref**
CT	1.13 (0.12-10.44)	1.03 (0.20-5.21)
CC	1.13 (0.29-4.44)	1.35 (0.10-17.94)
Allele		
T	**Ref.**	**Ref.**
C	1.12 (0.40-3.14)	1.10 (0.36-3.40)
rs4149056		
Genotype		
TT	**Ref.**	**Ref.**

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CT	-	-
Allele		
T	**Ref.**	**Ref.**
C	-	-
rs4648287		
Genotype		
AA	**Ref.**	**Ref.**
AG	1.53 (0.49-4.79)	0.59 (0.14-2.55)
GG	1.28 (0.14-11.98)	0.99 (0.07-14.68)
Allele		
A	**Ref**	**Ref**
G	1.34 (0.54-3.28)	0.77 (0.27-2.19)
rs6749447		
GG	**Ref**	**Ref**
GT	0.85 (0.28-2.65)	1.04 (0.27-4.01)
TT	0.56 (0.12-2.71)	1.35 (0.15-11.87)
Allele		
G	**Ref**	**Ref**
T	0.79 (0.38-1.64)	1.43 (0.57-3.58)
rs699947		
Genotype		
CC	**Ref**	**Ref**
CA	0.67 (0.23-1.95)	1.56 (0.44-5.59)
AA	-	-
Allele		
C	**Ref**	**Ref**

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A	0.85 (0.34-2.14)	1.32 (0.45-3.84)
rs7297610		
Genotype		
CC	**Ref**	**Ref**
CT	1.89 (0.61-5.87)	0.45 (0.12-1.68)
TT	1.16 (0.27-5.03)	0.70 (0.12-4.10)
Allele		
C	**Ref**	**Ref**
T	1.25 (0.58-2.67)	0.76 (0.32-1.81)
rs495828		
Genotype		
GG	**Ref**	**Ref**
GT	-	-
Allele		
G	**Ref**	**Ref**
T	-	-
rs1799722		
Genotype		
CC	**Ref**	**Ref**
CT	0.48 (0.14-1.59)	2.07 (0.53-8.12)
TT	0.42 (0,11-1.57)	4.31 (0.88-21.13)
Allele		
C	**Ref**	**Ref**
T	1.82 (0.26-1.14)	2.08 (0.90-4.81)

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5.3.5 Association between SNPs and enalapril-induced hyponatremia

The chi-square analysis revealed no significant relationships between the selected SNPs and enalapril-induced hyponatremia (Table 5.6.)

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Table 5.6: Chi-square analysis of the relationship between enalapril-induced hyponatremia and selected SNPs.

Variable	Tot al (n; %)	Na >136 (mmol/L) (n; %)	Na ≤145 (mmol/L) (n; %)	P-value
All	100 (100.00)	19 (19.00)	81 (81.00)	.
rs10267099				
Genotype				
GA	18 (18.00)	4 (22.22)	14 (77.78)	
AA	82 (82.00)	15 (18.29)	67 (81.71)	0.7
Allele				
G	18 (9.00)	4 (22.22)	14 (77.77)	
A	183 (91.00)	34 (18.58)	148 (80.87)	0.75
rs1042714				
Genotype				
GC	22 (22.00)	3 (13.64)	19 (86.36)	
CC	78 (78.00)	16 (20.51)	62 (79.48)	0.57
Allele				
G	22 (11.00)	3 (13.64)	19 (86.36)	
C	178 (89.00)	35 (19.66)	143 (80.34)	0.77
rs1104514				
Genotype				
GG	5 (5.00)	1 (20.00)	4 (80.00)	
AG	48 (48.00)	7 (14.58)	41 (85.42)	
AA	47 (47.00)	11 (23.40)	36 (76.60)	0.55
Allele				
G	58 (29.00)	9 (15.52)	49 (84.48)	
A	142 (71.00)	29 (20.42)	113 (79.58)	0.55
rs149711321				
Genotype				
TT	100 (100)	19 (100.00)	81 (100.00)	.

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Allele				
T	200 (100)	38 (100.00)	162 (100.00)	
rs2070744				
Genotype				
CC	6 (6.00)	1 (16.67)	5 (83.33)	
CT	18 (18.00)	4 (22.22)	14 (77.78)	
TT	76 (76.00)	14 (18.42)	62 (81.58)	0.92
Allele				
C	30 (15.00)	6 (20.00)	24 (80.00)	
T	170 (85.00)	32 (18.82)	138 (81.18)	
rs4149056				
Genotype				
CT	2 (2.00)	0 (0.00)	2 (100.00)	
TT	98 (98.00)	19 (19.39)	79 (80.61)	0.45
Allele				
C	2 (1.00)	0 (0.00)	2 (100.00)	
T	198 (99.00)	38 (19.20)	160 (80.80)	1.00
rs4648287				
Genotype				
GG	6 (6.00)	1 (16.67)	5 (83.33)	
AG	35 (35.00)	6 (17.14)	29 (82.86)	
AA	59 (59.00)	12 (20.34)	47 (79.66)	0.92
Allele				
G	47 (23.50)	8 (17.02)	39 (82.98)	
A	153 (76.50)	30 (19.61)	123 (80.39)	0.83
rs6749447				
Genotype				
TT	12 (12.00)	5 (41.67)	7 (58.33)	
GT	50 (50.00)	9 (18.00)	41 (82.00)	
GG	38 (38.00)	5 (13.16)	33 (86.84)	0.09

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Allele				
T	74 (37.00)	19 (25.68)	55 (74.32)	
G	126 (63.00)	19 (15.08)	107 (84.92)	0.92
rs7297610				
Genotype				
CC	40 (40.00)	8 (20.00)	32 (80.00)	
CT	45 (45.00)	9 (20.00)	36 (80.00)	
TT	15 (15.00)	2 (13.33)	13 (86.87)	0.83
Allele				
C	75 (37.50)	13 (17.33)	62 (82.67)	
T	125 (62.50)	25 (20.00)	100 (80.00)	0.71
rs699947				
Genotype				
AA	2 (2.00)	0 (0.00)	2 (100.00)	
CA	32 (32.00)	7 (21.88)	25 (78.13)	
CC	66 (66.00)	12 (18.18)	54 (81.82)	0.72
Allele				
A	35 (17.50)	7 (20.00)	28 (80.00)	
C	165 (82.50)	31 (18.79)	134 (81.21)	0.82
rs495828				
Genotype				
GT	13 (13.00)	2 (15.38)	11 (84.62)	
GG	87 (87.00)	17 (19.54)	70 (80.46)	0.72
Allele				
T	13 (6.50)	2 (15.38)	11 (84.62)	
G	187 (93.50)	36 (19.25)	151 (80.75)	1.00
rs1799722				
Genotype				
TT	20 (20.00)	5 (25.00)	15 (75.00)	
CT	31 (31.00)	6 (19.35)	25 (80.65)	

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CC	49 (49.00)	8 (16.33)	41 (83.67)	0.71
Allele				
T	71 (35.50)	16 (22.54)	55 (77.46)	
C	129 (64.50)	22 (17.05)	107 (82.95)	0.35

The multivariate logistic regression analysis (unadjusted) showed that carriers of the TT genotype of rs6749447 (COR=0.21, 95%CI0.04-0.94) were less likely to exhibit hyponatremia. None of the selected SNPs showed an association with enalapril-induced hyponatremia.

After adjusting for confounding factors, the direction of association for rs6749447 changed. Carriers of the TT (AOR=10.95, 95%CI1.35-88.77) genotype and the T (AOR=2.80, 95%CI1.18-6.70) allele were more likely to exhibit enalapril-induced hyponatremia (Table 5.7).

Table 5.7: Adjusted and unadjusted logistic regression models showing the SNPs association with enalapril-induced hyponatremia.

Variables	**Unadjusted odds ratios (95%CI)**	**Adjusted odds ratios (95%CI)**
rs10267099		
Genotype		
AA	**Ref**	**Ref**
GA	0.78 (0.23-2.72)	1.74 (0.37-8.07)
Allele		
A	**Ref**	**Ref**
G	1.24 (0.39-4.02)	1.12 (0.32-3.63)
rs1042714		
Genotype		
CC	**Ref**	**Ref**
GC	1.55 (0.41-5.91)	0.99 (0.21-4.73)
Allele		
C	**Ref**	**Ref**

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G	0.65 (0.18-2.30)	0.67 (0.17-2.63)
rs1104514		
Genotype		
AA	**Ref**	**Ref**
AG	1.79 (0.63-5.10)	0.51 (0.15-1.72)
GG	1.22 (0.123-12.11)	0.73 (0.06-8.50)
Allele		
A	**Ref**	**Ref**
G	1.40 (0.62-3.17)	0.54 (0.21-1.4)
rs2070744		
Genotype		
TT	**Ref**	**Ref**
CT	0.79 (0.23-2.77)	1.34 (0.29-6.23)
CC	1.13 (0.12-10.44)	0.46 (0.03-6.54)
Allele		
T	**Ref**	**Ref**
C	0.93 (0.35-2.46)	1.12 (0.39-3.23)
rs4648287		
Genotype		
AA	**Ref**	**Ref**
AG	1.23 (0.42-3.65)	0.44 (0.11-1.73)
GG	1.28 (0.14-11.98)	0.29 (0.02-4.61)
Allele		
A	**Ref**	**Ref**
G	1.19 (0.50-2.81)	0.60 (0.22-1.61)
rs6749447		

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Genotype		
GG	**Ref**	**Ref**
GT	0.69 (0.21-2.26)	1.89 (0.48-7.42)
TT	**0.21 (0.04-0.94) ***	**10.95 (1.35-88.77) ***
Allele		
G	**Ref**	**Ref**
T	0.51 (0.25-1.050)	**2.80 (1.18-6.70) ***
rs699947		
Genotype		
CC	**Ref**	**Ref**
CA	0.75 (0.26-2.13)	0.93 (0.26-3.27)
AA	-	-
Allele		
C	**Ref**	**Ref**
A	0.93 (0.37-2.31)	0.90 (0.32-2.59)
rs7297610		
Genotype		
CC	**Ref**	**Ref**
CT	1.00 (0.35-2.90)	1.15 (0.34-3.91)
TT	1.63 (0.30-8.70)	0.59 (0.09-4.06)
Allele		
T	**Ref**	**Ref**
C	1.19 (0.40-1.76)	0.82 (0.36-1.86)
rs495828		
Genotype		
GG	**Ref**	**Ref**

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GT	1.34 (0.27-6.60)	0.72 (0.11-4.55)
Allele		
G	**Ref**	**Ref**
T	1.31 (0.28-6.18)	0.90 (0.17-4.83)
rs1799722		
Genotype		
CC	**Ref**	**Ref**
CT	0.81 (0.25-2.62)	0.86 (0.22-3.38)
TT	0.59 (0.17-2.07)	2.38 (0.55-10.23)
Allele		
T	**Ref**	**Ref**
C	0.71 (0.34-1.45)	1.44 (0.64-3.23)

5.4 Discussion

The therapeutic effects of enalapril are well documented in the literature. However, the extent to which SNPs influence enalapril-induced adverse reactions among individuals of African origin is unknown. Therefore, this study investigated the association between selected SNPs and enalapril-induced dry cough and hyponatremia.

Eighteen per cent (18%) of the participants reported enalapril-induced dry cough. Therefore, this study's prevalence of enalapril-induced dry cough is within the range reported in previous studies (10-35%). In contrast, a prevalence between 16.9 and 63% of hyponatremia has been reported (151, 155). Furthermore, the incidence of enalapril-induced dry cough has been shown to vary from population to population. For instance, the prevalence of dry cough among the Chinese (209) and the Philippines was estimated at 32% and 22%, respectively (282). The differences in the numbers that were reported may be due to genetic variation.

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The study further assessed the effect of 12 selected SNPs on an enalapril-induced dry cough. None of the SNPs was found to be associated with enalapril-induced dry cough the in the Venda population. However, previous studies found that two SNPs, rs4149056 and rs495828, were significantly associated with enalapril-induced dry cough in the Chinese population (21, 209). Furthermore, a study in the Spanish population also found an association between the ABO gene and enalapril-induced dry cough (283). Of note, the minor alleles of both rs4149056 and rs495828 SNPs were not detected in our cohort. Furthermore, a study done in the Japanese population found that SNP rs1799722 was associated with enalapril-induced dry cough (284, 285). However, similarly to the current study, these findings were not replicated in the Korean and Spanish populations (286, 287). Furthermore, four other different SNPs within the BDKRB2 gene were associated with dry cough in Korean and Spanish populations (286). Therefore, rs1799722 may be deemed non-causal in the Venda population, but other untested SNPs in the BDKRB2 gene may be associated with dry cough. These findings suggest that gene expression and response to a particular stimulus may vary from population to population. Moreover, gene variants that may have a significant function on other populations may be less significant on others. Therefore, it is essential to establish a specific association between genetic variants within a specific population.

About 19% of the participants had sodium levels below 136 mmol/L and were classified as having hyponatremia. Hyponatremia is seen in 15-30% of hospital settings as the result of the inability of the kidney to excrete a water load or excess water intake (276). Few studies have reported enalapril-induced hyponatremia, most of which are case studies. Furthermore, previous studies have not been able to elucidate the factors behind enalapril-induced

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hyponatremia (288, 289). The present study examined the possible link between enalapril-induced hyponatremia and genetic variants (12 SNPs). Out of 12 SNPs, only rs6749447 was significantly association with enalapril-induced hyponatremia. We further demonstrated that patients with the minor allele T of rs6749447 were more likely to have low serum sodium levels, thus developing hyponatremia. Previous studies found that the minor allele T of rs6749447 was associated with a decrease in sodium chloride sensitivity in patients with hypertension (290, 291). A previous study found that patients taking angiotensin II receptor antagonists with the minor allele T of rs6749447 had low sodium levels. (292). Furthermore, other variants within the STK39 have been associated with increased renal sodium excretion (Wang et al., 2009).

5.5 Conclusion

The present study reports a high prevalence of enalapril-induced dry cough and hyponatremia within patients in the Vhembe district. The study demonstrated no association between the selected genetic variants and enalapril-induced dry cough. However, the genetic variant rs6749447 of the STK39 gene was positively associated with enalapril-induced hyponatremia. Therefore, the scientific community, clinicians and health authorities need to investigate other possible genetic variants that may be involved in ADRs observed in patients on enalapril therapy and other anti-hypertensive drugs.

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Chapter 6: Conclusion and recommendations.

Hypertension is a significant risk factor for CVDs and a leading cause of premature death worldwide. Studies have shown that the prevalence of hypertension is growing in low- and middle-income countries, especially in Africa. Many countries have implemented hypertension awareness, diagnostics, and control strategies. Despite such strategies, most patients receiving treatment for hypertension fail to achieve optimum control of their condition. As a result, uncontrolled hypertension poses additional challenges in countries such as South Africa, which are already facing financial difficulties and an overburdened healthcare system. Thus, establishing the prevalence and investigating the factors associated with uncontrolled hypertension is critically important in lessening the burden it imposes on the economy. In this study, we investigated the prevalence and factors associated with uncontrolled hypertension in a rural community-based in the Vhembe district of the Limpopo province. Our results showed that the prevalence of uncontrolled hypertension was 38.55%. This figure was lower than the numbers reported by similar studies conducted in South Africa. Although the prevalence of uncontrolled hypertension was low in this population, we found that participants with no known diagnosis of DM, participants who were on combination therapy of three anti-hypertensive drugs and participants who did not experience adverse reactions were less likely to have uncontrolled hypertension.

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Furthermore, the study was extended to investigate the factors associated with ADRs and non-adherence. We noticed plenty of ADRs (19.15%) and non-adherence (14.43) to anti-hypertensive medication among the study participants, which was lower than the figures reported in previous studies in similar settings. We further demonstrated that the number of hypertensive drugs was significantly associated with poor adherence. Our findings indicate that to improve hypertension control and avoid resource misuse in similar settings, clinicians

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should pay close attention to ADRs and prescription patterns of antihypertensive drugs. We further demonstrated that treatment for hypertension should be prescribed according to concomitant risk factors, including DM and other related metabolic abnormalities. Furthermore, the low figures of uncontrolled hypertension, ADRs and non-adherence that are reported in this study reflect the efforts of the South African government program that utilises community health workers (CHWs) under the supervision of facility-based nurses to provide health education, promote healthy behaviours and assess community health needs (232).

Enalapril has long been used to treat hypertension, heart failure, left ventricular dysfunction, and chronic kidney failure. However, adverse drug reactions (ADRs) have been reported and linked to uncontrolled hypertension and non-adherence. In this study, we observed many enalapril-induced ADRs including dry cough and hyponatremia. We further investigated SNPs associated with the development of both conditions. Our SNP panel included 12 SNPs in genes directly or indirectly involved in hypertension and the pathway associated with enalapril. None of the 12 SNPs were associated with enalapril, and only one rs6749447 was significantly associated with enalapril-induced hyponatremia. We further demonstrated that carriers of the genotype TT or allele T of rs6749447 (STK39) were more likely to develop the condition.

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To our knowledge, the present study is the first to investigate the genetic association of enalapril-induced ADR in an African population. Although most SNPs showed no association with both conditions, the study highlighted the need for more pharmacogenetics and pharmacovigilance research in Africa. Moreover, genetic testing is required, particularly in African populations, to determine the baseline incidence of adverse reactions.

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Appendices

Appendix 1-Ethical Clearance

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

UNIVERSITY of the WESTERN CAPE

Private Bag X17, Bellville 7535
South Africa
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www.uwc.ac.za

12 March 2018

Prof M Benjeddou
Biotechnology
Faculty of Natural Sciences

Ethics Reference Number: BM16/5/19

Project Title: Precision Medicine: Pharmacogenomics and Development of Individualized drug therapy for sub-Saharan African populations.

Approval Period: 23 February 2018 – 23 February 2019

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER -130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE

Appendix 2-Ethical Clearance

http://etd.uwc.ac.za/

UNIVERSITY of the
WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

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06 March 2019

Prof M Benjeddou
Biotechnology
Faculty of Natural Sciences

Ethics Reference Number: BM16/5/19

Project Title: Precision Medicine: Pharmacogenomics and development of individualized drug therapy for sub-Saharan African populations.

Approval Period: 15 February 2019 – 15 February 2020

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

BMREC REGISTRATION NUMBER -130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE

http://etd.uwc.ac.za/

Appendix 3 Approval from Limpopo department of health

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

Enquiries: Stols M.L (015 293 6169) Ref:4/2/2

Professor M Benjeddou
Department of Biotechnology
University of the Western Cape
Private Bag X17
Bellville
7535

Greetings,

RE: Precision Medicine: Pharmacogenomics and development of individualized drug therapy for Sub-Saharan African Populations

The above matter refers.

1. Permission to conduct the above mentioned study is hereby granted.
2. Kindly be informed that:-
   - Research must be loaded on the NHRD site (http://nhrd.hst.org.za) by the researcher.
   - Further arrangement should be made with the targeted institutions, after consultation with the District Executive Manager.
   - In the course of your study there should be no action that disrupts the services.
   - After completion of the study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   - The above approval is valid for a 3 year period.
   - If the proposal has been amended, a new approval should be sought from the Department of Health.
   - Kindly note, that the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated.

Head of Department

12/09/2017
Date

18 College Street, Polokwane, 0700, Private Bag x9302, POLOKWANE, 0700
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http://etd.uwc.ac.za/

Appendix 4: Approval from the department of health Vhembe district.

PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OFHEALTH
VHEMBE DISTRICT

Ref: S5/6
Enq: Muvari MME
Date: 26 September 2017

Dear Professor M Benjeddou

PERMISSION TO CONDUCT A RESEARCH ON THE "Precision Medicine: Pharmacologenomics and development of individualized drug therapy for Sub-Saharan African Population"

1. The above matter refers.

2. Your letter received on the 26 September 2017 requesting for Permission to conduct an investigation is hereby acknowledged.

3. The District has no objection to your request.

4. Permission is therefore granted for the study to be conducted within Vhembe District.

5. You are however advised to make the necessary arrangements with the facilities concerned.

Wishing you success in your endeavors.

..... 26/09/2017
DISTRICT CHIEF DIRECTOR DATE

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OLD parliamentary Building Tel (015) 962 1000 (Health) (015) 962 4958 (Social Dev) Fax (015) 962 2274/4623
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Appendix 5 Consent form

UNIVERSITY OF THE WESTERN CAPE

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Tel: +27 21 959 2080, Fax: +27 21 959 3505

E-mail: mbenjeddou@uwc.ac.za ; mongi.benjeddou@gmail.com

CONSENT FORM

Project Title: Precision Medicine: investigation of the association between genetic variations and response to diabetic and hypertensive drugs

The study has been described to me in language that I understand and I freely and voluntarily agree to participate in it. My questions about the study have been answered. I understand that my identity kept confidential and that I may withdraw from the study without giving a reason at any time and this will not negatively affect me in any way.

Participant's name: _____

Participant's signature: _____ **Date:** _____

Should participants have any questions regarding this study or which to report any problems they have experienced related to the study, they should please contact the study coordinator.

Study Coodinator's Name: Prof Mongi Benjeddou
Tel: 021 959 20180
E-mail: mbenjeddou@uwc.ac.za
Address: *Address: University of the Western Cape, Department of Biotechnology, Precision Medicine Unit, Private Bag X 17,*
Bellville 7535, South Africa.

Lab Code:	Hospital ID:

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