Sex Differences in the Modifiable Risk Factors for Atrial Fibrillation at Moi Teaching and Referral Hospital

by

Loise Ng'ang'a

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Duke University

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Joseph Egger

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Background: Evidence mainly from high-income countries has demonstrated sex related differences in the incidence, presentation and management of patients with non-valvular AF. Such evidence is scarce in sub-Saharan Africa, yet there is a rising prevalence of AF. This study aimed to determine sex differences in the distribution and treatment pattern for modifiable risk factors in Western Kenya.

Methods: The study included two phases. Phase 1 comprised of secondary data analysis from a case control study – Study of Genetics of Atrial Fibrillation in an African population. Phase 2 included retrospective analysis of medical records at the cardiac clinic in a large referral hospital in Kenya. We determined the distribution and treatment pattern for modifiable risk factors for AF using chi-square and fisher's exact test.

Results: Hypertension is the most prevalent modifiable risk factor for AF in western Kenya. The prevalence among men and women was 65% and 76% respectively, but this difference was not significant. Three percent of men were obese compared to 24 % of women ($p = 0.013$). Men were more likely to drink alcohol ($p = 0.001$) and have a history of smoking compared to women ($p = <0.001$). Among men, tetra choric correlation showed a very strong association between smoking and alcohol intake (correlation coefficient > 0.9), and hypertension and obesity/overweight (correlation coefficient >0.9). These correlations were weaker among women with a correlation coefficient of 0.40 and 0.38 respectively. Among the participants, only 21% had weight and height measurements recorded. Nutritional counselling was recorded for only 3% of those who had a BMI > 29.9. Similarly, less than 10% of those with a history of smoking or alcohol intake received counselling on cessation strategies.

Conclusion: Hypertension is the most common modifiable risk factor for AF in western Kenya. There are significant differences among men and women in the distribution of dyslipidemia, alcohol intake, smoking and obesity. These modifiable risk factors have strikingly low rates of interventions. Management of patients with AF should include both screening and interventions for modifiable risk factors. Packaging of intervention should consider sex-specific differences.

Dedication

I dedicate this thesis to my entire family, whose love, support and wisdom will always be my treasure.

My friends, Judith and Mwangi, whose consistent believe invaluable assistance and encouragement have always come through when most needed.

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Finally, I thank the Duke Global Health Institute who provided the opportunity and resources for my master's program and for the accomplishment of this project.

1. Introduction

1.1 *Definition & Pathogenesis of Atrial fibrillation*

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia that results from abnormal rapid impulses (Fuster et al., 2006). It is characterized by chaotic atrial activation that leads to ineffective atrial functioning (Wann et al., 2011)**.** The pathophysiology of AF is determined to be complex and typically results from the following four types of disturbances: ion channel dysfunction, calcium handling abnormalities, structural remodeling and autonomic neural dysregulation (Allessie et al., 2001). AF can be categorized based on its temporal patterns, etiology or whether it complicates valvular or structural heart disease.

1.2 *Epidemiology of atrial fibrillation*

AF is the most common sustained cardiac arrhythmia observed in clinical practice. It is a significant cause of mortality and morbidity (Go et al., 2001; Mensah et al., 2015) and attracts high health care costs (Wann et al., 2011). Approximately 0.5% of the world's population has AF (Chugh et al., 2013). Existing evidence indicates that the prevalence of AF is higher in high-income countries compared to the low and middle-income countries. In the United States alone, over 2.3 million adults have AF (Go et al., 2001). Similar statistics have been observed in Europe and Australia, where approximately 1% of the adult population has AF (Chugh et al., 2013; Rahman, Kwan, & Benjamin, 2014) .The prevalence of AF has been rising significantly worldwide. The Framingham Heart community based cohort study established that between 1967 to 2007 the age adjusted prevalence of AF had increased fourfold from 20.4 to 96.2 cases per 1000 person years among men and 13.7 to 49.4 per 1000 person years among women (Schnabel et al., 2015). It is projected that within the next 4-5 decades, AF will affect roughly 12 million adults in the United States (Miyasaka et al., 2006) and 17.9 million in the European Union (Krijthe et al., 2013). In Asia AF prevalence is also growing rapidly. Between 2001 and 2012, AF among adult Chinese population increased 20-fold from 0.01 in 2001 to 0.20 per 100 population in 2012 (Guo et al., 2015).

There is limited data regarding the burden of AF in sub-Saharan Africa (SSA). Nonetheless, literature has shown a substantial increase in the prevalence of AF in this region. The 2010 Global Burden of Disease study, conducted in SSA established that among cardiovascular diseases, AF had the largest relative increase between 1990 and 2010 going from 0.7% in 1990 to 1.0% in 2010 (Moran et al., 2013). Moreover, stroke which is the most significant complication associated with AF (Go et al., 2001) accounted for the highest proportion (38%) of cardiovascular related deaths and disability between 1990 and 2013 (Mensah et al., 2015). Compared to high-income countries, AF in SSA affects relatively younger individuals. A large prospective registry study, with findings from 10 African countries, showed that the mean age of individuals diagnosed with AF in Africa is 57 years. This stands in contrast to North America and Europe where the mean age is roughly 70 years (Oldgren et al., 2014). The AF prevalence among the younger population may be associated with negative socio-economic impact related to reduced labor work force and disrupted family income sources in the low and middle-income countries (Stambler & Ngunga, 2015).

The reason for the rising burden of AF is not well established (Go et al., 2001).The shift has been attributed to the changing demographic transition characterized by an increase of the elderly population (Krijthe et al., 2013). In SSA, rheumatic heart disease (RHD) has historically been considered a significant risk factor for AF, however this pattern may be changing. Between 1990 and 2010, the rank for RHD shifted from 5^{th} to 6^{th} position among the leading causes of cardiovascular disease (CVD) burden in SSA, accounting for 7.5 % of the disease burden in 1990 and 5.9% in 2010 (Moran et al., 2013). In addition, a study conducted within an urban setting in Kenya showed that valvular heart disease accounted for only 12% of participants with AF (Shavadia et al., 2013). Other factors such as the rising trend of the modifiable risk factors for AF could also account for the rising prevalence. Evidence from the 2013 Global Burden of Disease Study demonstrates an increase in the prevalence of obesity and overweight in both low and high-income countries. The increase is disproportionate between men and women. The proportion of overweight men increased from 29% in 1980 to 37% in 2013 while the proportion of women increased from 30% to 38% (Ng et al., 2014). Notably, the pattern differed between high and low income countries. While more men than women were obese or overweight in high-income countries, more women than men were obese or overweight in low-income countries (Ng et al., 2014). In addition, between 1990 and 2010 hypertensive heart disease moved to a rank higher among the leading cause of CVD in SSA, accounting for 7.0% of disease burden in 2010 up from 5.9% in 1990 (Moran et al., 2013).

1.3 ***Modifiable Risk factors for AF***

Modifiable risk factors associated with AF have been studied extensively. There is a substantial body of evidence associating obesity and development of AF (Goudis, Korantzopoulos, Ntalas, Kallergis, & Ketikoglou, 2015; Huxley et al., 2011; Wang et al., 2004). Findings from a prospective, community- based cohort study, which included a mean follow up of 13.7 years, showed a 4% increase in the risk of AF per 1-unit increase in BMI (Wang et al., 2004). Consistent findings were observed in the Women's Health study; with every 1 kg/m^2 increase in BMI the relative risk of AF increased by 4.7 % (Tedrow et al., 2010). In addition to obesity, blood lipid levels have also been linked with AF. An analysis conducted on two community-based studies in the Unites states showed an inverse association between high-density lipoproteins (HDL) and risk of AF (Watanabe et al., 2011). The study also showed a higher hazard of developing AF among participants with high triglyceride levels. Similarly, a cohort study from Japan established that among women, every 10% decrease in HDL increases the risk of AF by 28%. (Watanabe et al., 2011). Among all the modifiable risk factors, high blood pressure is established as the strongest risk factor associated with incident AF (Oldgren et al., 2014). Other modifiable risk factors associated with AF include heavy alcohol consumption and cigarette smoking. Several studies have explored the association between alcohol intake and atrial fibrillation (Larsson, Drca, & Wolk, 2014; Mukamal, Tolstrup, Friberg, Jensen, & Grønbæk, 2005; Psaty et al., 1997; Tolstrup, Wium-Andersen, Ørsted, & Nordestgaard, 2016). Although there have been inconsistent results regarding moderate alcohol intake and the risk of AF, most studies support a positive association between heavy alcohol consumption and the risk of AF. For example in the Copenhagen City Heart study, roughly 5% of all AF cases were attributed to heavy alcohol consumption (Mukamal et al., 2005). Smokers are also more likely to develop incident AF compared to non-smokers (Heeringa, Kors, Hofman, van Rooij, & Witteman, 2008).

1.4 *Sex and AF*

Evidence mainly from Western Europe and North America have demonstrated sex related differences in the incidence, presentation and management of patients with non-valvular AF. Incident AF is higher among men compared to women (Dagres et al., 2007). Conversely, women with AF are older, experience a lower quality of life and are more likely to present with heart failure (Dagres et al., 2007; Xiong et al., 2015). Women with AF are at a higher risk of developing stroke compared to men with AF. Evidence from the AnTicoagulation and Risk factors in Atrial fibrillation (ATRIA) study showed that women with AF have a 1.6 greater risk of developing stroke than men (Fang et al., 2005). Moreover, a recent systematic review established sex and regional related differences in the risk of mortality associated with AF. AF-related mortality is greater in males in developed countries. In contrast, in developing countries, women suffer greater mortality due to AF (Figure 1). These suggest that evidence on sex related differences established from developed countries may not be extrapolated to developing countries. In light of this evidence gap, our study aimed to determine the extent to which there are sex related differences in the treatment and distribution of modifiable risk factors among non-valvular AF patients at Moi Teaching and Referral Hospital in Kenya. Our specific aims included:

Aim 1*:* To determine the distribution of modifiable risk factors for non-valvular AF according to sex, among patients in MTRH.

Aim 2: To determine the differential effect of modifiable risk factors for non-valvular AF to mortality outcome according to sex.

Aim 3: To describe the treatment patterns of modifiable risk factors for non-valvular AF in both men and women.

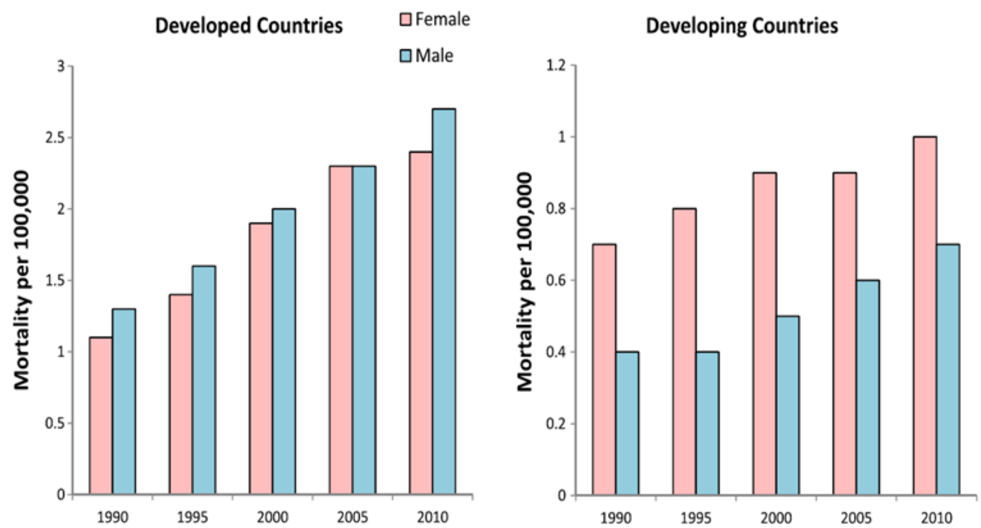

Figure 1: Mortality associated with atrial fibrillation stratified by sex and region

In developed countries mortality rates are slightly higher in males compared to females. By contrast, in developed countries mortality rates are significantly higher in females compared to males. **Source: Adapted from (Chugh et al., 2013)**

2. Methods

2.1 Study design

This study was conducted in two phases, using different, but complimentary, data sources.

Phase 1 was a secondary analysis of data obtained from a hospital based case control study entitled the Study of Genetics of Atrial Fibrillation in an African population (SIGNAL) (Bloomfield et al., 2015). The objective of Phase 1 was to describe the sex specific distribution of modifiable risk factors for non-valvular AF and to determine their differential effects on mortality outcomes according to sex.

Phase 2 comprised of a retrospective chart review of patients diagnosed with non-valvular AF at Moi Teaching and Referral Hospital. The objective of Phase 2 was to describe sex specific treatment patterns for modifiable risk factor for AF.

2.2 Setting

Both phases of the study were conducted at the Moi Teaching and Referral Hospital (MTRH) Kenya, primarily at the cardiac department. MTRH is the second largest referral hospital in Kenya, located in the western region, in Eldoret town. MTRH provides both inpatient and outpatient services to a catchment area of approximately 20 million people from both rural and urban settings. The majority of patients seeking health care services from this hospital come from either middle or poor social-economic background. The hospitals cardiac registry unit is located within the Chandaria Cancer Chronic and

Disease Management Centre (CCCDMC) building, which also houses the cardiac consultant clinics and is located within the MTRH grounds. This unit stores all the medical chart records of patients who attend the outpatient cardiac clinical services at MTRH as well as hospital discharge files for patients diagnosed with any cardiac condition. This setting was selected based on the following 2 reasons (1) It has a broad mix of patients and (2) is equipped to provide specialized cardiac services, moreover, it is the only hospital in Kenya that provides specialized cardiac care services (Binanay et al., 2015)

2.3 Study Population

Based on the two phases of the study, the study population is made up of two sets of participants:

Phase 1: The SIGNAL study enrolled a convenience sample of 148 AF patients. This sample included two groups of AF patients. Those with valvular AF (due to rheumatic heart disease) and those with non-valvular AF. The enrollment period occurred between October 2013 and June 2014. All patients at least 18 years of age seeking cardiac services at MTRH and with a confirmed diagnosis of AF were eligible to participate as cases. Patients were excluded if they had known genetic syndromes, congenital heart defects, and severe illnesses precluding ECG or echocardiogram. Both prevalent and incident AF cases were included in the SIGNAL study. All cases with valvular AF status were excluded from the phase 1 population.

Phase 2: The retrospective chart review included participants who had been active in the cardiac clinic follow-up for at least six months prior to the enrollment period. Similar to the participants included in Phase 1 analysis, the chart review included patients who were at least 18 years of age, with a confirmed diagnosis of non-valvular AF. Noteworthy, non-valvular AF participants enrolled in the SIGNAL study were eligible to participate. Participants who were pregnant, not under management in the cardiac clinic for at least six months and those with valvular heart disease were excluded from participating in this phase of the study.

2.4 Procedures

Phase 1: During the SIGNAL study, participants completed structured questionnaires, had physical examinations, 12-lead ECG and echocardiogram. In addition, they had venous blood samples collected for laboratory analysis (Bloomfield et al., 2015). Enrollment and all study procedures were mainly completed on a single hospital visit although on few occasions study procedures were completed a day later than the enrollment date. The diagnosis of AF was made if the irregular rhythm was recorded on at-least one ECG record. A majority of the ECGs were performed at MTRH using a page writer TC 30 ECG machine (Philips Health care, Andover MA), but a few ECGs conducted from private health care providers were also considered. To rule out rheumatic heart disease all participants, underwent an echocardiogram test performed by an experienced sonographer at MTRH. In addition, all participants enrolled in the

SIGNAL study underwent a 12-month follow up assessment to capture the cardiac and non-cardiac mortality, medication usage hospitalizations and change in life habits from baseline.

Phase 2: During the retrospective review, cardiac files at the MTRH cardiac registry unit were screened. The chart review process was conducted systematically. Consecutive files stored in the cardiac registry unit were reviewed, starting from the participants enrolled in 2012 to those enrolled in 2015 including patients who had been enrolled in SIGNAL. Data extracted from the medical charts primarily included information on five modifiable risk factors associated with AF namely: smoking status, alcohol consumption status, systolic and diastolic blood pressures and blood lipid levels. In addition, we extracted demographic information on the date of birth and sex of the participants. Data extraction and the definition of the modifiable risk factors are described in the following section. The campus institutional review and ethics board at Duke University and the institutional review and ethics board at Moi Teaching and Referral Hospital approved all study procedures.

2.5 Measures

2.5.1 *Ascertainment of non-valvular AF*

Phase I: To determine the AF status in the SIGNAL study, participants ECG records and echocardiographic reports were reviewed by a physician involved with the study to verify AF and rule out valvular heart disease respectively. In addition, the participants underwent a detailed physical and clinical assessment as recommended in the routine management of AF.

***Phase 2*:** Non-valvular AF status was based on confirmed diagnosis recorded on the patients' medical charts. In addition to this diagnosis, recorded interpretation of ECG results as well as echocardiographic results were reviewed to further confirm the non-valvular AF status.

2.5.2 *Dyslipidemia*

Based on the laboratory records available in the patient's charts, lipid values including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride and total cholesterol (TC) levels were extracted. The data were extracted based on the earliest recorded lipid levels, ideally recorded on the laboratory analysis tests performed during the participant's initial visit to the MTRH cardiovascular department. Follow up levels were obtained from the most recent laboratory levels recorded, defined as the most recent laboratory tests performed prior to this study's enrollment process. Dyslipidemia was defined as HDL < 1mm/l for males and HDL < 1. 3mm/l for females or LDL > 3.1 mmol/l or Triglycerides > 1.7 mm/l or Total cholesterol> 5.2 mmol/l or a combination of all or any of these abnormal lipid values. In addition, data regarding prescription of statin medication and diet counselling were extracted from the charts. This data was dichotomized to 'yes' if the information recorded in the charts indicated that the intervention of interest was performed and to ‘no’ if either the information indicated the intervention was not done or if the information was missing.

2.5.3 *Hypertension*

Earliest blood pressure readings were extracted based on the baseline systolic and diastolic blood pressure recorded on participants’ initial visit to MTRH. The follow up measurements were obtained from participants’ most recent visit prior to the enrollment period. Hypertension was defined as diastolic blood pressure >=90mmHg or systolic blood pressure >=140mm/hg or prescription of antihypertensive medication. In addition, we obtained information on whether participants received antihypertensive prescription, and counselling on lifestyle management. This information was dichotomized to ‘yes’ if the information recorded in the charts indicated that the intervention was performed and to ‘no’ if either the information indicated the intervention was not performed or if the information was missing.

2.5.4 *Alcohol Intake and Cigarette smoking*

Information on the status of alcohol consumption and cigarette smoking was obtained from the participant's medical history recorded during the initial visit as well as during routine clinic visits. In addition, information related to counselling associated with smoking and alcohol consumption was extracted. This information was dichotomized to ‘yes’ if the information recorded in the charts indicated that the intervention was performed and to 'no' if either the information indicated the intervention was not performed or if the information was missing.

2.6 Analysis

Study data from both phase 1 and 2 were entered using REDcap electronic data capture (Harris et al., 2009) tool hosted at AMPATH and Duke University respectively. All the statistical analyses were performed using STATA version 14. Overall, to obtain sex-specific results, we stratified our analysis by sex (men and women). To obtain descriptive statistics for continuous variables, we used independent sample t-test for normally distributed data (age) and Wilcoxon rank sum test for data (duration of AF) that did not meet the normality assumption. All the modifiable risk factors were defined as categorical variables. Hypertension, obesity and dyslipidemia were defined as binary variables (yes/no) and tobacco use and alcohol as categorical variables (yes/no/stopped). To address aim 1, we used chi-square test of independence or fisher's exact test to explore whether there was significant association in the distribution of modifiable risk factors between men and women. The chi-square test was used if the frequency counts of the data variables of interest were at least five in each strata and fishers exact test when the frequency counts in specific strata were less than five. Additionally, we performed tetrachoric correlation, test that is applicable to dichotomous variables, to determine the correlation of the modifiable risk factors among men and women.

In aim 2, we hypothesized that there was a significant difference in the association of modifiable risk factors and mortality among men and women. To test this hypothesis we used fisher's exact test. We described the modifiable risk factors for AF as the predictor variables and death (death/no death) associated with AF as the outcome variable.

In the third aim, we hypothesized that there was a significant difference in the treatment patterns for the modifiable risk factors between men and women. To test this hypothesis we used either chi-square or fishers exact test and restricted our analysis to participants whose modifiable risk factors were in the abnormal category (as described in section 2.5).

3. Results

***Phase 1**:* 72 non-valvular AF cases who had been enrolled in SIGNAL, case control study were included in the secondary analysis to address of aims 1 and 2.

***Phase 2**:* 3373, cardiac files were screened in this phase. Of these files, 87 non-valvular AF patients who met the study's inclusion criteria were included in the analysis to address the aim 3, which sought to determine the treatment patterns of the modifiable risk factors for AF (Figure 2)

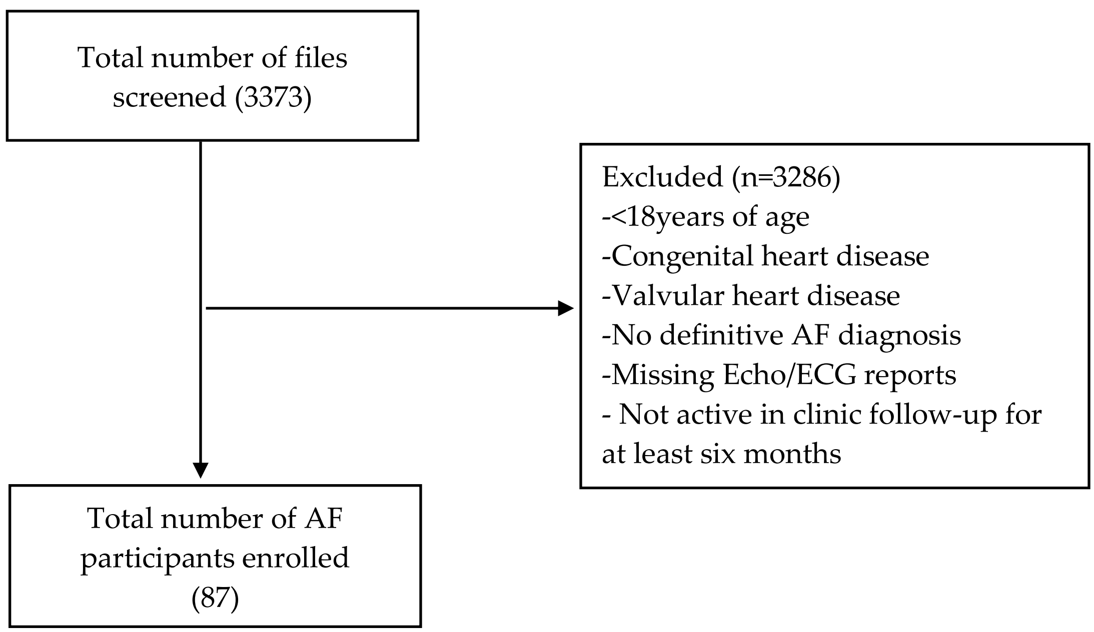

Figure 2: Flow diagram of the screening process in phase 2

The medical charts of all patients who were on active follow up in the cardiology clinic at Moi Teaching and Referral Hospital between 2012 and 2016 were reviewed. Patients were excluded following the criteria explained in the text (we did not obtain data on specific exclusion criteria).We also excluded participants who missed ECG and Echocardiographic records. The screening process took place from May 2016 – August 2016.

3.1 Distribution of modifiable risk factors for AF

3.1.1 *Distribution of modifiable risk factors according to sex*

Table 1 below summarizes basic demographic characteristics and the distribution of modifiable risk factors according to sex among the phase 1 population. Patients' age ranged between 18 and 93 years old, with an average of 68 years (see appendix B. for age summary for phase 2). Female patients were 53% of the study sample and were on average four years younger than the male patients. The average duration since diagnosis of non-valvular AF among the participants was 2 years. Females were more likely to have a higher body mass index than males. The difference in proportion of obese males and females was significant. Only 3% of males compared to 24% of all females were obese (BMI > 29.9) (p= 0.013). This difference was, however, not significant after inclusion of overweight (BMI >25 - <30) participants in this analysis. Females were more likely to have dyslipidemia (79%) compared to 55% among males (p=0.036). Males were however more likely to report tobacco smoking and alcohol intake compared to females (p= 0.001, p= <0.001 respectively). More females (76%) presented with hypertension compared to males (65%), although this difference was not statistically significant.

Table 1: Distribution of modifiable risk factors among non-valvular AF patients for phase 1

Characteristics	**Total (n=72)**	**Male (n=34)**	**Female (n=38)**	P value
Age, yrs. mean (SD)	72(13)	70 (15)	66 (11)	0.125[a]
AF duration(yrs.) Median (IQ)	2(0.5,4)	2 (0.7,4)	2 (0.5,3)	0.40[b]

Modifiable Risk Factors				
Alcohol % (n)				
No	31 (43)	15 (5)	68 (26)	< 0.001†
Yes	3 (4)	9 (3)	0	
Stopped	38 (53)	76 (26)	32 (12)	
Hypertension %(n)				
No	29(21)	35 (12)	24 (9)	0.279‡
Yes	71(51)	65(22)	76 (29)	
Obesity/overweight* % (n)				
No	67 (46)	78 (25)	57 (21)	0.076‡
Yes	33 (23)	22 (7)	43 (16)	
Obesity*% (n)				
No	86 (59)	97 (31)	76 (28)	0.016†
Yes	14 (10)	3 (1)	24 (9)	
Tobacco use %(n)				
Never	63 (45)	44 (15)	79 (30)	0.001†
Yes	6 (4)	3 (1)	8 (3)	
Stopped	31(23)	53 (18)	13 (5)	
Dyslipidemia(all)% (n)				
No	32 (23)	44 (15)	21(8)	0.036‡
Yes	68 (49)	56 (19)	79 (30)	
Dyslipidemia(each lipid category)				
Low HDL % (n)				
No	40(29)	35(12)	45 (17)	0.415‡
Yes	60 (43)	65 (22)	55 (21)	
High LDL % (n)				
No	72 (51)	71(24)	74 (28)	0.770‡
Yes	28 (21)	29 (10)	26 (10)	
High triglycerides % (n)				
No	79(57)	74 (25)	84 (32)	0.265‡
Yes	21(15)	26 (9)	16 (6)	
High cholesterol % (n)				
No	85(54)	74 (25)	76 (29)	0.785‡
Yes	25 (18)	26 (9)	24 (9)	

*(n) = 69

[a] t-sample t-test, [b] Wilcoxon rank sum test, †Fisher's exact test and ‡ chi-square tests used to generate p-values

The difference in the distribution of alcohol, obesity, tobacco use and dyslipidemia (all lipoproteins combined) among men and women is significant at 5% alpha level.

3.1.2 *Clustering of risk factors per participant*

Overall, most (62%) of the participants had at least 3 risk factors. This comprised of 69% of the men participants and 57% of the women (Figure.3). All men had at least 2 risk factors, 3% presented with all the 5 risk factors. Only 3% of women presented with no risk factor and none of them presented with a combination of all the five risk factors (Figure 3).

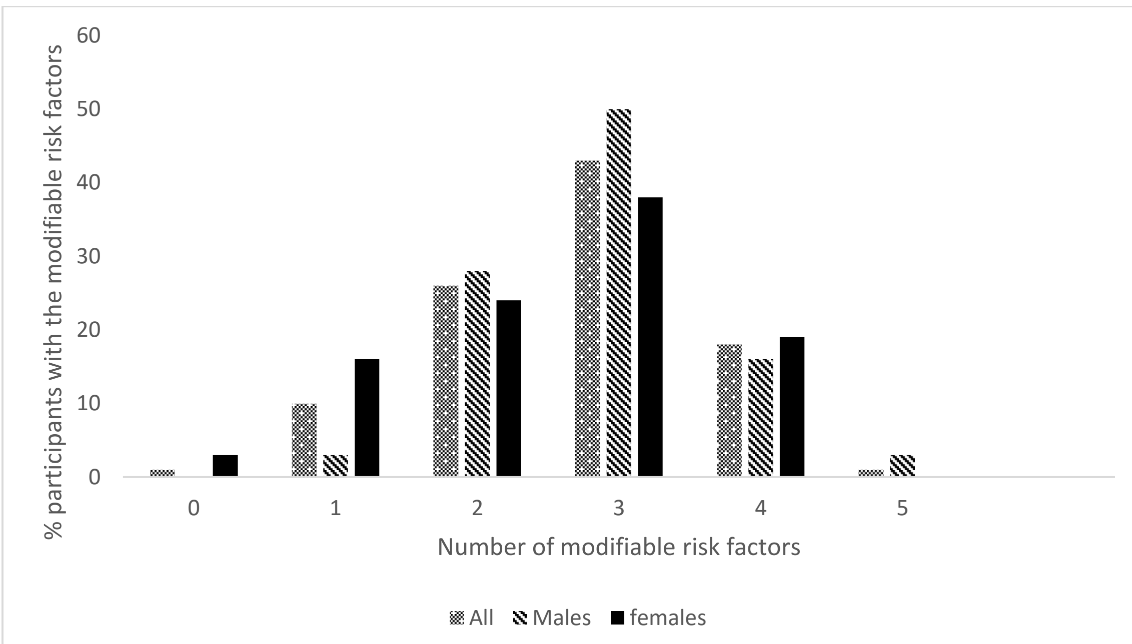

Figure 3: **Number of modifiable risk factors per participant**:
Majority of the participants had at least 3 modifiable risk factors

3.1.3 *Tetra choric correlation between the modifiable risk factors*

The correlation of the modifiable risk factors is roughly similar between men and women. There is a perfect positive correlation (1.0) between obesity/overweight and hypertension among men. Whereas the correlation of the two modifiable risk factors is also positive among women, it is relatively weaker (0.38). Smoking and alcohol intake are also perfectly positive correlated (1.0) among men with a weaker correlation among women (0.48). Tables 2 and 3 below summarizes the correlation of all the modifiable risk factors for this study.

Table 2: **Tetra choric correlation of the modifiable risk factors among males**

	Hypertension	Dyslipidemia	Alcohol	Smoking	Obesity
Hypertension	1.0000				
Dyslipidemia	-0.1030	1.000			
Alcohol	-0.2703	**-1.000**	1.000		
Smoking	0.1754	-0.5301	**1.0000**	1.000	
Obesity/ Overweight	**1.000**	-0.2348	-0.6455	-0.7233	1.000

Table 3: Tetra choric correlation of the modifiable risk factors among females

	Hypertension	Dyslipidemia	Alcohol	Smoking	Obesity
Hypertension	1.0000				
Dyslipidemia	-0.0628	1.000			
Alcohol	**-0.1302**	**-0.3560**	1.000		
Smoking	-0.1078	-0.3447	0.4880	1.000	
Obesity/ Overweight	0.3830	0.1299	-0.3969	-0.4476	1.000

3.2 *Association of modifiable risk factors with mortality outcomes*

Of the non-valvular AF patients included in phase 1, 14% (10), died within one year of enrollment. Table 4, below summarizes the association of the modifiable risk factors to mortality among the participants. Proportionally, more women (21%) compared to men (6%) died however this association is not statistically significant among both men and women (OR 3.87, 0.76-19.8).

Table 4: Association of modifiable risk factors with mortality for phase 1

	Overall (n=69)				Men (n=31)				Women (n=38)			
Modifiable Risk Factors	**No Death**	**Death**	**P Value**	**Odds Ratio**	**No Death**	**Death**	**P value***	**Odds Ratio**	**No Death**	**Death**	**P value***	**Odds Ratio**
Hypertension % (n)												
No	26 (18)	3 (2)		1.22	35 (11)	0			18(7)	6(2)		
Yes	41 (59)	12 (8)	0.7		58 (18)	6 (2)	0.5		33(23)	19(6)	> 0.9	0.90
Dyslipidemia % (n)												
No	29(20)	4(3)			48(15)	0			13(5)	8(3)		
Yes	57(39)	10(7)	> 0.9	1.20	45(14)	6(2)	0.3		66(25)	13(5)	0.3	0.33
Smoking % (n)												
No	54(37)	9(6)			39 (12)	3(1)			66(25)	13(5)		
Yes	32(22)	6(4)	> 0.9	1.2	54 (17)	3(1)	> 0.9	0.70	13(5)	8(3)	0.3	3.00
Alcohol % (n)												
No	86(25)	14(4)			10(3)	0			56(22)	11(4)		
Yes	85(34)	15(6)	> 0.9	1.10	84(26)	6(2)	> 0.9		22(8)	11(4)	0.232	2.75
Obesity/overweight* % (n)												
No	55(36)	12(8)			76(22)	3(1)			38(14)	19(7)		
Yes	30(20)	3(2)	0.4	0.45	17(5)	3(1)	0.3	4.40	40(15)	3(1)	0.1	0.13

*n = 66 Overall, 3 participants who were lost to follow up after initial enrollment were excluded from this analysis.
†Fisher's exact test used to generate all the p-values.

3.3 Treatment and Screening patterns for modifiable risk factors

3.3.1 Screening pattern

The general screening patterns assessed during phase 2, vary across various modifiable risk factors (Figure 4). While 100% of all non-valvular AF patients underwent screening for blood pressure, only 31% underwent screening for lipid levels. Screening for the history of smoking and alcohol intake was performed for less than 50% of the participants and 39% of participants underwent screening for height and weight measures. For patients screened for lipid levels, 85% presented with at least one abnormal lipid level. Obesity accounted for the least common of the modifiable risk factor, with only 21% of those screened presenting with obesity.

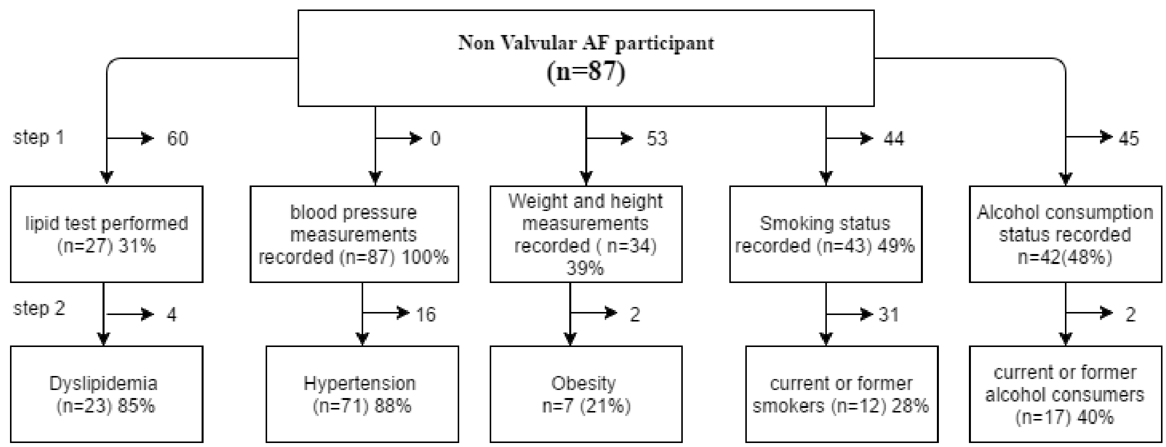

Figure 4: Screening and prevalence for modifiable risk factors

Step 1: number of participants without screening records, step 2: number of participants screened and have normal values. Other than hypertension, less than 50% of participants received screening for BMI, lipid levels, smoking status and alcohol consumption.

3.3.2 Intervention

Table 5 summarizes the treatment pattern of the five modifiable risk factors of interest in phase 2. All patients diagnosed with hypertension received antihypertensive treatment while only 1 participant (1%) underwent counselling on physical exercises. Approximately 8% (1) of those with an established history of smoking or alcohol consumption received counselling on cessation. Obese patients received no counselling on physical exercise while 3 (43%) underwent nutritional counselling. The intervention for the modifiable risk factors did not differ by gender (Table 6)

Table 5: Intervention for modifiable risk factors

Interventions	**Yes**	**No**
Hypertension (n=71), % (n)		
Antihypertensive prescribed	100 (71)	0
Nutritional counselling	63 (45)	37 (26)
Physical activity counselling	1(1)	99 (70)
Dyslipidemia (n=23), % (n)		
Statins prescribed	43 (10)	57 (13)
Nutritional counselling	61 (14)	39 (9)
Physical activity counselling	4 (1)	96 (22)
Smoking history (n=12), % (n)		
Counselling on cessation	8(1)	92 (11)
Alcohol consumption		
Counselling on cessation	6 (1)	94 (16)
Obesity		
Nutritional counselling	43 (3)	57 (4)
Physical activity counselling	0	100 (7)

Table 6: Intervention for modifiable risk by sex

Modifiable risk factor/ Intervention	Sex Male	Female	P value
Hypertension			
Antihypertensive prescribed % (n)			
Yes	82 (28)	84 (31)	0.872‡
No	18 (6)	16 (6)	
Counselling % (n)			
Yes	65 (22)	61 (23)	0.824‡
No	35 (12)	39 (14)	
Dyslipidemia			
Statin prescribed % (n)			
Yes	45 (5)	41 (5)	0.855‡
No	55 (6)	59 (7)	
Obesity			
Counselling % (n)			
Yes	33 (1)	50 (2)	0.659†
No	67 (2)	50 (2)	

The intervention for modifiable risk factors do not differ by gender
‡Chi-square test †fishers exact test

4. Discussion

This study sought to determine the extent to which there are sex related differences in the distribution and treatment pattern of common modifiable risk factors associated with AF in western Kenya. Findings indicate that hypertension is the most common modifiable risk factor in this population but that this does not differ by gender. Most patients had at least three risk factors. Obesity and dyslipidemia were common among women while men had a higher history of smoking and alcohol consumption. Overall, modifiable risk factors were not significantly associated with death; however, the study could not definitively determine whether this differs by gender. The findings also show low intervention rates for common modifiable risk factors in this population and that this does not differ among men and women.

Globally hypertension is the most common modifiable risk factor for AF (Oldgren et al., 2014; Schnabel et al., 2015). In SSA, the Randomized Evaluation of Long term Anticoagulation Therapy (RE-LY) study, which included 10 sites from the region found that 53% of AF subjects in SSA had AF (Oldgren et al., 2014). The proportion was relatively higher in a study conducted in Kenya, which demonstrated that 68% of individuals with AF had hypertension (Shavadia et al., 2013). These findings are consistent with our results, that show 65% and 76% of men and women had AF respectively. The high rates of hypertension can be attributed to the increased awareness and screening patterns of this condition in SSA (Michael et al., 2016). Moreover, this study also suggest that all non-valvular AF participants undergo routine blood pressure screening during clinic visits. Other than hypertension, there were significant differences in the distribution of other modifiable risk factors. While obesity and dyslipidemia were more common among women, more men had a higher history of drinking alcohol and smoking. Consistent findings have been published previously (Sobngwi et al., 2002). An observational cohort study in South Africa, showed that more women (73%) compared to men (40%) were likely to be obese (Sliwa et al., 2010). The same study also showed that men had 2.9 greater likelihood of smoking history and 2.6 greater chance of drinking alcohol compared to women (Sliwa et al., 2010). Notably, majority of the participants presented with a combination of at least three modifiable risk factors. Similar findings related to cardiovascular risk factors have been reported in German, where participants had clustering of at least 2 or 3 risk factors (Müller-Riemenschneider, Nocon, & Willich, 2010; Truthmann et al., 2015).

The correlation between alcohol intake and smoking is yet to be well understood, but studies have found that people who smoke are more likely to take alcohol and vice versa. Compared to the general population, individuals who are dependent on alcohol are three times more likely to be smokers and those who are dependent on tobacco are four times more likely to depend on alcohol than the general population (Grant et.al, 2004). Although this evidence does not take into account sex differences regarding the correlation between alcohol intake and smoking, it is consistent with our results that show positive correlation between alcohol intake and cigarette smoking. Additionally, evidence from a study conducted in Tanzania also showed significant correlation between blood pressure and BMI among men and women (Njelekela et al., 2009). These findings provide significant clinical implication for packaging treatment intervention for the highly correlated risk factors in western Kenya. For example, patients diagnosed with BMI > 25 should receive regular monitoring and education on high blood pressure.

Studies mainly from high-income countries have shown an association between modifiable risk factors and increased likelihood of death among individuals with AF. Data from the cardiovascular health and ARIC studies demonstrated that individuals with AF who had a history of smoking had between 1.1 to 1.6 times hazard risk of death compared to non-smokers with AF (Kwon et al., 2016). Contrary to these findings, this study demonstrates no significant association between modifiable risk factors and death among the overall study population. This disparity may be attributed to the small number of deaths and a short period of follow up experienced in the study cohort. Arguably, given the small proportion of participants eligible for enrollment in this study, atrial fibrillation is not common condition among patients who receive cardiac care at MTRH. Perhaps, future studies that include a larger sample population and longer follow up to time of event may provide more insights regarding this association. Notably, the number of events (10) observed in the study population was too small to test the difference of this association by gender.

This study also found very low screening and intervention rates for the common modifiable risk factors. Other than hypertension, screening for the other modifiable risk factors was less than 50% among the study subjects. Moreover, among those diagnosed with obesity, only 3% received nutritional counselling. Similar results were observed for participants with a history of smoking and alcohol consumption. Van der Sande et al. (2001), suggests that, in developing countries most health workers training curricula have not put much emphasis on intervention strategies related to cardiovascular risk factors. This may explain the low rates of intervention observed in the study. These findings provide important clinical and public health implications on potential for innovative strategies to manage AF in western Kenya. With the high costs associated with the management of AF, increasing the screening rates for modifiable risk factors may inform a low cost strategy for the management of AF in western Kenya.

4.1 Study limitations

This study has a number of limitations. To determine the treatment pattern of the modifiable risk factors, we relied on retrospective analysis of medical data. As is true for many retrospective studies, there were challenges with missing data. Charts that were missing a definitive diagnosis of non-valvular AF were excluded from this study. Additionally participants with missing variables were excluded from study analysis hence introducing potential for selection bias. Notably, for Phase 2, detailed information on the number of charts excluded for specific reasons was not available. If this data was missing not at random and that the excluded patients had differential information from those included in the analysis, there is potential for a non-representative sample that would weaken the validity of the study findings. The retrospective design also posed a potential for misclassification bias. We relied on physicians records to ascertain diagnosis of non-valvular atrial fibrillation. However, we remain uncertain regarding the validity of physician's diagnosis among non-valvular AF patients within this setting. The presence of this bias would also weaken the internal validity of the findings. Thirdly, our study had low statistical power to detect true effects; when exploring the association between modifiable risk factors and death our analysis was limited by the small number of the event. Consequently, our analysis was limited to the use of fisher's exact test and could not perform more advanced testing such as multivariable regression. Similarly, although one of the aims was to assess sex-differences we were not able to simultaneously adjust for sex and the modifiable risk factors due to the small number of events.

5. Conclusion

In conclusion, much of the previous studies has attributed rheumatic heart RHD as the main contributor to AF in sub-Saharan Africa. However new evidence suggest that compared to other factors, RHD is declining in this region. Consequently, there is a need to put more focus on other established factors such as modifiable risk factors. This study has identified significant sex differences in the distribution of modifiable risk factors. Additionally, it supports the knowledge that hypertension is an important cause of AF in sub-Saharan Africa and reveals strong correlation among various risk factors. This provides significant implications to the MTRH and the public health sector in its entirety. Preventative strategies such as health promotion with particular focus on targeted risk factors for men and women could potentially reduce the burden of AF.

Appendix A: Data Abstraction form

AF Risk Factors **Data Abstraction Form**	STUDY ID: RF __ __ __ __	**Today's Date:**

Date of birth (date/month/year) ______________ Sex ☐ M ☐ F

Modifiable risk factors

Hypertension

1. Blood pressure measurements present ☐ Yes ☐ No If Yes ↓
2. Systolic blood pressure _______ mm/Hg Diastolic blood pressure________mm/Hg **Date:**
3. Was patient on blood pressure medication ☐ Yes ☐ Not recorded

Interventions

4. Patient currently on antihypertensive treatment ☐ Yes ☐ No ☐ Not recorded
5. Patient counselled on
   Diet ☐ Yes ☐ Not recorded
   Weight management ☐ Yes ☐ Not recorded
6. What is the most recent blood pressure? **Date:** day/ month/ year
   Systolic blood pressure ______________mm/Hg Diastolic blood pressure________mm/Hg

Cholesterol

1. Lipid test ever performed ☐ Yes ☐ No if yes ↓
2. What are the earliest recorded values? **Date**: (Day/month/year)
   HDL ______________mmol/l
   LDL __________________mmol/l
   Triglycerides ________________mmol/l
   Total Cholesterol ______________ mmol/l

Interventions

3. Any statin medication prescribed. ☐ Yes ☐ No
4. Patient counselled on diet ☐ Yes ☐ Not recorded
5. Physical exercise: ☐ Yes ☐ Not recorded ☐ Not applicable

6. Follow up lipid test levels ever performed ☐ Yes ☐ Not recorded if yes ↓
7. What are the most recent recorded values? **Date:** (Day/month/year)

   HDL ______________ mmol/l
   LDL __________________mmol/l
   Triglycerides ________________mmol/l
   Total Cholesterol ______________mmol/l

Cigarette smoking

1. Recorded history of cigarette smoking ☐ Yes ☐ No if yes ↓

Smoking status: ☐ current smoker ☐ Former smoker ☐ Never smoked ☐Not recorded

Intervention (current/former smokers)

Counselled on smoking cessation: Yes ☐ No ☐

Referred for other counseling (e.g. support groups) Yes ☐ ☐ Not Recorded

Alcohol Consumption

1. Recorded history of alcohol consumption ☐ Yes ☐ No if yes ↓

Consumption status: ☐ Current ☐ Former ☐ Never ☐Not recorded

Intervention (current)

2. Counselled on alcohol intake cessation/ moderation: Yes ☐ No ☐
3. Referred for other counseling (e.g. support groups) Yes ☐ ☐ Not Recorded

Obesity/overweight

1. Recorded measurement of: height Yes ☐ No ☐ if yes ↓

weight Yes ☐ No ☐ if yes ↓

2. Earliest recorded measurements: Height _____________ cm **Date**

Weight ____________ kg **Date**

Intervention

1. Patient counselled on:

Dietary therapy: ☐ Yes ☐ No

physical activity: ☐ Yes ☐ No

2. Follow up weight measurements performed ☐ Yes ☐ No if yes ↓

Most recent recorded values: Weight _____________ kg **Date:**

Appendix B: Age summary of participants in phase 2

Characteristic	Overall (n=87)	Male (n=39)	Female (n=47)
Age (SD)	73 (12)	75 (13)	72 (10)

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