

The Prevalence and Clinical Correlates of Atrial
Fibrillation in Those Aged 70 and Over in the Hai District
of Northern Tanzania

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Abstract

Background The elderly population in sub-Saharan Africa (SSA) is increasing rapidly, with a consequent rise in non-communicable disease (NCD). The prevalence of stroke disease is already known to be higher in SSA than in high-income countries (HICs). There are currently no community-based data on the prevalence of atrial fibrillation (AF) or hypertension (HTN) specifically in elderly SSAs.

Design Cross-sectional community-based observational study, with case-control sub-group analysis.

Methods Approximately one quarter of the population (n=2232) aged 70 and over of a demographic surveillance site in the rural Hai district of Northern Tanzania underwent screening for AF by 12-lead electrocardiography (ECG), in addition to a sub-group undergoing ambulatory cardiac monitoring looking for paroxysmal AF (n=232). Demographic data were also collected along with disability level, body mass index and blood pressure (BP). The gender-specific prevalence of AF, paroxysmal AF and hypertension in each 5-year age band was determined. ECGs were examined digitally, and P wave indices in this population were described.

Results There were only 15/2232 (12 female) participants with AF, giving an age-adjusted prevalence of 0.64%. 6/233 (2.6%) had at least 1 paroxysm of AF, suggesting a total overall prevalence of AF as high as 3.2%. 1553/2232 had a BP $\geq 140/90$, giving an age-adjusted prevalence of hypertension of 69.7%. Women had a higher mean systolic (166.0 vs. 154.3mmHg) and diastolic (89.3 vs. 83.1mmHg) BP.

Conclusions The prevalence of AF is much lower in this population than elsewhere in the world and points towards potential protective genetic and environmental factors and some differences in risk factor profile. However, the low

prevalence of AF is particularly interesting in the setting of a prevalence of hypertension and stroke that is similar to African-Americans in HICs.

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Statement of Candidate's Contribution to the Work

Prior to travelling to Tanzania in November 2009, I identified the need for an atrial fibrillation (AF) prevalence study in sub-Saharan Africa (SSA) following a review of the current literature. The literature review was performed using various search engines including Medline, Pubmed and Google, and then by following references quoted from sourced articles. Search terms used for the initial AF prevalence literature review included 'atrial fibrillation AND prevalence', 'atrial fibrillation AND incidence', 'atrial fibrillation AND Africa / sub-Saharan Africa' and 'cardiac disease AND Africa'. For the hypertension section the same search terms were used, except that 'atrial fibrillation' was changed to 'hypertension'. For the ambulatory monitors section search terms used were 'paroxysmal atrial fibrillation' and 'paroxysmal atrial flutter' with the combinations described as for AF, and also 'ambulatory monitoring AND elderly'. For the P wave indices section, I searched initially using terms 'P wave indices AND elderly' and 'P wave indices AND Africa'. Several references were obtained from the British Library. A search of thesis titles was not carried out as I felt it would not be helpful given the general paucity of data regarding AF in SSA.

I spent just over 9 months in Tanzania (Nov 2009 – Aug 2010) collecting data for my MD thesis. I performed or supervised the performance of all the ECGs and BP recordings, and performed the focused CV history and examination, echocardiogram and blood-letting on all AF patients and controls. On my return to the UK, I have analysed the collected data with the help of Dr. Keith Gray - AF and HTN sections (Northumbria NHS Trust), and Drs. Philip Langley and Luigi

DiMarco – P wave indices section (Newcastle upon Tyne NHS Trust).

I was responsible for follow up of all AF patients that were started on treatment and I have recently returned from a visit to Tanzania to perform further follow-up. To my knowledge, this will be the first large-scale community-based prevalence study of atrial fibrillation in sub-Saharan Africa.

Reasons for Performing the Study

The main reason for carrying out this study was to 'close the loop' on epidemiological data regarding hypertension, stroke and AF in a rural SSA population. A 3-year stroke incidence study had already been performed in this area, finding significant levels of stroke morbidity and mortality.

Hypertension has been studied in similar populations in SSA previously but it was apparent that there were no community-based prevalence studies of AF, both a consequence of hypertension and a risk factor for stroke. The decision to 'target' an elderly population was made for 2 main reasons. Firstly because I felt that, given that AF prevalence increases with age, I would maximise ascertainment of subjects with AF and beneficially treat a greater proportion of the population.

Secondly, because older adults are significantly disadvantaged in SSA when it comes to health-care provision, their ailments often wrongly ascribed to the natural ageing process, thereby enabling us to 'raise the profile' of an ageing population and an impending epidemic of non-communicable disease in this rapidly growing population. This study was performed in conjunction with another looking at the prevalence of neurological disability in an elderly population and, as resources and infrastructure were limited, I decided to study the same elderly population.

Aims

Primary Aim

1. To accurately document the prevalence of atrial fibrillation in those aged 70 years and over in a community-based setting in rural Tanzania

Secondary Aims

2. To identify clinical associates of atrial fibrillation in AF patients by comparing them to age- and sex-matched controls
3. To document the prevalence of paroxysmal AF in a sub-group of this population
4. To describe reference values for electrocardiographic P wave indices (PWI) in this population
5. To document the prevalence of hypertension (HTN) in this population given its close relationship with AF

Glossary of Terms

ACE-I = angiotensin converting enzyme inhibitor

AERP = atrial effective refractive period

AF = atrial fibrillation

AFI = atrial flutter

AHRE = atrial high rate episode

AMO = assistant medical officer

AMMP = adult morbidity and mortality project

APD = action potential duration

ARBs = angiotensin receptor blockers

ASD = atrial septal defect

Asl = above sea level

ATP = adenosine tri-phosphate

AV = aortic valve

Bd = twice daily

BI = Barthel Index

BMI = body mass index

BP = blood pressure

Ca = calcium

CABG = coronary artery bypass graft

CAD = coronary artery disease

CCF = congestive cardiac failure

CHF = congestive heart failure

CI = confidence interval

CKD = chronic kidney disease

CMR = cardiac magnetic resonance

CPAP = continuous positive airways pressure

CRP = C-reactive protein

CT = computed tomography

CV = cardiovascular

CVD = cardiovascular disease

DADs = delayed after-depolarisations
DCCV = direct current cardioversion
dL = deci-litre
DM = diabetes mellitus
DMO = district medical officer
DSS = Demographic Surveillance Site
EADs = early after-depolarisations
ECG = electrocardiograph(y)
EF = ejection fraction
ESC = European Society of Cardiology
ESRD = end-stage renal disease
GI = gastrointestinal
GWAS = genome-wide association study
HB = heart block
HbA1c = glycated haemoglobin
HDL = high-density lipoprotein
HR = hazard ratio
ICU = intensive care unit
IHD = ischaemic heart disease
K = potassium
KCMC = Kilimanjaro Christian Medical Centre
Km = kilometre
KW = Kruskal Wallis
LA = left atrial
LAA = left atrial appendage
LAE = left atrial enlargement
LDL = low-density lipoprotein
LMIC = low and middle income countries
LV = left ventricular
LVF = left ventricular failure
Mcg = micrograms
Mg = magnesium
mg = milligrams
MI = myocardial infarction

MR = mitral regurgitation
MRI = magnetic resonance imaging
MS = mitral stenosis
ms = millisecond
MV = mitral valve
mV = millivolt
Na = sodium
NCD = non-communicable disease
NCT = narrow complex tachycardia
NHS = National Health Service
n-3 PUFA = n-3 polyunsaturated fatty acids
Od = once daily
OPD = out-patient department
OR = odds ratio
OSA = obstructive sleep apnoea
PACs = premature atrial complexes
PAF = paroxysmal atrial fibrillation
PAFI = paroxysmal atrial flutter
PAMP / P_{AMP} = P wave amplitude
PD / P_D = P wave duration
PDISP = P wave dispersion
 P_{ON} = P wave onset
 P_{OFF} = P wave offset
PR(%) = normalised PR interval
PV = pulmonary vein
PWI = P wave indices
PWIF = P wave initial force in lead V1
PWTF / P_{TNF} = P wave terminal force in lead V1
QOL = quality of life
 QRS_{ON} = QRS onset
RAAS = rennin angiotensin aldosterone system
RAE = right atrial enlargement
RHD = rheumatic heart disease
s = second

SNPs = single nucleotide polymorphisms

SR = sinus rhythm

SSA = sub-Saharan Africa

SSS = sick sinus syndrome

SVE = supra-ventricular ectopic

SVT = supraventricular tachycardia

TC = total cholesterol

TDI = tissue Doppler imaging

USA = United States of America

VE = ventricular ectopic

WHO = World Health Organisation

WL = wavelength

WPW = wolf-parkinson-white

μV = microvolt

Chapter 1. Introduction

1.1 Atrial Fibrillation

AF is a cardiac arrhythmia characterised by seemingly disorganised atrial depolarisations without effective atrial contraction (1). Control of the heart rhythm is taken away from the sinus node by rapid electrical activity in the atria. It is the most common cardiac rhythm disturbance and contributes significantly to cardiac morbidity and mortality worldwide (2).

1.1.1 *Pathophysiology*

There have been multiple theories as to the initiation and propagation of AF, and thus multiple therapies aimed at combating the disease based on these theories. Initially it was thought that AF was caused by simultaneous, rapidly discharging ectopic atrial foci (3), or by single circuits of electrical re-entry (4). Over the past fifty years, multiple-circuit re-entry has been the dominant conceptual model of AF, heavily influenced by work done with regard to the effect of multiple re-entry wavelets on the perpetuation of AF (5), and wavelengths of re-entry (6).

Over the past 15 years however, our understanding of AF pathophysiology has advanced significantly through an increased awareness of the role of 'atrial remodelling' (7). Any change in structure or function of the atria constitutes atrial remodelling and this remodelling is the dominant reason for AF perpetuation, leading to a direct relationship between time spent in AF and difficulty in restoring sinus rhythm (i.e. 'AF begets AF').

For the initiation of AF, there needs to be present both trigger, as well as susceptible tissue and electrophysiological substrate that perpetuates it (dual substrate paradigm) (8). Examples of vulnerable substrate include atrial tissue that is acutely ischaemic, inflamed or dilated (7). It is now understood that most AF is initiated by rapidly firing ectopic foci often located in the muscular sleeves of the pulmonary veins (9), or less frequently from the proximal superior vena cava (10), ligament of Marshall (11), or other parts of the left or right atria (as previously suggested by Engelman).

The principle mechanisms of ectopic activity generation include phase 4 depolarisations, delayed after-depolarisations (DADs) and early after-depolarisations (EADs) (7). Phase 4 depolarisation establishes the time required to reach threshold potential and generate a spontaneous action potential. If this occurs in the atrial cells of an ectopic focus at a faster rate than in the sinus node cells, then ectopic beats and sustained tachycardias may occur. Abnormalities in cellular calcium handling, particularly calcium overload, can cause DADs, spontaneous hump-shaped depolarisations occurring just after full repolarisation. When they become large enough to reach threshold potential, they cause cell firing either as a single ectopic beat or a sustained tachycardia. EADs occur when action potentials become abnormally prolonged, allowing L-type calcium channels to recover from inactivation and generate abnormal depolarisations at plateau potentials. Both phase 4 depolarisations (12) and EADs (13) have been shown to be related to atrial tachyarrhythmias, yet their relation to AF and atrial remodelling specifically is not fully understood. DADs are thought to be promoted by congestive heart failure through cellular calcium loading (14), a strong candidate mechanism to underlie AF-generating ectopic foci (7). Again, how they relate to triggered activity in AF is controversial (15) (16).

The maintenance of AF is facilitated by the presence or development of abnormal tissue substrate that allows multiple re-entrant wavelets of excitation (as mentioned by Moe et al) to propagate within the atrial myocardium, through atrial remodelling.

There are two components to atrial remodelling – electrical and structural. Electrical remodelling develops within hours of onset of AF and includes the electrophysiological alterations of shortening of the atrial effective refractory period (AERP), action potential duration (APD) and wavelength (WL) (7) (8). The AERP is directly related to APD, as sodium channels that govern cardiomyocyte excitability inactivate when cells are depolarised, and require repolarisation to approximately -60mV before they become active again (7). Therefore, the shorter the APD, the quicker the sodium channels become reactivated and thus the shorter the AERP. APD itself is governed by the balance of inward calcium currents (keeps cells depolarised) and outward potassium currents (repolarises cells). In atrial remodelling it has been shown that sustained rapid atrial activation, as occurs in AF, reduces inward L-type calcium current and enhances outward potassium currents (17) thereby shortening APD. This has been shown to be a major contributor to clinically relevant AF promotion (18) (19). Reduced wavelength is also an important factor in electrical remodelling. Wavelength is the distance travelled by an impulse in one refractory period, and is given as the product of refractory period and conduction speed (7). It approximates the shortest path length for re-entry and determines the size of functional re-entry circuits. Consequently, reduced atrial wavelength decreases re-entry circuit dimensions and thereby increases the potential number of simultaneous circuits and augments the probability of AF maintenance (7).

Structural remodelling is a slower process involving myocyte degeneration, myocardial fibrosis, left atrial enlargement, and results in heterogeneity of conduction (8). It is an important contributor to the AF substrate (20).

The main driver of structural remodelling is sustained atrial tachycardia. Evidence suggests it suppresses expression of the atrial selective connexin-40 (21), which provides electrical coupling between cells and minimises lateral dissipation of current, essential to normal impulse conduction and thus leading to heterogeneity of conduction (7). It also reduces sodium current (22), which provides the source and energy for conduction, and is the other essential part of normal impulse conduction.

Atrial tachycardia impairs atrial contractility, principally by causing calcium handling abnormalities (23) which causes atrial dilatation(24), further promoting re-entry. Atrial dilatation increases the amount of atrial tissue that can accommodate re-entry circuits, and atrial dimensions are a particularly important determinant of the occurrence of multiple-circuit re-entry (25).

In addition, atrial tachycardia up-regulates the expression of pro-fibrotic factors such as angiotensin II (26), and transforming growth factor β 1 (27), and evidence is growing for the roles of platelet derived growth factor (20) and connective tissue growth factor (28), both of which activate fibroblasts and hence encourage atrial fibrosis. AF is known to enhance oxidant stress(29, 30) which also enhances fibrosis through cell death and pro-inflammatory pathways(7).

Both electrical and structural remodelling create a susceptible substrate that has been implicated in the perpetuation of AF (8).

1.1.2 Classification

Clinically, it is reasonable to distinguish five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (31).

(1) Every patient who presents with AF for the first time is considered a patient with first-diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.

(2) Paroxysmal AF (PAF) is self-terminating, usually within 48 hours. Although AF paroxysms may continue for up to 7 days, the 48-hour time point is clinically important—after this the likelihood of spontaneous conversion is low and anticoagulation must be considered.

(3) Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCCV).

(4) Long-standing persistent AF has lasted for ≥ 1 year when it is decided to adopt a rhythm control strategy.

(5) Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia is re-designated as 'longstanding persistent AF'.

This classification is useful for clinical management of AF patients, especially when AF-related symptoms are also considered. Many therapeutic decisions require careful consideration of additional individual factors and co-morbidities.

Silent AF (asymptomatic) may manifest as an AF-related complication (ischaemic stroke or tachycardiomyopathy) or may be diagnosed by an opportunistic ECG. Silent AF may present as any of the temporal forms of AF.

1.2 Epidemiology

Prevalence and incidence rates of AF vary around the world according to region and ethnicity. There have been many large studies conducted in the developed, high income countries of Europe and the United States of America (USA), whilst fewer studies have been performed in developing countries, particularly in SSA. AF prevalence rates are thought to be underestimated overall due to the fact that AF often remains undiagnosed for long periods of time ('silent AF') (32) and many patients with AF never present to hospital (33). Examining the literature, there appears to be a consistent theme in differences in incidence and prevalence between Caucasians (higher prevalence) and African-Americans (lower prevalence). This is despite an increased prevalence of 'traditional' risk factors for AF in African-Americans and suggests there must be other contributing factors. It has previously been suggested that AF prevalence is particularly underestimated in certain ethnic groups (e.g. African-Americans in the USA) with poorer access to health care (34), and this theme may well be extrapolated to low income countries with poor healthcare infrastructure. However, this is unlikely to be the whole explanation, with genetics and environment both likely to be playing significant parts. The following AF prevalence studies are summarised in Table 1.

1.2.1 Europe and North America

A large community-based study (15,406 participants) in the West of Scotland by Stewart et al (35) looking at the prevalence and incidence of AF in 45-64 year olds found an overall prevalence of AF in this population of 0.65%. The prevalence was higher in males (0.8%) than females (0.5%), and prevalence not only increased with age, but the disparity between male and female prevalence increased from 0.3% vs. 0.35% in those aged 45-49 up to 1.5% vs. 0.8% in those aged 60-64 years. Incident AF in this study followed a similar pattern, with overall incidence of 0.54 cases / 1000 patient years, and a higher incidence in males versus females (0.9 / 1000 vs. 0.25 / 1000). Again, this was true throughout the age bands, and disparity increased with age, from an incidence of 0.65/1000 in males versus 0.2/1000 in females aged 50-54, up to 1.8/1000 versus 0.7/1000 in males and females respectively, aged 60-64 years.

Another study by Sudlow et al (36) in the North-East of England looked at community-based prevalence of AF in 4843 people aged 65 years and older. They found an overall prevalence of 4.7%, which increased with age and had preponderance for male sex. In the 65-74 year old group, prevalence was 3.5% in men and 2.4% in women, rising to 10.0% in men 75 years or older and 5.6% in women in the same age bracket.

These two studies make no mention of the ethnic background of participants and this is probably because it was exclusively Caucasian. However, a study by Lip et al (33) looking at AF in those aged 50 years and over in a general practice setting in Birmingham contained small numbers of different ethnic groups. Of 4522 patients studied, 111 (2.4%) had AF of whom 2.7% were Afro-Caribbean, 0.9% Asian and 0.9% mixed-race, whilst the majority (77.5%) were Caucasian. The mean age of

the patients was 76.6, and the prevalence increased 10-fold between the ages of 50-55 (3.6%) and over 80 (36.9%). It was noted that 73% of patients had chronic AF and 27% had paroxysmal AF.

A European study by Heeringa et al (37) looked at the prevalence, incidence and lifetime risk of AF using a large (6808 participants) population-based prospective cohort of people aged 55 years and above. This suggested a higher prevalence than UK studies of 5.5% overall with a higher prevalence in men than women (6.0% vs. 5.1%), but higher absolute numbers in women (207 vs. 169). As with previous studies, prevalence of AF increased markedly with age, from 0.7% in the 55-60 year age group, to 17.8% in those aged 85 years and above. Incidence tended to follow this trend, with an overall level of 9.9 cases/1000 person years, increased incidence across all age groups in men, and a rising incidence level with age (1.1/1000 in the 55-60 age group up to 18.2/1000 in the 85 and above age group). Lifetime risk of AF was fairly similar between sexes, being 23.8% for men aged 55 and 22.2% for women at the same age. This risk was fairly stable until the age of 75, when lifetime risks decreased steadily independent of gender. It was noted that at follow-up of the same cohort after two and 7 years, the prevalence of AF had increased from 6.1% at baseline to 6.7% and 8.3% respectively. This was felt to be due to both increased awareness of AF by practitioners and ageing of the cohort.

Studies based in North America suggest similar patterns of AF prevalence and incidence to those based in Europe. As part of the Framingham study, Kannel et al (38) reported the prevalence of AF to be 0.5% at aged 50-59 years, with prevalence increasing to almost 9% at age 80-89 years. The

odds ratio for developing AF if male as opposed to female was 1.5.

A large study by Go et al (39) looked at the prevalence of diagnosed AF in adults (aged 20+ years) in California (USA) in a population of 1.89 million, finding 17974 people with AF. The overall prevalence was 0.95%, with 45% of AF sufferers aged 75 or over. AF was again more common in men than women (1.1% vs. 0.8%) and prevalence increased with age (0.2% men / 0.1% women aged <50, to 11% men / 9.1% women aged 85+). The study included ethnicity status in 89% of patients, and 84.7% of the study population were white, 3.6% were black and 2.5% were Hispanic / Latino, with 9.1% classified as other / multiple. Overall, AF was more common in whites than blacks (2.2% vs. 1.5%) with this disparity persisting with age (5.2% vs. 4.4% in the 70-79 age group and 9.9% vs. 7.7% in those aged 80+).

The findings of reduced prevalence of AF in black people is further supported in a study by Upshaw et al (40) looking at the prevalence of AF using electrocardiography in people presenting to an urban hospital in Georgia (USA). There was a fairly even mix of white (1201) and black (922) patients. The overall prevalence was found to be 7.8% in white patients, but only 2.5% in black patients. Again, prevalence increased with age, but the increase was steeper in whites (2.0% in 50-59 age group up to 19.3% in the 90-99 age group) than blacks (0.7% 50-59 up to 7.0% 90-99). The difference between men (5.6%) and women (5.5%) was minimal.

In the Large Health Survey by Veteran Enrollees Study by Borzecki et al (41), 664,754 males responded to a health questionnaire. Overall prevalence of AF was 5.3%. By race, the age-adjusted prevalence was 5.7% in whites, 3.4% in blacks, 3.0% in Hispanics, 5.4% in native Americans/Alaskans, 3.6% in

Asians and 5.2% in Pacific Islanders ($p < 0.001$). The OR of a white male having AF versus a black male was 1.84, despite a higher prevalence of hypertension in black males.

This racial difference in prevalence appears to extend to patients with heart failure. Ruo et al (42) studied 1,373 HF patients (223 African Americans, 1,150 Caucasians), finding an overall prevalence of AF of 36.9%. African-Americans were again more likely to be hypertensive, but also to be younger and more likely to have been previously diagnosed with heart failure. Despite this, the prevalence of AF was significantly lower in African-Americans (19.7%) than Caucasians (38.3%).

The Cardiovascular Health Study by Furberg et al (43), reported the prevalence of AF in 5201 elderly patients aged 65 years and over. The prevalence of AF was 4.8% in women and 6.2% in men, with prevalence being strongly associated with advanced age in women. Another study by Feinberg et al (44) in Arizona (USA) looked at recent epidemiological studies in the US and estimated that 2.2 million people in the US had AF, with a prevalence of 2.3% in those aged 40+ and 5.9% in those aged 65+. The absolute number of men and women with AF was found to be roughly equal, with about 60% of AF sufferers aged 75+ being female.

A study by Miyasaka et al (45) in Minnesota (USA) reported trends in AF incidence over a 20-year period between 1980 and 2000. They report that the age- and sex- adjusted incidence of AF was 3.04 per 1000 person-years in 1980 and rose to 3.68 in 2000. This was a statistically significant rise in incidence over 21 years, and suggested a relative increase in incidence of 12.6%. The authors suggest that if this increase in incidence continues, then the number of persons with AF by 2050 would be 15.9 million, rather than the 12.1 million as projected by the US Census Bureau. This study is in line with

other studies (39) (46) that suggest the prevalence of AF is increasing.

Another study in Manitoba, Canada, by Krahn et al (47) looked at the incidence of AF in 3983 male air crew recruits over 44 years of follow-up. 299 (7.5%) developed AF during 154,131 person-years of observation, with the incidence of AF rising from 0.5 / 1000 person-years in those aged <50, to 9.7 / 1000 in those aged >70.

1.2.2 Elsewhere in the World

A study by Lake et al (48) in Busselton, Western Australia, looked at the prevalence of AF in 1770 people aged 60+, and found similar results to those found in elderly Caucasian populations elsewhere in high-income countries. The prevalence increased with age, from 1.7% overall in the 60-64 age group, up to 11.6% in those aged 75+, and AF was more common in men than women (5.6% vs. 4.2% overall).

The majority of epidemiological work on AF outside Europe and the USA comes from Asia. A large study by Inoue et al (49) in Japan looked at data from 630,138 subjects aged 40 years and over. The overall prevalence of AF was 0.56%, lower than rates reported in Europe and the USA. However, similar to Europe and the USA, AF was more common overall in men than women (1.35% vs. 0.43%) and increased with age, although not by as much as seen elsewhere (4.4% in men aged 80 years and over but only 2.2% in women in the same age range). The prevalence of AF in Japan is expected to almost double from 0.56% currently to 1.09% in 2050. Another Japanese study by Iguchi et al (50) looked at 41,436 people aged 40 years and over, finding a higher prevalence rate of 1.6% overall, closer to that found in a Western population. As

part of the follow-up from this study, Iguchi et al (51) also produced incidence figures for 30,449 people assessed at follow-up. Of these, 278 (0.9%) developed AF over 1 year follow-up, giving an incidence rate of 9.3 / 1000 person-years.

A large study across 13 provinces in mainland China by Zhou et al (52) looked at 29,079 adults aged 30 years and over. The overall prevalence rate was 0.65%, similar to rates found in the study by Inoue et al in Japan, yet lower than Europe and the USA. Men had a higher prevalence rate than women (0.91% vs. 0.65%) and again, prevalence increased with age. This pattern was repeated in another study of 1839 Chinese residents of Singapore aged 55 years and older (53).

In a study of 14,540 adults aged 40 years and over in Korea by Jeong et al (54), the overall prevalence rate was 0.7%, again similar to other Asian studies. This rate rose to 2.1% in those aged 65 years and older, and AF was more common in men than women (1.2% vs. 0.4%).

There has also been prevalence research done in the Middle East. A study by Habibzadeh et al (55) looked at 463 people aged 50-79 years at a primary care centre in Iran. The mean age of participants was 64.0 years and the overall prevalence of AF was 2.8%. The prevalence was noted to be higher in women than men (4.3% vs. 1.3%), unlike elsewhere in the world. It was also noted that the prevalence increased ten-fold between the ages of 50-59 (0.6%) and 70-79 (6.4%).

A study in Turkey by Uyarel et al (56) looked at 3450 adults with a mean age of 52.0 years, with an overall prevalence rate of 1.25% and incidence of 1.35 / 1000 person-years. Again, unlike elsewhere, prevalence and incidence rates for women were higher in all age groups.

There have been two AF prevalence studies of note in Latin America, both based in Sao Paulo, Brazil. The first, by De Carvalho Filho et al (57), found a prevalence of 4.8% of chronic atrial fibrillation in a geriatric out-patient clinic, with AF sufferers having a mean age of 76.1 years. The second, by Kawabata-Yoshihara et al (58) looked at electrocardiographic findings of 1524 people aged >65 years as part of the Sao Paulo aging and health study. They found an AF prevalence rate of 2.4% overall (men 3.9%, women 2.0%), slightly lower than that found in Europe and the USA.

1.2.3 Sub-Saharan Africa

There are very few published data regarding AF in SSA, particularly community-based studies. Most reports are either hospital-based or focus on the prevalence of stroke risk factors.

A study by Sliwa et al (59) in South Africa looked at the spectrum of heart disease as part of the Heart of Soweto study at Baragwanath Hospital in Johannesburg. Of 1593 new presentations (mean age 52.8 years) to this tertiary hospital, 102 (7%) had AF. 59% were women, and all had concomitant presentations with heart failure, hypertension, valve disease or coronary artery disease.

Another study by Sliwa et al (60), again as part of the Heart of Soweto study, looked at incident AF in a hospital population. Of 5328 consecutive cardiac cases presenting to the hospital, 246 (4.6%) had AF. This translated to an estimated 5.6 cases / 100,000 population / annum. Mean age was younger than in epidemiological studies elsewhere in the world at 59.0 years, but as with other areas incidence rose with age, from 0.78 / 100,000 in the 15-24 year age group up to 49.6 / 100,000 in those aged 75+. 61% of total cases were found in women, and

this higher rate was seen in every age group for women over the age of 25 years. Peak incidence for men was in the 55-64 age group.

A study by Lodenyo et al (61) looking at cardiovascular disease in an elderly hospital population in Nairobi, Kenya, evaluated 200 consecutive in-patients aged 60+. Their findings are reported in a rather confusing manner in that they report 6 out of 200 ECGs (3%) showing AF, yet subsequently say that of 43 patients with arrhythmia (out of the same study population of 200), 11 (5.5%) had AF. Therefore their exact prevalence rate is difficult to determine but is either 3% or 5.5%.

A study by Connor et al (62) looked at the prevalence of stroke risk factors in a general practice population in South Africa. The study sent questionnaires out to 200 general practices, with 9133 questionnaires analysed. Mean age of participants was 50.7 years, with 73% in the age range 30-59 years. 59% were white, 23% black, 10% Asian and 7% of mixed race. The prevalence of AF was reported to be highest in white South Africans at 5%, 4% in those of mixed race, and 2% in both the black and Asian population.

Finally, a study by Ntep-Gweth et al (63) looked at clinical characteristics of AF in an out-patient population in Cameroon. 172 AF patients (56% female) were included from 10 cardiologists' out-patient clinics, with a mean age of 65.8 years. The prevalence of paroxysmal, persistent and permanent AF was 22.7%, 21.5% and 55.8% respectively.

Author / Country / Year	Study Population Size / Location	Study Population Ethnicity	Age Range Studied	AF Prevalence	Other Important Findings
Stewart et al, UK, 2001	15,406 Community-based	Not stated	45-64	Men 0.8% Women 0.5% Overall 0.65%	Prevalence increases with age and AF is more common in men than women
Murphy et al, UK, 2007	362,155 Community-based	Not stated	Overall	Men 0.9% / women 0.8%	Prevalence increases with age and AF is more common in men than women. Prevalence decreases with increasing socioeconomic deprivation
			65+	Men 5.3% / women 4.0%	
			75+	Men 7.5% / women 5.8%	
			85+	Men 8.4% / women 6.6%	
Majeed et al, UK, 2001	1.4 million Community-based	Not stated	70-74	Men 4.6% / women 3.3%	Prevalence increases with age and AF is more common in men than women.
			75-79	Men 9.1% / women 7.2%	
Sudlow et al, UK, 1998	4843 Community-based	Not stated	65 – 74	Men 10.6% / women 10.9% Men 3.5% / Women 2.4%	Prevalence increases with age and AF is more common in men than women
			75+	Men 10.0% / Women 5.6%	
			50+	2.4% overall	
Lip et al, UK, 1997	4522 Community-based	77.5% Caucasian 2.7% Afro-Caribbean 0.9% Asian	50-55	3.6% overall	Prevalence increases with age and AF is more common in men than women. Suboptimal use of anticoagulation
			85+	36.9% overall	
			55+	Men 6.0% / women 5.6%	
Heeringa et al, Netherlands, 2006	6808 Community-based	Not stated	70-74	Men 6.9% / women 5.4%	Prevalence increases with age and AF is more common in men than women
			75-79	Men 13.0% / women 6.5%	
			80-84	Men 15.2% / women 12.7%	
			85+	Men 17.9% / women 17.5%	
Friberg et al, Denmark, 2003	8606 Community-based	Not stated	50-89	Men 3.3% / Women 1.1%	Prevalence increases with age, is increasing over time and AF is more common in men than women

Wolf et al, USA, 1991	5070 Community-based	Not stated	50-59	0.5%	Prevalence increases with age and increases risk of stroke
			60-69	1.8%	
			70-79	4.8%	
			80-89	8.8%	
Kannel et al, USA, 1998	4731 Community-based	Not stated	65 – 84	Men 9.1% Women 4.7%	Prevalence increases with age, is increasing over time and AF is more common in men than women
Go et al, USA, 2001	1.89 million Community-based	84.7% white 3.6% black 2.5% Hispanic	20+	White 2.2%, black 1.5%	Prevalence increases with age and AF is more common in black Americans than white in all age groups
			70-79	White 5.2%, black 4.4%	
			80+	White 9.9%, black 7.7%	
Upshaw et al, USA, 2002	2123 Hospital admissions (consecutive)	57% white 43% black	Age range 20-99	White 7.8%, Black 2.5%	Prevalence increases with age and AF is more common in black Americans than white
			70-79	White 9.3%, black 2.4%	
Borzecki et al, USA, 2008	664,754 males	Veteran Enrollees	80+	White 15.7%, black 8.2% Whites 5.7% Blacks 3.4% Hispanics 3.0% Asians 3.6% Pacific Islanders 5.2%	
Ruo et al, USA, 2004	1373 F patients	223 African-Americans 1150 Caucasians	Mean age 67	Blacks 19.7% Whites 38.3% Overall 36.9%	
Furberg et al, USA, 1994	5201 Community-based	94.7% white 4.7% black	Mean age 74		Prevalence increases with age and AF is more common in men than women overall
			Overall 65+	Men 6.2% / women 4.8%	
			70-79	Men 5.8% / women 5.9%	
Philips et al, USA, 1990	2122 Community-based	Not stated	80+	Men 8.0% / women 6.7%	Prevalence increases with age and AF is more common in men than women overall
			65-74	Men 6.0% / Women 3.0%	
			75+	Men 16.1%/Women 12.2%	
Feinberg et al, USA, 1995	14,163 Review of 4 large prevalence studies	Not stated	70-74	5.0%	Prevalence increases with age and is higher in men, yet absolute numbers in older age groups higher in women. 70% AF
			75-79	7.0%	

			80+	10.0% (arbitrarily chosen due to low numbers)	sufferers aged 65-85
Lake et al, Australia, 1989	1770 Community-based	Not stated	70-74	Men 8.6% / Women 5.5%	Prevalence increases with age and AF is more common in men than women overall. AF cases had increased mortality from any cause incl. stroke
			75+	Men 15.0% / Women 8.4%	
Inoue et al, Japan, 2009	630,138 Community-based	Not stated	40+ overall	Men 1.35% / women 0.4%	Prevalence increases with age and AF is more common in men than women overall, but is lower than in the USA
			70-79	Men 3.4% / Women 1.2%	
Iguchi et al, Japan, 2008	41,436 Community-based	Not stated	80+	Men 4.4% / Women 2.2%	Prevalence increases with age and AF is more common in men than women overall. AF cases had lower cholesterol levels than non-AF cases
			40+ overall	Men 2.4% / Women 1.2%	
Jeong et al, Korea, 2005	14,540 Community-based	Not stated	60-79	Men 2.3% / Women 1.0%	Prevalence increases with age and AF is more common in men than women overall
			80+	Men 3.5% / women 2.5%	
			40+ overall	Men 1.2% / Women 0.4%	
Zhou et al, China, 2008	29,079 Community-based	Not stated	70-74	Men 2.5% / Women 1.1%	Prevalence increases with age and AF is more common in men than women overall. Similar rates overall to other Asian studies, but higher rates in older age groups
			75-79	Men 3.4% / Women 0.5%	
			80+	Men 4.5% / Women 3.5%	
			30+ overall	Men 0.9% / women 0.65%	
Habibzadeh et al, Iran, 2004	463 Community-based	Not stated	70-74	Men 3.0% / women 2.6%	Prevalence increases with age and AF is more common in women than men overall
			75-79	Men 4.8% / Women 2.6%	
			80-84	Men 5.0% / Women 7.0%	
			85+	Men 15.4% / Women 8.6%	
			50-79	Men 1.3% / women 4.3%	
			50-59	0.6% overall	
			70-79	6.4% overall	

Uyarel et al, Turkey, 2008	3450 Community-based	Not stated	32-59	0.46%	Prevalence increases with age and AF is more common in women than men overall
			60-69	2.09%	
			70-79	2.49%	
De Carvalho Filho et al, Brazil, 1991	49 Hospital – based Geriatric out-patient clinic	Not stated	66-87	4.8%	Prevalence increases with age
Kawabata-Yoshihara et al, Brazil, 2009	1524 Community-based	Not stated	65+	Men 3.9% / women 2.0%	
Connor et al, South Africa, 2005	9133 Community-based	59% white 23% black 10% Asian 7% mixed race	Mean age 50.7 years	White 5% Black 2% Mixed race 4% Asian 2%	AF more common in white and mixed race than black and Asian people

Table 1. Summary of AF Prevalence Studies Worldwide

1.2.4 *The 'African-American paradox' – potential genetic factors influencing epidemiology*

As can be seen from my literature review, a clear pattern emerges, such that there appears to be significant differences in the prevalence of AF in different racial and ethnic groups. The most widely studied groups in high-income countries are Caucasians and African-Americans and despite the literature suggesting that African-Americans not only have higher rates of 'traditional' risk factors for AF (discussed in detail in next section), such as hypertension and obesity, but also significantly increased problems with sequelae of AF, such as stroke (discussed in section 1.5.1), they appear to have a much lower prevalence of AF itself. Thus, a paradox is present, one which has as yet remained unexplained although there have been several suggestions as to the potential reasons for this paradox. These include differential access to healthcare and therefore population bias, disease subtypes such as paroxysmal AF being more common in African Americans and therefore inadequately sensitive diagnostic methods (64), and survival bias i.e. exclusion of people from epidemiological surveys who die from their AF (65). However, there is growing evidence that these factors cannot explain the paradox fully, and that there are also potentially influential genetic factors. The evidence for a genetic predisposition to AF has been growing and a report by Fox et al (66) from the Framingham Heart Study suggested that if 1 parent had AF, their offspring had an OR of 1.85 of developing AF. This OR rose to 3.23 if the parent had developed AF <75 years of age, and most 'genetic evidence' for familial AF has arisen in studies of families with 'lone AF' (i.e. AF at a young age with no structural heart disease) (67-69). Current attention has turned towards the renin-angiotensin-aldosterone system (RAAS). Evidence is accumulating that RAAS may be an important risk factor for AF and inactivating RAAS through the use of angiotensin converting enzyme inhibitors may help prevent AF. There are known to be differences in the expression of genes coding for RAAS between white and black people (70) and, whilst most studies have been undertaken to show genetic polymorphisms that increase risk of AF, there of course must be polymorphisms that potentially protect against AF development. A study by Shreieck et al (71) looked at the C825T polymorphism in the coding region of

the G-protein β 3-subunit (GNB3), which modulates atrial inward rectifier potassium current. Their study reported a 54% decrease in AF in people with this polymorphism. There is a paucity of genetic data in African-Americans although the Vanderbilt-Meharry AF registry seeks to fill this knowledge gap (72). I could find no data on the genetics of AF in a SSA population.

1.3 Aetiology and Risk Factors

1.3.1 Hypertension

Hypertension (HTN) is the most common condition associated with AF in population-based studies (73). The suggested pathophysiological mechanism is adverse left atrial (LA) remodelling (dilatation and fibrosis) because of decreased ventricular compliance, increased ventricular stiffness and increased left ventricular (LV) diastolic filling pressures. This is one of the particular reasons for looking at hypertension in this elderly Tanzanian cohort (see chapter 7).

In the Framingham study (38) it was reported that HTN was responsible for more AF in the population (14%) than any other risk factor. It conferred an odds ratio for the development of AF of 1.5 for men and 1.4 for women after adjustment for other risk factors. In another study by Psaty et al (74), for every 10mmHg increase in Systolic blood pressure (BP), the relative risk of incident AF was 1.11. In the Manitoba Follow-up study (47), the risk of AF was increased by 1.42 times in men with a history of hypertension. The Women's Health Study (64) looked at systolic and diastolic BP in 34,221 women and subsequent risk of incident AF. They studied 34,221 women and found there was a statistically significant trend in increasing systolic and diastolic BP with incident AF.

Interestingly, a study by Schnabel et al (75) looked at risk factors for AF in whites versus African-Americans using data from 3 large population-based studies (Framingham, Cardiovascular Health Study and Age, Gene/Environment Susceptibility-Reykjavik Study), including 1552 African-Americans. Of these, 35.8% were men with a mean age of 75.3 years. The study reports that whilst HTN was more prevalent in African-Americans and

derived similar hazard ratios to whites (1.17 vs. 1.14/1.14/1.18) this did not translate into an increased incidence of AF and thus suggests that HTN may not be such an important risk factor for AF in African-Americans. In the previously mentioned Heart of Soweto study (59), HTN was only present in 12 of the 102 (12%) AF cases.

1.3.2 Ischaemic Heart Disease

In the Manitoba Follow-up Study (47), risk for AF was not only higher in participants with previous myocardial infarction (MI) (RR 3.62) and known angina (RR 2.84), but also in those with ST and T wave abnormalities on their ECG in the absence of overt ischaemic heart disease (IHD) (RR 2.21). It was noted that the RR for AF was strongest at the onset of IHD and diminished over time. In the Framingham study, only men with previous MI suffered increased risk (OR 1.4). However, in the Renfrew/Paisley study (35) it was reported that the odds ratio of incident AF was higher for women with myocardial ischaemia than men (OR 5.6 vs. 2.2, 4.5 overall). Chronically ischaemic myocardial tissue is an ideal substrate for AF perpetuation.

However, risk of AF is not only increased in chronic IHD, but also in acute MI, reported to complicate 6-21% of all MIs in a review by Schmitt et al (76). The underlying mechanisms suggested in the acute setting include atrial ischaemia or infarction, right ventricular infarction, pericardial inflammation, acute hypoxia or hypokalaemia, and haemodynamic impairment secondary to LV dysfunction (77, 78).

Interestingly, it has previously been noted that black Africans suffer less IHD than do white people. Bertrand et al (79) reported that IHD accounted for only 6% of all forms of cardiovascular disease (CVD) in black Africans, and a study by Walker et al (80) in South Africa reported that IHD was responsible for <1% deaths. This compares to a prevalence of IHD in the general population in the USA of 6.9%, with IHD responsible for 20% of all deaths in the USA in 2003 (81).

1.3.3 Age

Advancing age has consistently been shown to be a risk factor for the development of AF. Please see epidemiology section (1.2) where age as a risk factor for AF is discussed with specific reference to the appropriate literature.

1.3.4 Cardiac Failure

The Framingham study (38) showed there to be 4.5x risk in men of AF if they had heart failure and a 5.9x risk in women. Diastolic dysfunction associated with increased LV filling pressures is common in the elderly and has also been shown to increase risk of AF by 5.26x in one study by Tsang et al (82). In a review of papers looking at AF risk factors by Schnabel et al (75), prevalent heart failure provided a hazard ratio for incident AF of 1.78 – 4.45 in whites (dependent on study) and 3.21 in black Americans.

The EuroHeart Failure survey conducted in 2000 - 2001 in 24 countries in Europe has reported that up to 45% of patients with congestive heart failure (CHF) also presented with intermittent or established AF (83). According to this survey, the overall prevalence of new onset AF in patients hospitalised for CHF is 13%, ranging from 8% to 36% in different European regions. The prevalence of AF generally depends on the severity of the underlying pathology, between 10% and 20% in mild to moderate CHF and up to 50% in patients with more advanced disease (84). Patients with CHF due to diastolic dysfunction have the same prevalence of AF as their counterparts with LV systolic dysfunction. AF was present in 29.1% of patients with an ejection fraction <40% enrolled in the Candesartan in Heart Failure Assessment of Reduction in Mortality (CHARM)-Preserved trial (85) and in 23.4% patients with an ejection fraction <50% who participated in the New York Heart Failure Consortium Registry (86).

Further studies have shown heart failure to be a common concomitant diagnosis with AF. Murphy et al (87) reported that heart failure was concomitantly diagnosed in 15.3% of men and 19.8% of women with AF in a community-based study of general practices in Scotland. Sliwa et al (59)

reported heart failure concomitantly in 48 of 102 (47%) consecutive cases of AF in a hospital-based setting in South Africa.

Because of the nature of the two conditions occurring together it is difficult to ascertain in the majority of cases which came first, AF or heart failure. In the majority of cases it is likely that heart failure predisposes to AF rather than the other way around although, in the Manitoba Follow-up study (47), whilst it was noted that congestive cardiac failure (CCF) was a risk factor for AF, AF itself increased the risk for CCF (RR 2.98).

1.3.5 Atrial Enlargement

The Framingham study (38) reported increased LA diameter as a risk factor for AF, with a 39% increase in risk with each 5mm incremental rise in LA diameter. This finding was supported by the Cardiovascular Health Study findings (43), and by data from the Olmsted County study (88) that showed a 30% increase in LA size was associated with a 48% higher risk of AF.

As discussed previously, atrial dilatation and structural remodelling not only changes ionic currents through atrial myocytes (23) but also the process of an enlarged LA means there is simply a bigger volume for micro re-entry circuits to flourish (25).

1.3.6 Intra-Cardiac Conduction Abnormalities

PR interval (79) and sinus node dysfunction (80) are known to increase the risk of AF. RR increases with increasing PR interval length, and previously published studies suggest chronic AF occurs in up to 11% of SSS cases at 19 months, 16% at 5 years, and 28% at 10 years.

Wolf-Parkinson-White Syndrome (WPW), a syndrome in which an accessory conduction pathway between atria and ventricles is present, also confers increased risk of development of AF. AF occurs in a fifth to a third of WPW patients, and can continue to occur in up to 24% even following ablation of the accessory pathway (89).

1.3.7 Obesity and Metabolic Syndrome

Obesity in both women (82) and men (83) has been shown to increase risk of AF development. The Women's Health Study in the USA showed a 4.7% increase in risk with each kg/m².

A study by Rosengren et al (90) looking at 6903 men (mean age 51.5 years) in Sweden showed recalled increased body surface area (BSA) at age 20, increased BMI at assessment and the increase in weight over time all had a positive correlation with risk of AF.

A recent meta-analysis found that obesity increased the risk of developing AF by 49% in the general population and the risk escalated in parallel with increased BMI (91).

The Metabolic Syndrome (≥ 3 of abdominal obesity, elevated triglycerides, low HDL cholesterol levels, elevated blood pressure and impaired glucose tolerance) has also been shown to increase risk of AF, with obesity being the most significant contributor to AF risk (85).

Another study, by Chamberlain et al (92) looked at 15,094 participants in the ARIC study, which was notable for its significant percentage of African-Americans included. 45.7% of blacks and 39.6% whites at baseline had metabolic syndrome. Over a mean follow-up of 15.4 years, 1238 cases of AF were identified. Age-adjusted incidence rates were higher in those with metabolic syndrome than without (60/10,000 person-years vs. 36). Hazard ratio for incident AF was 1.67 for those with metabolic syndrome vs. those without and there was no significant inter-racial difference. The population attributable risk was 22% (i.e. 22% of AF events could have been prevented with elimination of metabolic syndrome). HTN and obesity appeared to confer greatest increased risk, their respective multivariable-adjusted hazard ratios being 1.95 and 1.4. Other components measured were low high-density lipoprotein (HDL) (HR 1.2), impaired fasting glucose (1.16) and elevated triglycerides (0.95). Increasing number of components of metabolic syndrome conferred increasing risk of AF, with a hazard ratio of 4.40 for those with all 5 components vs. those with none.

Reasons suggested for the trend of increased AF incidence in people with increased body size include the fact that as body size increases, so does LA

size/volume (87), in addition to the correlation between obesity and IHD and thus, potentially, heart failure (86).

1.3.8 Hyperthyroidism

Whilst the prevalence of hyperthyroidism in the elderly ranges from 0.4-2.0% (93) and is thus not high, studies have shown increased prevalence (88) and incidence (89) of AF, with biochemical abnormalities more pronounced in those hyperthyroid patients with AF (92).

1.3.9 Electrolyte Abnormalities

AF is more common in patients with primary aldosteronism (93), post cardiac surgery in patients with low potassium levels (94) and in patients with diuretic-induced hypomagnesaemia (95)

Suggested mechanisms for increased AF in patients with hypokalaemia and hypomagnesaemia centre around the ideas that reduced levels of K^+ and Mg^{2+} not only increase automaticity by increasing premature atrial complexes (PACs) (through increased intra-cellular Ca^{2+}) but also shorten AERP and increase wavelet dispersion, thereby creating a substrate for the initiation and propagation of AF (94).

1.3.10 Valve Disease

The Framingham study (38) reported an odds ratio for AF development in patients with valvular heart disease of 1.8 in men and 3.4 in women. This finding is supported by other large population-based studies in North America such as the Cardiovascular Health Study (43) and the Manitoba follow-up study (47). Aortic stenosis (97) and aortic regurgitation (98) have been shown to be related to AF, particularly in the elderly. Left ventricular hypertrophy (LVH) results from a ventricle contracting against a stenosed aortic valve, and LV dilatation results from a regurgitant aortic valve. Both eventually lead to increased LV diastolic filling pressures and decreased LV compliance, meaning increased LA pressure and atrial remodelling.

Whilst the aetiology of valve disease in these studies is primarily likely to be related to chronic degeneration and the result of other co-morbidities such as MI leading to functional valve incompetence, the situation in SSA is very different. In SSA, valvular disease is encountered in the young, not infrequently in children of school-going age or young females of child-bearing potential, and with a course that is much more rapid. This is usually as a result of infectious disease, either directly through infective endocarditis or indirectly as in the case of acute rheumatic fever. The incidence of acute rheumatic fever (in large part secondary to Group A streptococcus infection) has been said to be 100 times greater in SSA (data from Sudan) than in high-income countries. The prevalence of chronic rheumatic heart disease (RHD) has been estimated mainly from surveys of school-going children and varies from 2.7/1000 in Nairobi to 14.3/1000 in Kinshasa (95). In a survey of 12,050 black school children in Soweto, South Africa, in 1975, McLaren et al (96) found a prevalence of 6.9/1000 with a maximum of 20/1000 in seventh- and eighth-grade children. With an improvement in the standards of living in the Soweto population, a distinct decline in the incidence of acute rheumatic fever presenting to Baragwanath Hospital has been observed (97), although chronic rheumatic valve disease remains commonplace.

The Heart of Soweto study (60) found that valve disease was a common concurrent diagnosis in incident AF cases, occurring in 107/246 (43%) cases. A primary diagnosis of valve disease was made in 71 of these cases, with the remaining 36 as a result of other cardiac pathology leading to valvular dysfunction (e.g. ischaemic cardiomyopathy leading to functional mitral regurgitation). 51 cases were diagnosed as rheumatic (of which 43% were mitral stenosis), with the other 20 degenerative, perhaps highlighting the different underlying aetiology of valvular heart disease in SSA. Potential reasons for the fact that mitral valve disease increases risk of AF include the idea that both mitral stenosis and mitral regurgitation increase left atrial pressure, thus causing atrial dilatation and structural atrial remodelling over time. There are very little data on valve disease in the elderly in SSA, potentially this is a result of a combination of the majority dying at a young age and that same age group being an understudied demographic.

1.3.11 Pulse Pressure

In a study by Mitchell et al (98), pulse pressure and systolic pressure were both associated with a higher risk of developing AF, with an odds ratio of 1.23 for pulse pressure and 1.14 for systolic BP, although their population was one of almost exclusively Caucasian background and there is little data in different racial groups. Elevated pulse pressure is used as a surrogate for increased proximal aortic stiffness (98) and has been shown to predispose to increased LA size chronically (99) as well as being thought to increase LA distending pressure (and thus provide substrate for AF initiation) when pulsatile load increases acutely (100).

1.3.12 Other Risk Factors

Pulmonary embolus (106), sepsis (107, 108), atrial myxoma (109-111), atrial septal defect (112, 113), the post-cardiac surgery state (31) (due to a number of mechanisms including acute atrial distension, atrial inflammation from surgical trauma or pericarditis, ischemic injury caused by cardioplegia, and electrolyte and volume shifts during bypass that can alter atrial repolarization (101)) have all been shown to increase risk of AF. AF is less common in patients following non-cardiac surgery but can still be a potential problem and, as one might expect, has been noted to be more common in those with underlying cardiovascular disease (115, 116).

1.4 Associations

1.4.1 Diabetes

AF prevalence is significantly greater among patients with diabetes mellitus (DM) and a study looking at 17,000 diabetic patients with an equivalent number of age- and sex-matched controls showed an exaggerated increase of AF incidence over time in diabetic vs. non-diabetic patients, particularly in women (117). Newly-diagnosed AF is also more likely to occur in diabetics than non-diabetics (118), translating into a 40% increase in risk of AF in those with treated DM. This is primarily thought to be due to increased

diastolic dysfunction and thus LA pressure, chronic inflammation and cardiac autonomic neuropathy.

1.4.2 Cognitive Function

There have been many studies looking at the association between AF and cognitive function, often reporting conflicting results. A systematic review (120) and a meta-analysis (121) of the current literature (with some overlap in studies analysed) found similar results in the general population in that there remains uncertainty of a link between AF and dementia. However, the meta-analysis looked at studies involving patients having had a stroke (7 out of 15), with the association much more convincing, with an OR of 2.4 ($p < 0.001$) in patients with AF and stroke for developing dementia compared with patients without AF or stroke.

1.4.3 Chronic Kidney Disease

Two reasonably-sized studies looked at the association of AF with CKD, one including 50% African-Americans finding that in CKD patients the prevalence of AF was 18% overall, higher than in previous studies (123-126). The REGARDS study more recently found a prevalence of AF of only 1.0% although the prevalence did increase significantly with worsening renal function (127).

1.4.4 Pericardial Fat

CT-estimated pericardial fat volume (128) has been linked to an increased risk of AF, patients with persistent AF having been shown to have a greater volume than paroxysmals, who in turn have a higher volume than those in sinus rhythm (129).

1.4.5 Obstructive Sleep Apnoea

Incident AF is higher in patients with obstructive sleep apnoea (OSA) (130). OSA is more prevalent in patients undergoing DC cardioversion (DCCV)

versus those controls without past / current AF referred to a cardiology OPC (131) and AF is more likely to recur in patients with OSA who have undergone DCCV who are not treated with nocturnal CPAP versus those who are (132).

1.4.6 Diet (Caffeine, Alcohol and Fatty Acids)

A recent systematic review by Gronroos and Alonso (102) reviewed the evidence regarding the influence of dietary factors on risk of AF. The review identified 4 factors that have been looked at in relation to subsequent AF – alcohol, caffeine, fish-derived n-3 polyunsaturated fatty acids (n-3 PUFAs) and ascorbic acid. Alcohol appears to increase risk of AF, particularly heavy drinking (134-137), whilst n-3 PUFAs may decrease risk by as much as 85% in 1 study (138). Caffeine intake showed a U-shaped curve in 1 study (139), whereby moderate caffeine intake may have a protective effect, and ascorbic acid may be protective in high doses post-cardiac surgery (140).

1.4.7 Inflammation and Inflammatory Conditions

It remains controversial as to whether inflammation is the initiating event in the development of AF or, conversely, if it occurs as a consequence of AF. Evidence implicating inflammation in the initiation of AF include the increased incidence of AF in the setting of inflammatory states such as cardiac surgery and the observation that baseline CRP levels predict future occurrence of AF (103). On the other hand, the observation of decreasing highly sensitive CRP levels following restoration of sinus rhythm has led some to believe inflammation is a consequence rather than a cause of AF (104).

Chung et al were the first to report an association between AF and elevated CRP in non-postoperative AF (105). The association between elevated CRP and presence of AF was further supported with the findings from a large population-based cohort study of 5,806 elderly individuals followed for a mean of 6.9 years (103). CRP was not only associated with the presence of AF but, in patients without AF at baseline, elevated CRP levels were significantly and independently associated with the future development of AF. In one study, every 1 mg/dL increase in serum CRP was associated with

a 7-fold increased risk of recurrent AF and a 12-fold increased risk of permanent AF compared with controls (106). Raised CRP has also been associated with failed DCCV in those with persistent AF (107) and also with recurrence of AF post-DCCV (108).

The exact mechanism for increased serum CRP in AF patients is uncertain. It has been suggested that it may contribute to cellular membrane dysfunction and therefore have a direct effect (109) or may just be a marker of systemic inflammation and reflect underlying disease processes associated with AF. Raised Interleukin-6 (IL-6) has also been shown to be related to presence / duration of AF and LA diameter (110), and IL-8 was found to be elevated in AF patients in a small study (111).

1.5 Sequelae

1.5.1 Stroke and Thromboembolism

A study by Wolf et al (112) looked at 34 years of follow-up in 5070 (almost exclusively) Caucasian patients from the Framingham study. They assessed AF as an independent risk factor for stroke and found that there was a five-fold excess of stroke in patients with AF. In persons with IHD or heart failure, AF doubled the stroke risk in men and trebled the risk in women. The attributable risk of stroke in AF sufferers increased from 1.5% in those aged 50-59 to 23.5% in those aged 80-89 years. The data suggest the elderly are particularly vulnerable to stroke when AF is present.

In a report by the Stroke Prevention in AF Investigators (1992), 568 AF patients were followed up for a mean of 1.3 years. They looked at the incidence of stroke in AF patients with and without three clinical predictors (recent CCF, HTN and previous thromboemboli). Risk of stroke was 2.5% per annum in AF patients with none of these predictors, rising up to 17.6% per year with 2 or 3 of the clinical predictors.

In a population based study (113) looking at long term (20 year) risks, AF was a strong independent risk factor for stroke (in women OR 3.2 and in men OR 1.8). In another study one in six strokes occurred in a patient with AF (114). In the Framingham study ischaemic stroke occurring with AF was almost twice as likely to be fatal as stroke not associated with AF, with

recurrence more frequent and functional deficits more severe in survivors (115). Lone AF increases the risk of stroke 4-fold while AF associated with mitral RHD increases the risk 17-fold. The prevalence of AF in patients with ischaemic stroke may be increasing independently of age and gender (116).

It has been noted in other previous studies in high-income countries that AF and AFI account for about 10% of all strokes and 50% of cardioembolic strokes (117) and about 35% of AF patients will experience ischaemic stroke during their lifetime (118) (119) (120).

Risk of stroke in lone AF is less certain. Whilst data from the Framingham study suggest a four-fold increase in stroke risk with lone AF (121), a study by Kopecky et al (122) looked at 97 patients with lone AF (aged ≤ 60 at diagnosis) and followed them up for a mean of 14.8 years. They found a low risk of stroke in these younger patients with no structural heart disease, with only 1.3% of patients suffering stroke during follow-up.

There are currently fewer data on the role of AF in stroke in blacks. A study by Yuan et al (123) of 4 million Medicare recipients in the USA, followed for 4 years, showed that compared with those without AF, black men and women had 4.3 and 7.3 times the risk of embolic stroke, and 1.4 and 1.7 times the risk of non-embolic stroke respectively.

There are data on the contribution of AF to cardioembolic stroke in SSA. In a South African study 21% of ischaemic strokes were cardioembolic (124) with 13% due to RHD and AF present in 7%. In Zimbabwe, 19% of ischaemic strokes were cardioembolic due to AF, cardiomyopathy or valvular heart disease (125). In one hospital series, AF was found in 2% of strokes (126), in 5-7% of strokes in hospital series using imaging (127) (128) and in 7% of a hospital cohort in the Gambia (129).

Paroxysmal AF is thought to confer a very similar risk of stroke to permanent AF. A study by Friberg et al (130) looked at 855 patients with paroxysmal AF and 1126 patients with permanent AF with respect to their stroke incidence over a 3.6 year follow-up period. They found the incidence of stroke in paroxysmal AF patients to be 26 / 1000 person-years, versus 29 / 1000 person-years in those with permanent AF. The multivariable-adjusted HR for

ischaemic stroke in paroxysmal AF vs. permanent AF was 1.07, and for all strokes (ischaemic and haemorrhagic) was 0.89.

Atrial Flutter is thought to confer a similar risk of stroke as AF, although the evidence for this is not as clear-cut. A study by Leloir et al (131) followed 881 patients with AF / AFI from the Canadian Registry of Atrial Fibrillation (CARAF) for an average of 6.9 years. They found a stroke incidence of 1.33 / 100 patient-years in the AF group, versus 1.24 / 100 patient-years in the AFI group. A retrospective study by Wood et al (Wood K, 1997) suggests a 3% annual risk of stroke with AF and a series by Seidl et al (132) suggests it may be as high as 7%. However, it is noted in the Leloir study that 28% of AFI patients did convert to AF over time, thus suggesting perhaps AFI patients also suffered AF that was the ultimate catalyst for stroke.

1.5.2 Heart Failure and Tachycardiomyopathy

It is well recognised that chronic tachycardia in patients with AF and fast ventricular response may result in extensive changes in ventricular function and structure (tachycardiomyopathy) (133). Importantly, tachycardiomyopathy with proper ventricular rate control is completely reversible.

Our present understanding of tachycardia-induced cardiomyopathy relies mainly on experiments in animal models. Sustained rapid atrial or ventricular pacing can produce severe biventricular systolic and diastolic dysfunction in animals. The heart failure is characterized by elevated ventricular filling pressures, impairment of left and right ventricular systolic function, increased left and right end-systolic and end-diastolic volumes, reduction of cardiac output, and elevation of systemic vascular resistance. Subsequently, the plasma atrial natriuretic peptide, epinephrine, norepinephrine, renin activity, and aldosterone levels are markedly elevated. AF is also known to reduce cardiac output by 10-20%, irrespective of ventricular rate (133).

In large population-based studies, AF has been shown to increase risk of subsequent heart failure. In a 20-year follow-up study by Stewart et al (113) AF was a strong independent risk factor for heart failure, with an OR of 3.1 in women and 3.4 in men. In support of these findings, Krahn et al (47) found in

the Manitoba follow-up study that AF independently increased the risk of heart failure with an OR of 2.98.

1.5.3 Impaired Quality of Life

AF can be a highly symptomatic arrhythmia, with patients reporting palpitations, dizziness, breathlessness, exercise intolerance and fatigue. These symptoms can be particularly troublesome in the elderly (134). Therefore it is unsurprising to find that several studies have reported AF patients to have a reduced quality of life (QOL) compared with an age- and sex- matched general population in sinus rhythm (135-137).

A systematic review by Thrall et al (138) looking at the impact of AF on QOL found that in the domains of general health, vitality, physical, social and emotional role functions, AF patients have poorer QOL than age-matched healthy controls. However, it was noted that there was significant improvement in all these domains as patients' symptoms were alleviated through various rate and rhythm control methods.

Symptomatic relief may involve multiple psychological factors. In addition to the obvious effect of the medical or surgical intervention, it has been suggested that patients may report fewer symptoms because they believe their treatment has been successful. Furthermore, perhaps simply being informed that their heart rate is beating in a 'normal' rhythm may reduce patient anxiety and increase psychological well-being (139). Clearly, symptom control is a key factor in determining QOL in AF patients and many current management strategies for AF are very much 'symptom driven'.

1.5.4 Mortality and Medical Costs

There is a significant mortality burden from untreated AF. Risk of death was shown to increase by 1.5 times in men with AF, and 1.9 times in women, after adjustment for pre-existing cardiovascular conditions as reported by Framingham study investigators (2). Another study from Australia (48) reported that relative mortality for those with AF versus those without was 1.92 for all causes, 1.82 for death from cardiovascular causes (excluding

stroke) and 3.78 for deaths from stroke. In the Manitoba follow-up study (47) total mortality rate in AF patients was increased 1.31 times compared to that of the background population. Cardiovascular mortality including and excluding fatal stroke was also increased (RR 1.41 and 1.37 respectively). A four-year follow-up of patients in the Marshfield Clinic Epidemiologic Study Area population also showed a 2.4-fold increased risk of death even after adjustments for sex, age, and other cardiovascular risk factors in patients with AF or Afl (140).

AF imposes a substantial cost burden on the healthcare system due to therapeutic interventions intended to reduce morbidity and mortality. Based on data from the National Hospital Discharge Survey, the number of AF-related hospitalizations almost tripled in 2000 compared with two decades ago (141). A good estimate of the involved costs was provided by a large UK-based survey that revealed that the direct cost of managing AF increased from 0.6–1.2% of the total National Health Service (NHS) budget in 1995 to 0.9–2.4% by 2000 (142). A study from France showed similar figures, with a significantly higher number of hospitalizations and deaths in patients with persistent or permanent AF compared with those with paroxysmal AF (143), AF-associated heart failure, coronary disease, use of class III antiarrhythmic drugs, hypertension, and metabolic disease were significantly associated with higher costs. Based on retrospective analyses of three federally funded databases in the US (2001 data), total annual costs for treatment of AF were estimated at US\$6.65 billion, including US\$2.93 billion (44%) for hospitalizations for AF, US\$1.95 billion (29%) for the incremental inpatient cost of AF as a co-morbid diagnosis, US\$1.53 billion (23%) for outpatient treatment of AF, and US\$235 million (4%) for prescription drugs (144). A recent study by Kim et al (145) looking at medical costs of AF versus non-AF controls in the US showed mean annual inpatient costs per patient were \$7841 versus \$2622 (incremental cost, \$5218), outpatient medical costs were \$9225 versus \$5629 (\$3596), and outpatient pharmacy costs were \$3605 versus \$3714 (-\$109) (all $p < 0.001$). The total incremental cost of AF was \$8705 per patient. The national incremental cost of AF was \$26.0 billion (AF, \$6.0 billion; other cardiovascular, \$9.9 billion; non-cardiovascular, \$10.1 billion).

1.6 Risk Stratification

1.6.1 CHADS₂ and Other Risk Stratification Tools

As has been shown previously, AF is a significant risk factor for stroke, but the presence or absence of other clinical factors in AF patients and the application of a validated risk stratification tool allows their stroke risk to be more accurately calculated. There have been many risk stratification tools produced and compared for validity (146) but the one which has gained most acceptance for general use, partly because of its reliability but also its ease of use, is the CHADS₂ score. In non-valvular AF patients, it stratifies stroke risk based on a points-scoring system. 1 point is scored for each of 'C' for congestive heart failure / LV dysfunction (EF ≤40%), 'H' for hypertension, 'A' for age ≥75 and 'D' for diabetes mellitus. 2 points are scored for the patient having had a previous stroke ('S') or TIA. The maximum score is 6 and the higher the score the higher the stroke risk, from a 1.9% stroke risk per year in a patient with a CHADS₂ score of 0 up to 18.2% per year with a score of 6 (147). This risk stratification tool, as with others, allows the patient to be stratified (albeit artificially) as low, intermediate or high risk and thus determines how the patient should be treated. Traditionally with the CHADS₂ scoring system, a score of 0 was low risk and aspirin or no treatment recommended, a score of 1 intermediate risk and aspirin or warfarin recommended and a score of >1 high risk and warfarin recommended if no contraindications.

1.6.2 CHA₂DS₂-VASc

The 2010 European Society of Cardiology (ESC) guidelines (31) have encouraged physicians to move away from categorising AF patients as either low, intermediate or high risk and see risk as a continuum. An attempt at refining and improving on the CHADS₂ score has been made in the form of the CHA₂DS₂-VASc score where more importance is placed on age ≥75 years (the first 'A' scoring 2 points). Furthermore, female sex ('Sc' for sex correlate) is recognised as a risk factor in its own right, providing a RR of 1.6 for thromboembolism, as is known vascular disease ('V') such as previous MI

and peripheral vascular disease (148). Age 65-74 is also known to increase stroke risk, although less so than the 75 and over group.

These risk stratification tools are currently somewhat arbitrary with respect to treatment decisions in rural Tanzania and most of SSA given the lack of infrastructure for safe anticoagulant use and monitoring. However, I feel these tools are helpful to demonstrate just how high the risk of stroke is in the majority of my AF cases and these risk scores highlight a situation in my Study Population which needs to be addressed.

1.6.3 Assessment of Bleeding Risk

As with any medication, a risk-benefit profile should be considered prior to commencement. With respect to AF patients and their risk of bleeding prior to commencement of oral anti-platelet / anti-coagulant therapy, this comes in the form of the HASBLED tool. Again, the patient scores 1 point for each of hypertension (H) with a systolic BP >160mmHg, abnormal renal and liver function (A) with 1 point for each, stroke (S), previous bleeding (B), labile INRs (L), elderly (E) >65 years and drugs / alcohol (D) again scoring 1 point each. This gives a total score of 9, with a score of ≥ 3 considered high-risk of having a major bleed. ESC guidelines (31) recommend caution and regular review in these high risk patients.

The HASBLED scoring system was derived from a 'real world' cohort of 3978 Euro Heart Survey AF patients (149). Again, whilst some of the scoring system is less relevant to risk assessment in SSA (i.e. labile international normalised ratios (INRs) and liver dysfunction more relevant to warfarin than aspirin), it has also been noted previously that in the elderly the risk of major bleeding is similar with either aspirin or warfarin treatment (150). Therefore it was useful to my study in order to assess bleeding risk in AF patients to whom I was considering prescribing aspirin.

1.7 P wave predictors of atrial fibrillation

The P wave morphology, if abnormal, can provide information on disease processes involving the atria and traditionally the P wave area (PWA) has

been used as a surrogate for atrial size. There is growing evidence of the importance of the P wave on 12-lead electrocardiogram, not only in assessing immediate electrical function of the atria but also in predicting future problems such as AF and stroke. P wave duration (PD), P wave dispersion (PDISP) (i.e. maximum P wave duration – minimum P wave duration), PWA, PWTF in lead V₁ and P-R interval have all been looked at in more detail to assess their ability to predict PAF, future AF and stroke. However, it has been noted that PD, PWA and PR interval show a significant circadian variation in healthy individuals and the relationship between P area / RR, PR / RR, and P duration / RR also demonstrate a significant diurnal pattern (151). This variation has also been demonstrated on a seasonal basis, with a study by Kose et al (152) demonstrating that P wave maximum duration and PDISP were significantly shorter in summer than in winter in 523 healthy male army recruits. Multiple physiological factors are suggested to play a part in these variations, including changes in left atrial volume, left atrial pressure, autonomic tone and atrial conduction characteristics (151). It is also noted that apart from the paper by Soliman et al (153), most of the other papers involve small numbers of participants and further work is suggested in this area.

1.7.1 P wave duration

Studies have shown prolonged PD to be more common in patients with PAF (195), to predict recurrence of AF (196), but also that a small minimum PD was more prevalent in PAF (197), suggesting that extremes of P wave measurement (either very long or very short) may be the important factor in predicting AF. PD \geq 110ms correlates well with LA enlargement when compared to CT-derived LA volume and index (154).

In another study by Soliman et al (153) looking at the ethnic distribution of ECG predictors of AF as part of the ARIC (Atherosclerosis Risk In Communities) study, 15,429 participants' (27% black) ECGs were analysed. The study found not only that, overall, black Americans had more evidence of ECG predictors of AF but also, importantly to this section, that maximum PD and PD in lead II (upper 5th percentile vs. first 95th percentile) were the

most strongly associated predictors of incident AF (HR 4.07 and 3.90 respectively after adjustment for demographic and clinical variables).

1.7.2 P wave Dispersion

Increased PDISP has been shown to be more common in people with PAF (195) and to predict the development of AF, both in the general population (199) and following cardiac surgery (200).

1.7.3 P wave Area

In the Soliman paper (153), mean and maximum PWA were both significantly associated with incident AF, with HRs of 2.83 and 2.61 respectively. In addition, as predictors of incident ischaemic stroke the respective HRs were 1.11 and 1.13 after adjustment for demographic and clinical variables.

1.7.4 P wave Terminal Force (V_1)

Again, in the Soliman paper (153),PWTF had a HR of 1.9 for incident AF and 1.22 for incident ischaemic stroke. This was the strongest ECG predictor of incident stroke in their population of 15,429. In another study by Ishida et al (155), 78 patients with LA overload (based on a PWTF in V_1 of ≥ 0.12 mV/sec) were chosen from 102,065 in the database. During a mean follow-up of 43 months, 15 patients developed AF whilst 63 did not. There was no significant difference in the PWTF but there was a significantly larger mean PW initial force in V_1 in the AF group, giving a HR after multivariate analysis of 4.02.

1.7.5 P-R interval

A study by Cheng et al (156) looked at 7575 individuals from the Framingham study with >30 years follow-up. When examining PR interval on the ECGs, they found that for each 20ms increase of PR interval, HR of developing AF was 1.11. For participants with 1st degree AV block (i.e. PR interval >200ms), HR of AF development was 2.06.

In the Soliman paper (153), 1 standard deviation of change in PR duration resulted in a HR for development of AF of 1.41 after adjustment for demographic and clinical variables but there was no significant difference in the effect on incident ischaemic stroke (HR 1.00).

1.8 Pharmacological Management

There are many pharmacological treatments currently available for the management of acute and chronic AF. In this next section I will concentrate particularly on the chronic management of atrial fibrillation given that my AF Study Population was community-based. Treatment options in SSA are limited to basic reduction in stroke risk and control of ventricular rate to help reduce symptoms and heart failure risk.

1.8.1 Anti-platelets

Eight independent randomized controlled studies, together including 4876 patients, have explored the prophylactic effects of anti-platelet therapy, most commonly aspirin compared with placebo, on the risk of thrombo-embolism in patients with AF (157). When aspirin alone was compared with placebo or no treatment in seven trials, treatment with aspirin was associated with a non-significant 19% (95% CI –1% to –35%) reduction in the incidence of stroke. There was an absolute risk reduction of 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention by using aspirin. The bulk of the positive results came from one large trial, SPAF-1, that compared aspirin 325mg / day versus placebo and showed a 42% RRR in the risk of stroke. Pharmacologically, near-complete platelet inhibition is achieved with aspirin 75 mg. Furthermore, low-dose aspirin (<100 mg) is safer than higher doses (such as 300 mg), given that bleeding rates with higher doses of aspirin are significant. Thus, if aspirin is used, it is reasonable to use doses in the lower end of the allowed range (75–100 mg daily) (31).

However, having said this, there is a small amount of evidence that aspirin may be detrimental to stroke prevention in some AF patients, particularly those with no obvious underlying structural cardiac disease. In the Japan

Atrial Fibrillation Stroke Trial (150), patients with lone AF were randomized to an aspirin group (aspirin at 150– 200 mg/day) or a control group without anti-platelet or anticoagulant therapy. The primary outcomes (3.1% per year) in the aspirin group were worse than those in the control group (2.4% per year), and treatment with aspirin caused a non-significant increased risk of major bleeding (1.6%) compared with control (0.4%).

1.8.2 Anti-coagulants

In a meta-analysis, the RR reduction with Vitamin K antagonists (such as Warfarin) versus placebo was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7% (157). When only ischaemic strokes were considered, adjusted-dose Vitamin K antagonists use was associated with a 67% RR reduction. Direct comparison between the effects of Vitamin K antagonists and aspirin has been undertaken in nine studies, demonstrating that Vitamin K antagonists were significantly superior, with a RR reduction of 39% (31). It was also noted in the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study that there was no increase in major haemorrhage in the Warfarin group (158), but in studies prior to BAFTA, risks of intracranial haemorrhage were doubled when results were taken together (although absolute risk increase was small at 0.2% / year).

In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events–Warfarin arm (ACTIVE W) trial, anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (RR reduction 40%; 95% CI 18–56), with no difference in bleeding events between treatment arms (159, 160).

The major problem with warfarin treatment is the need for regular monitoring of levels using the INR. This is a particular stumbling block to anticoagulation in rural SSA, given poor access to health care and sporadic compliance with medication. However, several new anticoagulant drugs - broadly in two classes, the oral direct thrombin inhibitors (e.g. dabigatran etexilate and AZD0837) and the oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, YM150, etc.) - are being developed for stroke

prevention in AF (of which Dabigatran has just been granted a licence in the US by the FDA). These newer anticoagulant drugs are novel in that they do not require regular monitoring and perhaps provide hope for the treatment of AF and other conditions requiring anticoagulation in SSA in the future (where there is little infrastructure for INR monitoring away from large urban centres). These agents are showing good early promise in terms of being at least as good as warfarin from a thromboembolism protection perspective, whilst not unduly increasing bleeding risk, with some results suggesting reduced overall (and particularly intracranial) bleeding risk (205-207).

1.8.3 Rate Control Versus Rhythm Control

Control of ventricular rate versus restoration of sinus rhythm has long been a contentious issue in the treatment of AF, particularly with regard to outcomes in terms of morbidity, mortality and quality of life. In SSA, with the lack of drug availability and affordability, it is the cheaper generic rate control drugs that are most prevalent. There is good evidence to suggest that a rate control strategy is non-inferior in terms of hard outcomes such as morbidity and mortality (208-210), as well as suggestions that symptomatic quality of life may differ very little also (208-212).

In terms of rate control treatment, β -blockers and non-dihydropyridine calcium channel antagonists are normally used as first-line rate control therapy. They have been shown to control ventricular rate (on exertion and at rest) quickly and effectively (161). Digoxin has also been shown to control resting pulse rate well.

What is deemed acceptable rate control is still open to some debate. The AFFIRM trial suggested that resting PR should be 60-80bpm with PR on moderate exertion 90-115bpm. However, this has been deemed somewhat strict by the more recent RACE II (Rate Control Efficacy in permanent atrial fibrillation) trial that randomised 614 patients to either lenient rate control (resting PR <110bpm) or strict rate control (resting PR <80bpm) (162). 81 patients (38 lenient, 43 strict) reached the primary endpoint including CV death, stroke, heart failure hospitalisation and pacemaker insertion, proving non-inferiority for a more lenient rate control approach.

1.8.4 Other Upstream Therapies

Upstream therapy to prevent or delay myocardial remodelling associated with hypertension, heart failure or inflammation (e.g. after cardiac surgery) may defer the development of new AF (primary prevention) or, once established, its rate of recurrence or progression to permanent AF (secondary prevention) (163). Treatments with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone antagonists, statins, and omega-3 polyunsaturated fatty acids (PUFAs) are usually referred to as 'upstream' therapies for AF. Again, many of these therapies are unavailable in SSA and are not discussed, but ACEIs and ARBs are worth mentioning. ACEIs and ARBs have been shown to inhibit the arrhythmogenic effects of angiotensin II, which include stimulation of atrial fibrosis and hypertrophy, uncoupling gap junctions, impaired calcium handling, alteration of ion channels, activation of mediators of oxidative stress, and promotion of inflammation. There is good experimental evidence of anti-fibrillatory and anti-fibrotic actions of ACEIs and ARBs in various AF models (31). I saw evidence of them being used for the treatment of hypertension in Tanzania and, although they remain expensive and not recommended as first-line therapy in the treatment of hypertension in black people of African descent / origin (164), they may well have a role to play in controlling BP and therefore potentially reducing the incidence of AF in SSA.

1.9 Further Management

The field of invasive management for the treatment of AF is growing rapidly. Atrio-ventricular node ablation (31), catheter ablation (31, 216, 217), surgical ablation (31) and left atrial appendage occlusion devices (218) have all been shown to have some benefit in either reducing AF burden or reducing the symptoms and incidence of sequelae associated with the disease. However, these interventions currently have no place in the management of AF in SSA, particularly in rural areas, and therefore they are not discussed in more detail.

1.10 Background Information about Tanzania and the Hai District

Tanzania is situated in sub-Saharan East Africa at 6°S and 35°E and has a population of 41.8 million. It covers an area of 947,300 square km. It has a very pyramid-shaped population profile (see figure below) in that 43% of the population are <15 years old, 54.1% are between 15-64 years, and only 2.9% are aged 65+. The median age is 18.3 years and the life expectancy at birth for men is 50.99 years and for women 54.03 years. Estimated population growth rate in 2010 was 2.03% per year.

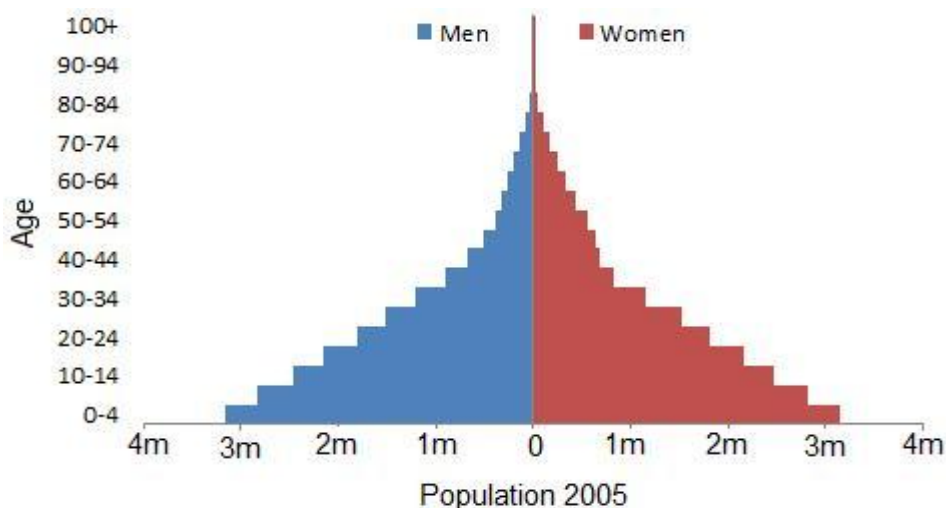


Figure 1: Tanzanian Population Pyramid in 2005

The birth rate as of 2010 was 33.44 live births / 1000 population and the death rate was 12.31 / 1000 population. The net migration rate was -0.81 migrants / 1000 population. The sex ratio of male to female is 1.03:1 at birth, and 0.98:1 overall. In the elderly population (65+) the ratio is 0.77:1. The infant mortality rate remains high at 68.13 deaths / 1000 live births and 6.2% of adults are HIV positive. 25% of the population live in urban areas, with the rate of urbanisation 2005-2010 estimated at 4.2% / year. The literacy rate for men is 77.5% and for women 62.2%.

Independence from colonial rule was achieved on 9th December, 1961, and the current President of the Republic of Tanzania, Jakaya Kikwete, has been in office since 21st December 2005. Tanzania remains one of the poorest countries in terms of per capita income, although 7% gross domestic product (GDP) growth per year between 2000 and 2008 as a result of tourism and

gold production has resulted in slow improvement. The economy depends heavily on agriculture, which accounts for more than one-fourth of GDP, provides 85% of exports and employs about 60% of the work force (165).

The Hai District, covering an area of 13,000 square km, is situated in north-eastern Tanzania on the south-western slopes of Kilimanjaro and the surrounding plains (see arrow in Figure 2 below). The district has 4 administrative divisions, 11 wards, and 61 villages. The Hai demographic surveillance site (DSS) lies between latitudes 3.13° and 3.46°S and longitudes 37.11° and 37.36°E, and it covers three of the four divisions of the district. The DSS contains 56 villages.

A recent census completed in June 2009 revealed the DSS population to be 161,119, of whom 8869 (5.50%) were aged 70 years and above. The Chagga are the predominant tribe and most work in agriculture, either on subsistence farms or 'shambas', or for larger companies that own coffee plantations. The two main religions are Christianity (79%) and Islam (20%), with most of the population speaking Kiswahili (official language) in addition to their local tribal language. There is not a large population flux overall and most villagers live their whole lives in the same village. There is slightly more movement in the lower-lying villages close to the main road from Moshi to Arusha.

The Hai District comprises three distinct ecological zones. The two lower zones are populated. The lowland zone lies between 750 and 1000m above sea level (asl), with minimal rainfall (about 325 mm a year), moderate to high temperatures and sparse population density (about 70 people per km²). The midland zone lies between 1000 and 1600m asl and has higher rainfall (about 1560 mm a year), moderate temperatures and higher population density (about 150–160 per km²). The highest zone is above 1600m and is uninhabited, with heavy rainfall, cool temperatures, and mountain forests and grasslands. It constitutes the largest water source (from rainfall and glacial runoff) and forest reserve in Kilimanjaro. Multiple springs and rivers flow from this zone supplying water to both the midland and lowland zones. These are sometimes used as a drinking water source, although piped water from higher up the mountain is available in most villages from the Hai district

water supply. Water is plentiful in the highland and midland zones but is often polluted with microbes, toxic minerals and agricultural chemicals.

The Hai District has 3 district hospitals in Machame, Kibongoto and Boman'gombe (the district capital), with 2 further government health centres, 39 dispensaries and 61 village health posts. There is disparity in the services available at each of these but most offer basic assessment and treatment. The main tertiary referral hospital, Kilimanjaro Christian Medical Centre (KCMC), is situated in Moshi, approximately 20km from Boman'gombe. However, the nearest specialist cardiological opinion is 600km away in Dar-es-Salaam.

The district has 139 primary schools, 13 secondary schools (both public and private) and 5 post-primary technical schools. About 85% of children below the age of five are vaccinated against five major communicable diseases. Community-based data show that main causes of death in the district are HIV/AIDS, cancer, perinatal causes, acute febrile illness including malaria, pneumonia, diarrhoeal diseases, injuries (both intentional and unintentional), nutrition and maternal causes.

Wood is the main source of fuel. 36 of the 61 villages have electricity but the use of this source of energy is limited because of the costs and even in those villages with electricity this power source extends to very few households.

There are 710 kilometres (km) of road and an international airport (The Kilimanjaro International Airport) 10km from the nearest border. Most roads are unpaved and are often impassable for vehicles during the rainy season.

As a DSS, the Hai study area has permanent delineated boundaries, recognizable on the ground (for example, rivers, roads, and clearly demarcated administrative boundaries). In this thesis the Hai DSS study area is the same as the project study area, so all references to Hai are in relation to the geographical DSS.

The majority of the Hai District has been a DSS as part of the Adult Morbidity and Mortality Project (AMMP) since 1992, initially as part of a project set up between the Tanzanian Ministry of Health and Newcastle University (funded through the Department for International Development – DFID). This project developed an infrastructure in the District from the District Medical Officer

(DMO) in Boman'gombe to the 5 Assistant Medical Officers (AMOs) who act as supervisors within the community (in addition to them acting as medical translators from Kiswahili to English for the purposes of the project), through to the village enumerators (usually nurses, teachers and village leaders) who identified patients for the study from the census which they helped to perform in their respective villages (in addition to translating local tribal languages). Without this established infrastructure and the blessing of local politicians (through the DMO) it would not have been possible to conduct this research. In addition to this, the study employed a nurse who acted as a further translator and received additional training in the management of AF and related cardiovascular problems.



Figure 2: Map of Tanzania

1.11 Healthcare in Tanzania and Patient Access to Treatment

There is no National Health Service in Tanzania and there are major disparities in accessibility, availability and quality of health care across Tanzania. Even within the Hai District, which is considered a reasonably 'affluent' rural district, there are major disparities between villages with regard to the quality and staffing of local health centres and the availability

and prescribing practices of essential medicines. There were 5 ways of obtaining health care and, particularly pertinent to this project concerning chronic disease, repeat medication prescriptions:

1. Being (or having a family member who was) a government employee allowed free access to healthcare and prescriptions.
2. A yearly fee of 10,000 Tanzanian Shillings (TzS) (around £5 or the equivalent of one chicken) would provide an exemption card for the person and their family from prescription charges and free repeat prescriptions.
3. If over the age of 65 years, applying to the village council and then, if subsequently approved, to the district medical officer, for an exemption card providing free repeat prescriptions for chronic disease medications. As may be envisaged, this was often a laborious process entailing much bureaucracy and was supposedly means-tested.
4. Paying a 'contribution' to repeat prescriptions (usually around 2500TzS or just >£1). This tended to work out more expensive than option 2 for tablets needed to be taken daily as it was very dependent on medication stocks at a particular health centre which dictated how many tablets a repeat prescription would buy. Often hypertensive patients (who may have walked for several hours to get to the health centre) would be given only a 1 week supply of Bendrofluazide. This was due not only to meagre drug supplies but also inadequate understanding and education on the part of the dispensary workers.
5. Buying medication from private dispensaries at full value. This meant that one could buy as many tablets as one wanted but often meant patients were not always advised to buy the cheapest, even if it was the most effective.

One of my more difficult tasks during the project would be to educate patients and health care workers on the importance of managing chronic diseases and taking daily medication for diseases such as hypertension, that were often completely without symptoms. Another would be to raise the profile of non-communicable disease and particularly the hypertension epidemic to the DMO, and encourage the reduction in disparities across the district with regard to availability of medication and quality of prescribing

habits. This was not helped just as we were departing Tanzania by a government announcement confirming a 33% health budget cut (166).

1.12 Importance of Non-Communicable Disease Research in SSA

In May 2009 the non-communicable disease (NCD) Alliance was formed (bringing together 4 international federations: the World Heart Federation, the International Diabetes Federation, the Union for International Cancer Control, and the International Union against Tuberculosis and Lung Disease), with the aim of “putting non-communicable diseases on the global agenda”. A campaign has resulted in a United Nations summit on NCDs that took place in New York in September. In preparation for the summit, the WHO released its *Global Status Report on NCDs* that states that of the 57 million deaths worldwide in 2008, 36 million were due to NCDs. The burden is growing fastest in low income countries, imposing large, avoidable costs in human, social and economic terms (167). Despite this, NCDs did not feature in the millennium development goals and account for <3% of global health aid (168). The Lancet’s NCD Action Group has identified five priority interventions for NCDs as follows (169):

1. **Tobacco Use:** accelerated intervention of WHO Framework Convention on Tobacco Control
2. **Dietary Salt:** Media campaigns and voluntary action by food industry to reduce consumption
3. **Obesity, unhealthy diet and physical inactivity:** Media campaigns, food taxes, subsidies, labelling and marketing restrictions
4. **Harmful alcohol intake:** Tax increases, advertising bans and restricted access
5. **Cardiovascular risk reduction:** combination of drugs for people at high risk

Total cost for the implementation of all 5 interventions per person per year has been estimated to be US\$1.72 in China, US\$1.52 in India and US\$4.08 in Russia (169).

Prior to focusing well-needed resources on these interventions, accurate data on the scale of the problem are needed. One of the intentions of my research is to demonstrate the urgent need to document prevalence rates of such NCD, and hopefully to attract appropriate resource allocation. A recent article in the BMJ (170) highlighted the importance of improved surveillance of NCDs and their risk factors in low and middle income countries (LMICs).

Whilst the figures tell us that NCDs are on the increase in LMICs, it should also be acknowledged that if population health is good and people are enabled to live into old age, then most people will die of NCD (171).

Therefore, naturally, as life expectancy increases, so will mortality rates from NCD. It is thus important to clarify premature deaths as opposed to timely deaths from NCD and concentrate resources on the former rather than the latter. Additionally, the UN summit should take care to establish realistic rather than misplaced risk factor thresholds. For instance, in the treatment of hypertension, if they employ 'Western' values of 140/90mmHg as a cut-off, it risks diverting resources from the sick to the well and the poor to the rich (171). With my hypertension patients, I have employed a 160/100mmHg cut-off for treatment in order to identify those most at risk, in addition of course to education and awareness of what non-pharmacological measures may be taken to reduce BP. In resource-poor countries these will be the most important measures taken as steps such as stopping smoking and reducing dietary salt are free interventions and merely rely upon education and a change in attitude rather than potentially costly infrastructures for the delivery and monitoring of medication.

Chapter 2. General Methodology

This section covers general methodology and logistics of the project. More specific methodology with regard to the 4 main results chapters (prevalence of AF, prevalence of PAF, PWI analysis and prevalence of hypertension) can be found in the specific chapter.

2.1 Inclusion and Exclusion Criteria

To be included in the study, participants had to:

1. Be alive and living in the Hai District in one of the 12 randomly selected study villages on the prevalence date of 1st January 2010.
2. Be aged 70 years or over on 1st January 2010.
3. Have given informed consent to take part in the study (or informed assent by a family member if participant was unable).

People excluded from the study were:

1. Either dead, or not living in one of the 12 randomly selected study villages on 1st January 2010.
2. Not aged 70 years and over on 1st January 2010.
3. Not providing informed consent (or assent from family member).

2.2 Prevalence Studies

The prevalence of a disease in a population is defined as the number of people in that population who have that disease at a defined point in time. It is usually expressed as the number per 100,000, although can be per 1000 if the disease is more common. There are a number of different ways to

determine prevalence, including case-finding studies, pharmacy searches and door-to-door surveys.

Case-finding studies involve looking through medical notes to assess the prevalence of a particular disease and identify cases. This approach, whilst efficient in countries where people have good access to healthcare and there is an infrastructure for recording and treating disease, is impractical in SSA given that few people have reasonable access to health care, or can afford treatment. This therefore means that there will be potentially many previously undiagnosed cases in the community.

Pharmacy searches entail searching for cases through medication prescriptions for drugs only used for the condition being searched for. There are two problems with this method in searching for AF cases in SSA. Firstly, there are many different treatments available for AF most, if not all of which, are used for treating other conditions as well (e.g. aspirin – previous stroke, propranolol - hypertension, digoxin – heart failure), so the search would be non-specific. Secondly, and more specifically to SSA, there is a lack of infrastructure for a pharmacy database in SSA. In the Hai District, there are many governmental dispensaries, often with very limited drug supply and run by dispensary workers with very little knowledge of treating medical disease. These compete with private dispensaries, often with adequate drug stocks but selling treatment (not always correct) at inflated prices. Again, many people do not present to drug dispensaries for treatment of their condition because of access and price.

Door-to-door surveys are seen as expensive and time-consuming for population-based research. However, in order to accurately define community burden of a disease and to identify previously undiagnosed cases, they are seen as the gold-standard approach. A two-tiered approach has been advocated to increase efficiency, whereby non-medically trained personnel perform an initial screening test to determine whether a person may have a disease, and then medically trained personnel perform more in-depth assessment of the identified patients. In the case of AF, the screening test was an ECG, which the non-medically trained personnel (the village enumerators) were taught to perform at a workshop prior to study commencement. However, it quickly became clear that it would not be sufficient simply to see AF patients, as all of the elderly participants wanted

to see me, and I needed to see most of them in order to prescribe treatment for HTN, osteoarthritis etc. Therefore, to maximise case ascertainment in each village (fewer people were turning up when I was absent from the health centre) and to ensure all participants received appropriate treatment, I decided to adopt a one-tiered approach in that I saw all study participants regardless of whether they had AF or not. This approach was at the expense of overall numbers for my study.

2.3 Case-Control Studies

Within my prevalence study, there was a nested case-control study that was designed to enable me to look at the characteristics of, and risk factors for, AF, by comparing known risk factors in those diagnosed with AF on 12-lead ECG, versus an age and sex-matched group of controls. Case-control studies are often inexpensive and can be performed by a small research team / single researcher in a confined time period, unlike more structured experimental studies / prospective cohort studies. They are often used as a preliminary study where little is known about the association between the risk factor and disease of interest. Whilst this is not the case with AF risk factors in high-income countries, it remains the case in SSA. Difficulties with case-control studies include determining a person's risk factor exposure over time, and the presence of realised and unrealised confounding factors.

2.4 Timing of the study

This study ran in conjunction with another study investigating the prevalence of neurological disorders in the same study population. This used a screening questionnaire and therefore a pilot study was performed in one village (Mudio) prior to the main study. The village enumerators in Mudio were trained separately in ECG and BP measurement, prior to the main study workshop at the end of January 2010, when the study was rolled out across the other villages. The majority of data collection took place from January – June 2010, with initial follow-up of AF patients and controls through July 2010 (meaning an interval of 1-6 months between initially being seen and follow-up).

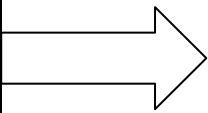
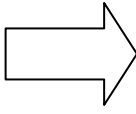
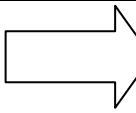
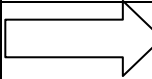
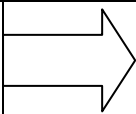
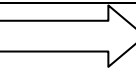
Date	Literature review and study development	Data Collection	Initial Follow-up	Writing up MD thesis	Further Follow-up
October 2008 – October 2009					
November 2009 – January 2010					
January 28th		Workshop			
January 2010 – June 2010					
July 2010					
August 2010 – October 2011					
October 2011					

Figure 3: Timeline of Study

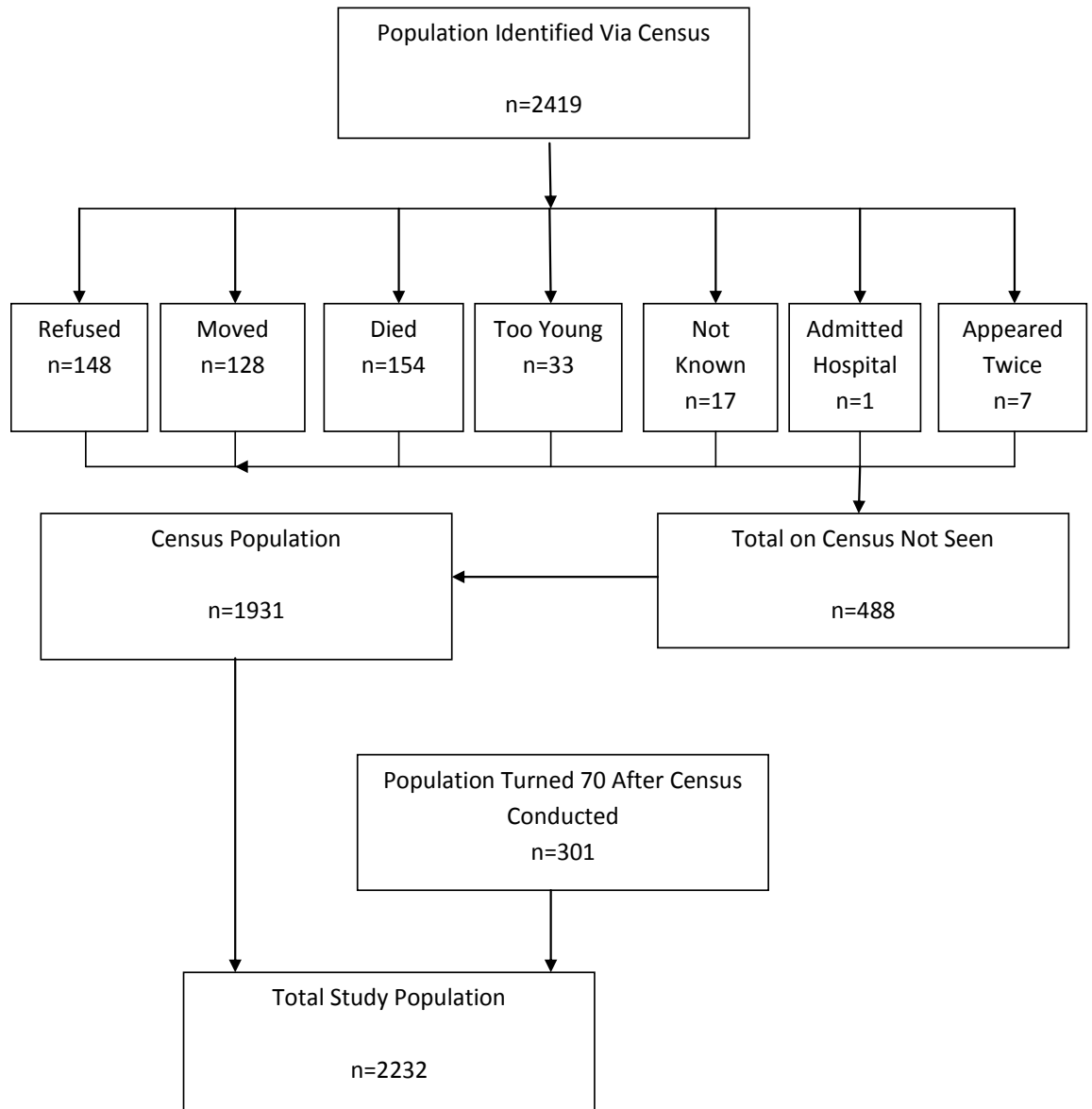
2.5 Identification of Study Population

The Study Population was identified via census details of those aged 70 years and over and through village enumerators (as mentioned in section 1.10), who invited people known to have reached 70 years between the census and our data collection period. Collecting accurate information on patient age can be difficult in SSA as few people have a birth certificate (172). Age was calculated from birth year and confirmed using memory prompts (e.g. age at independence) where necessary. This method has been previously validated (173).

I planned to assess approximately one-quarter of the 70 years and over population in the DSS. I visited 12 villages, with a total census population of

2419. Our final cohort consisted of 2232 people and cohort assembly is shown below.

Figure 4. Identification of the study population



2.6 Choosing the study villages

Villages were chosen using a random number generator, with stratification to allow a representative spread of upland and lowland villages. In the Hai DSS, of those aged 70 years and over, 76.5% live in upland areas and 23.5% in lowland areas. We studied eight upland villages (n = 1683, 75.4%) and four

lowland villages (n = 549, 24.6%), giving a final cohort of 2232 people. The breakdown by village is shown in the table below.

Village	Patients Seen	Patients 70+ on census	Difference	Geography	Patients refused	Patients moved	Patients died	Patient too young	not known	Admitted hospital	recorded on census twice	Total not possible to see	extras
Mudio	277	344	-67	Upland	39	22	21	12	0	0	5	99	32
Roo	265	305	-40	Upland	10	14	14	2	0	0	0	40	0
Saawe	192	185	7	Upland	1	11	6	0	0	0	0	18	25
Kyuu	118	121	-3	Upland	3	4	10	0	0	0	0	17	20
Mbweera	194	194	0	Upland	1	1	7	0	0	0	0	9	9
Lukani	115	117	-2	Upland	10	4	12	2	0	0	0	28	26
Nshara	386	411	-25	Upland	47	3	32	3	0	0	0	85	60
Urori	136	142	-6	Upland	5	4	2	5	0	0	2	18	6
Kware	148	189	-41	Lowland	12	13	12	4	0	0	0	41	0
Kwasadala	83	79	4	Lowland	2	10	12	0	0	0	0	24	28
Shirumgungani	182	120	62	Lowland	2	2	6	0	0	0	0	10	72
Boman'gombe	136	218	-82	Lowland	22	40	20	5	17	1	0	105	23
Total	2232	2425	-193	N/A	154	128	154	33	17	1	7	494	301

Table 2: Breakdown of Chosen Study Villages

2.7 Workshop and Training

The main workshop took place in Boman'gombe on January 27th 2010. It was a full day workshop and was designed to educate village enumerators, AMOs and the DMO not only to teach specific skills to enumerators in order that they could help with screening, such as performing ECGs and BPs, but also to outline what I was trying to achieve with my research. Village enumerators from all DSS villages were invited to the initial sessions highlighting the diseases I was hoping to find and treat to raise the profile of these NCDs in the Hai District. The more detailed sessions later in the day were for the enumerators of the 12 villages that had been randomly chosen

for my study and concerned performing the screening tests that would identify AF cases and risk factors for AF. The training and standardisation procedures undertaken for study measurements are discussed in more detail in the relevant chapters.

2.8 Developing the Proforma

The proforma was designed to record data in the field that was accurate, efficient and in a format that was subsequently relatively easy to enter into a Microsoft Excel™ spreadsheet for analysis. The proforma recorded important data pertaining to demographics, associated symptoms, examination and echocardiographic findings. It was also where treatment decisions were initially recorded. There were 2 parts to the proforma. The first part concerned demographic details (see appendix 2a), was performed on all 2232 study participants and was primarily completed by village enumerators. The second part concerned more in-depth detail regarding symptoms, examination and echocardiographic findings and blood sampling (see appendix 2b) and was performed on AF patients and controls and was completed by me, with the aid of an AMO acting as a medical translator for the history and examination components. This will be discussed in more detail in Chapter 4. In addition to this, a follow-up proforma was subsequently developed (see appendix 3), based on collecting data on whether patients had had an improvement in their symptoms, had had any side-effects from medication, whether they were still taking their medication, what their BP was and whether there was any change to their initial management plan.

2.8.1 Demographic details

This recorded important information such as name, age and year of birth. Other information recorded on the demographic details sheet can be found in Appendix 2a. It will be noted that there is space for answers to a 'screening questionnaire'. This was for the prevalence of neurological disorder study that ran in parallel as previously mentioned. In addition, BP measurements were recorded for 2232 participants in this section, and a 12-lead ECG was recorded at the same time.

2.9 General Critique of study design

In this section I will only mention a few general limitations and strengths to the study design. More specific limitations and strengths are mentioned in relevant results and discussion chapters.

2.9.1 Limitations

The methodology was limited by a number of factors. The choice of controls and participants willing to wear an ambulatory ECG monitor was not entirely at random and was based more on a pragmatic approach for the reasons explained previously.

Precision in the history was sometimes an issue. There are not as many descriptive medical words in Swahili as there are in English. One word in Swahili may mean several different things in English with regard to a patient's symptoms. I tried to minimise this effect by educating the translators as to exactly what I was looking for.

Ideally, the echo machine would have had a video loop recorder such that I could ask a second independent observer to report a random selection of my echocardiograms. However, this was not the case and I had to report the echocardiograms at the time knowing whether the patient had AF or not.

Methodologically it would have been better if I had been blinded to whether the echo was on an AF case or control when reporting so that it did not bias my assessment of LV function. However, given a rhythm strip along the bottom of the echo screen blinding would have been impossible.

When identifying risk factors such as hypertension, I only had one opportunity to decide on whether the patient required treatment or not. In normal clinical practice patients would have several readings over the course of months to decide if BP was consistently high. To try to combat this limitation and target those at highest risk, I only initiated treatment in patients with very high BP (>160/100) at the time. In those with Grade I hypertension, I recommended they get their BP re-checked in another month.

2.9.2 Strengths

There were also many strengths to the study design. As the team of enumerators and supervisors employed within this study had previously worked on a stroke incidence study, a PD prevalence study and an epilepsy

prevalence study in the same area with the same principal investigator, the basic infrastructure was robust. The hierarchy and chain for passing of information was well used and had been tried and tested over the past 7 years. This meant that the population were used to being approached for censuses or research and had developed trust in the people involved. Also, apart from myself and the research doctor from the neurological disorder study (FD), all of the other day to day people involved in the study were Tanzanian and local to the area and many worked in health care centres in the villages or at the local hospital. This added to the acceptability of the project to the local community.

The study villages were chosen at random yet reflected well the spread of the population living in upland and lowland areas. The AF cases and controls were seen and assessed by the same doctor every time, and I performed all the echocardiograms, reducing inter-rater variability. Identification of cases was by the currently accepted gold standard in epidemiological studies, the 12-lead ECG, and I maximised ascertainment of cases by using the door-to-door survey method.

2.10 Ethical Considerations

Ethics committee approval was sought from the Newcastle and North Tyneside Health authority Joint Ethics Committee in the UK, Tumaini University Ethics Committee locally in Tanzania and the National Institute of Medical Research (NIMR) ethics committee nationally in Tanzania. Ethical approval was granted from Tumaini University and NIMR. The UK committee deemed it unnecessary to be considered as all the research was being carried out in Tanzania. All patients were given an information sheet in Kiswahili. Any patient who could not speak Kiswahili had the information sheet translated verbally into their tribal language. All patients signed written consent forms in Kiswahili (or in the case of those who could not write, a thumb print was obtained) and were free to withdraw from the study at any stage should they wish to do so. All information sheets and consent forms were translated by the Cardiology Nurse Specialist and then back translated by another specialist research nurse to ensure accurate translation. See appendices for consent forms and information sheets.

There were several important ethical points that arose from the study:

1. Treatment offered to patients for AF / hypertension etc. should be treatment that is available at government dispensaries and health centres in the Hai District, that is, cheap (as in the majority of cases the patients had to pay themselves) and effective (e.g. ACE-I not as good as thiazide diuretics at controlling BP in black Africans).
2. Prescribing practices in the elderly in rural Tanzania were very ethically challenging at times. I had to balance the potential benefit of initiating treatment with risks of side-effects and inability to access healthcare easily. Hypertension treatment was a particular challenge, given that I quickly found most dispensaries were fortunate if they had 1 anti-hypertensive available (usually bendrofluazide) and most patients struggled to remember instructions for taking more than 1 medication, coupled with the challenges of economic viability and availability. Bendrofluazide was the only widely available anti-hypertensive and was significantly cheaper than nifedipine (at an effective dose), the next most available. I decided prior to the start of the study that it was clinically reasonable to begin treatment immediately if average BP was $>160/100$ mmHg. If BP was very high ($>180/100$) then a higher dose of bendrofluazide (5mg rather than 2.5mg) would be instituted. This is a dose that would not be used in the UK (where there are freely available effective alternatives) due to side-effects, but is recommended by the Tanzanian Ministry of Health Prescribing Guidelines due to a slightly better BP lowering effect (174). I decided on balance, taking into account the very high BPs of some patients (and therefore the very high risk of stroke), the added BP lowering effect of 5mg (albeit minor), the lack of additional / alternative drugs and also in keeping with national prescribing policy, that patients could be given 5mg bendrofluazide provided they were given additional 'safety net' advice and monitored any side-effects closely.
3. There would be a way of referring patients on for other tests at the local hospital if they presented with something that could not be dealt with in the community. This was done through the development of a prescription / investigation sheet on which a 'referral' of sorts was written (see Appendix 4). Also, an agreement was made that I could refer patients with cardiac abnormalities that required follow-up to the OPD at KCMC.
4. Blood results should be returned in good time to AF cases and controls following analysis in the UK. This was done within 2 months of return, and

abnormalities were highlighted and followed-up by one of the study nurses in Tanzania.

5. With regard to ambulatory monitoring, patients were identified with significant brady or tachyarrhythmias either symptomatic or asymptomatic. Fortunately, no patients were identified with significant ventricular arrhythmias, but several people were identified with varying degrees of heart block, the most significant of which was an asymptomatic man with 9 second ventricular standstill on his 24-hour tape. He was asymptomatic as it was nocturnal but would be a class Ia indication for pacing in the UK/USA (175). Pacemakers were prohibitively expensive and the closest place they were available was in Nairobi, Kenya. All I could do was advise what would be done in the UK, ask about potential sources of funding that he may have (e.g. through the church) and refer him in the usual way. Ultimately, it was the patient's decision after that as to what course of action to take.

Chapter 3. Census and Demographic Details

3.1. Results

3.1.1 The Census

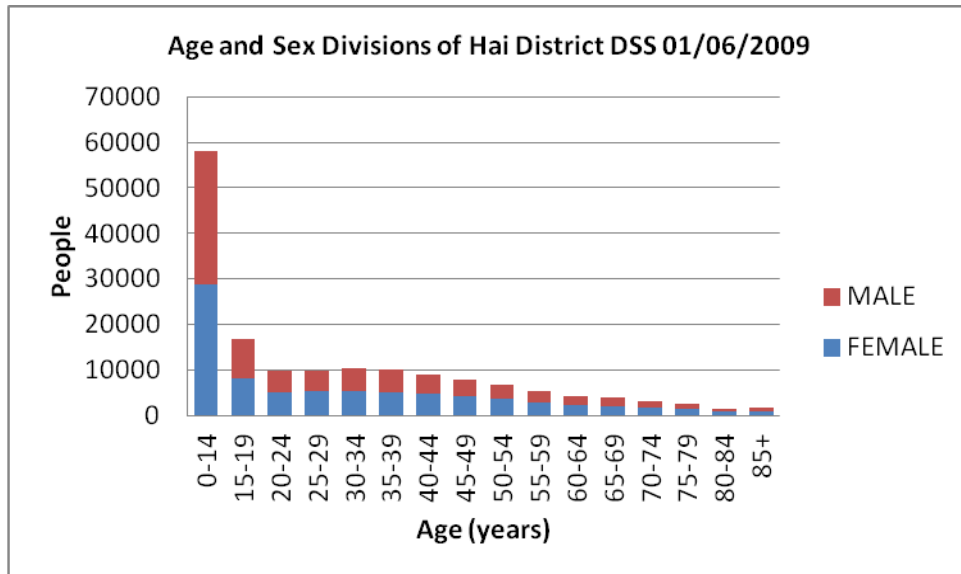
The Hai District DSS census was completed on the 1st of June 2009, with the population of the Hai district DSS being 161,119. 83,180 (51.63%) were women and 77,939 (48.37%) were men. 8869 (5.50%) were aged 70 and over, 103025 (63.94%) were aged 15 and over and 58,093 (36.06%) were aged less than 15. 3159 (1.96%) were 70-74, 2531 (1.57%) were 75-79, 1447 (0.90%) were 80-84 and 1732 (1.07%) were aged 85 and over. Of the 70 and over population 4844 (54.62%) were women and 4025 (45.38%) were men. Age and sex divisions are detailed in the table below.

Table 3 Age and Sex divisions In the Hai District DSS from the 01/06/2009 census

AGE GROUPS	FEMALE	%	MALE	%	TOTAL (MALES AND FEMALES)	%
0-14	28794	34.62	29299	37.59	58093	36.06
15-19	8114	9.75	8648	11.10	16762	10.40
20-24	5225	6.28	4719	6.05	9944	6.17
25-29	5487	6.60	4467	5.73	9954	6.18
30-34	5381	6.47	4961	6.37	10342	6.42
35-39	5216	6.27	4852	6.23	10068	6.25
40-44	4800	5.77	4234	5.43	9034	5.61
45-49	4156	4.99	3630	4.66	7786	4.83
50-54	3727	4.48	2986	3.83	6713	4.17
55-59	2911	3.50	2437	3.13	5348	3.32
60-64	2390	2.87	1949	2.50	4339	2.69
65-69	2135	2.57	1732	2.22	3867	2.40
70-74	1684	2.02	1475	1.89	3159	1.96
75-79	1351	1.62	1180	1.51	2531	1.57
80-84	824	0.99	623	0.80	1447	0.90
85+	985	1.18	747	0.96	1732	1.07
TOTAL	83180	100	77939	100	161119	100

This is demonstrated pictorially in the following graph.

Graph 1 Age and Sex Divisions In the Hai District DSS from the 01/06/2009 census



Division of the Census Population by village

The number of patients aged 70 and over, as well as the population and geographical location of each village (highland or lowland) in the Hai district is shown in Table 5. The villages highlighted in bold are those 12 that were randomly selected to take part in the study. They represent approximately 1/4 of the 70 and over population of the Hai District DSS. The population of these villages recorded on the census was slightly different from the population seen as part of the study due to reasons detailed in Figure 4 (page 92).

Table 4 Division of the Hai District DSS population by village demonstrating representation from the 70 and over population

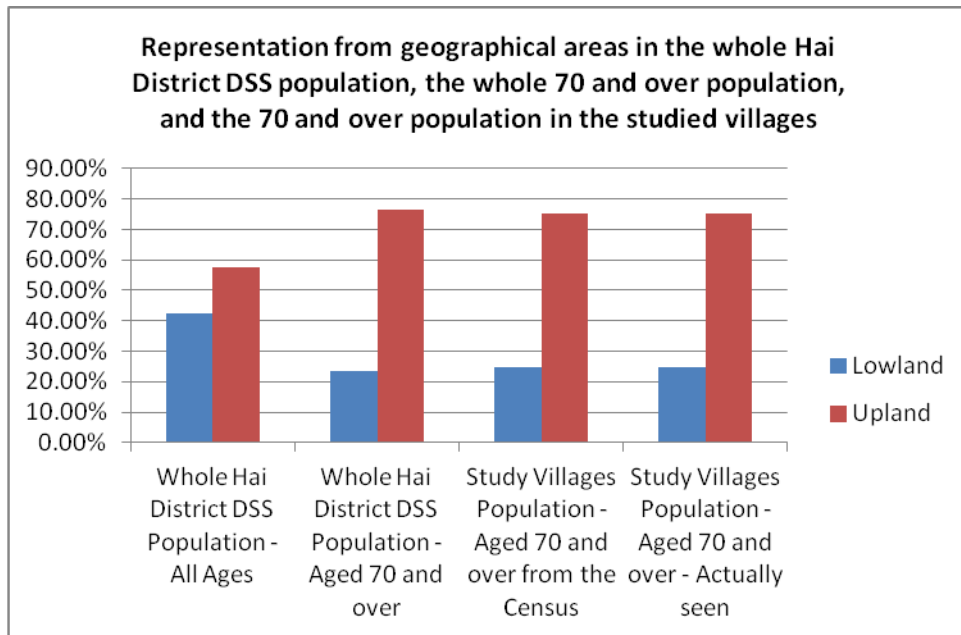
Village	Total population of each village	Percentage of whole population of Hai District DSS represented in each village	Population aged 70 and over from the census	Percentage of population 70 and over represented in each village	Population aged 70 and over seen as part of the Study	Percentage of population aged 70 and over represented in each of the Study Villages	Geographical location	Altitude (metres asl)
BOMAN'GOMBE	11558	7.2	216	2.4	136	1.53	LOWLAND	995
FOO	3969	2.5	394	4.4	N/A	N/A	UPLAND	1565
ISUKI	1853	1.2	126	1.4	N/A	N/A	UPLAND	1399
KAWAYA	2722	1.7	88	1.0	N/A	N/A	LOWLAND	851
KIA	1501	.9	16	.2	N/A	N/A	LOWLAND	919
KIKAVU CHINI	3743	2.3	116	1.3	N/A	N/A	LOWLAND	805
KILANYA	1848	1.1	151	1.7	N/A	N/A	UPLAND	1588
KIMASHUKU	2452	1.5	79	.9	N/A	N/A	LOWLAND	909
KWA SADALA	3018	1.9	78	.9	83	0.94	LOWLAND	1033
KWARE	3251	2.0	189	2.1	148	1.67	LOWLAND	1071
KWATITO	1083	.7	28	.3	N/A	N/A	LOWLAND	909
KYEERI	2959	1.8	195	2.2	N/A	N/A	UPLAND	1670
KYUU	1778	1.1	120	1.4	118	1.33	UPLAND	1396
LEMIRA KATI	1514	.9	139	1.6	N/A	N/A	LOWLAND	1420
LENGOI	2013	1.2	62	.7	N/A	N/A	LOWLAND	833
LOSAA	1345	.8	77	.9	N/A	N/A	UPLAND	1560
LUKANI	1272	.8	116	1.3	115	1.30	UPLAND	1594
LYAMUNGO KATI	2254	1.4	190	2.1	N/A	N/A	UPLAND	1520
LYAMUNGO SINDE	1869	1.2	138	1.6	N/A	N/A	UPLAND	1315
MAMBA	1952	1.2	157	1.8	N/A	N/A	UPLAND	1340
MASHUA	2394	1.5	137	1.5	N/A	N/A	UPLAND	1353
MBATAKERO	669	.4	18	.2	N/A	N/A	LOWLAND	940
MBORENI	1371	.9	86	1.0	N/A	N/A	UPLAND	1330
MBOSHO	1740	1.1	139	1.6	N/A	N/A	UPLAND	1295
MBWEERA	3297	2.0	194	2.2	194	2.19	UPLAND	1330
MIJONGWENI	3681	2.3	130	1.5	N/A	N/A	LOWLAND	820
MKALAMA	2605	1.6	91	1.0	N/A	N/A	LOWLAND	864
MTAA WA SHABAHA	1023	.6	33	.4	N/A	N/A	LOWLAND	915
MTAKUJA	1685	1.0	43	.5	N/A	N/A	LOWLAND	920
MUDIO	5522	3.4	345	3.9	277	3.12	UPLAND	1257
MULAMA	1824	1.1	123	1.4	N/A	N/A	UPLAND	1274
MUNGUSHI	7884	4.9	184	2.1	N/A	N/A	LOWLAND	1050
MUROMA	1874	1.2	119	1.3	N/A	N/A	UPLAND	1296
NGIRA	2234	1.4	160	1.8	N/A	N/A	UPLAND	1275
NGOSERO	968	.6	35	.4	N/A	N/A	LOWLAND	822
NGUNI	2498	1.6	159	1.8	N/A	N/A	UPLAND	1580
NKUU NDOO	2038	1.3	222	2.5	N/A	N/A	UPLAND	1620
NKUU SINDE	2132	1.3	234	2.6	N/A	N/A	UPLAND	1314
NKWANSIRA	2080	1.3	133	1.5	N/A	N/A	UPLAND	1240
NRONGA	2299	1.4	287	3.2	N/A	N/A	UPLAND	1670
NSHARA	7805	4.8	411	4.6	386	4.35	UPLAND	1170
ROO	5308	3.3	305	3.4	265	2.99	UPLAND	1250
RUNDUGAI	7686	4.8	225	2.5	N/A	N/A	LOWLAND	861
SAawe	2609	1.6	185	2.1	192	2.16	UPLAND	1476
SANYA STATION	3219	2.0	91	1.0	N/A	N/A	LOWLAND	933
SHARI	3611	2.2	318	3.6	N/A	N/A	UPLAND	1390
SHIRI NJORO	2841	1.8	111	1.3	N/A	N/A	LOWLAND	1018
SHIRIMGUNGANI	3090	1.9	118	1.3	182	2.05	LOWLAND	860
SONU	2926	1.8	257	2.9	N/A	N/A	UPLAND	1306
TELLA	2692	1.7	163	1.8	N/A	N/A	UPLAND	1241
TINDIGANI	1250	.8	25	.3	N/A	N/A	LOWLAND	915
UDURU	2289	1.4	167	1.9	N/A	N/A	UPLAND	1296
URORI	2825	1.8	142	1.6	136	1.53	UPLAND	1086
USARI	2231	1.4	134	1.5	N/A	N/A	UPLAND	1190
USWAA	3218	2.0	269	3.0	N/A	N/A	UPLAND	1190
WARI	3745	2.3	401	4.5	N/A	N/A	UPLAND	1440
Total	161119	100.0	8869	100.0	2232	25.2	N/A	

The table and graph below highlights geographical variations in the study population. It clearly shows that more elderly live in upland villages. There is no documented reason for this although we can speculate that this may be due to either younger people migrating towards more low-lying villages closer to main transport links (and therefore work), or that those living in lowland villages may die earlier. The table and graph also demonstrate that the studied population is representative of the 70 and over population in the whole of the Hai District DSS with regard to the percentage of people that come from upland and lowland areas.

Table 5 Representations from geographical areas in the whole Hai District DSS population, the whole 70 and over population, and the 70 and over population in the studied villages

Geographical Location	Whole Hai District DSS Population – All Ages - Frequency	Whole Hai District DSS Population – All Ages - Percentage	Whole Hai District DSS Population – Aged 70 and over - Frequency	Whole Hai District DSS Population – Aged 70 and over - percentage	Study Villages Population Aged 70 and over from the census – frequency	Study Villages Population Aged 70 and over from the census – Percentage	Study Villages Population Aged 70 and over actually seen – frequency	Study Villages Population Aged 70 and over actually seen – Percentage
Lowland	69456	43.1%	2115	23.8%	601	24.8%	549	24.6%
Upland	91663	56.9%	6754	76.2%	1818	75.2%	1683	75.4%
Total	161119	100.0%	8869	100.0%	2419	100.0%	2232	100.0%

Graph 2



3.1.2 Demographic Details

Detailed below are results of the demographics part of the questionnaire. Values do not always add up to 100% due to missing data.

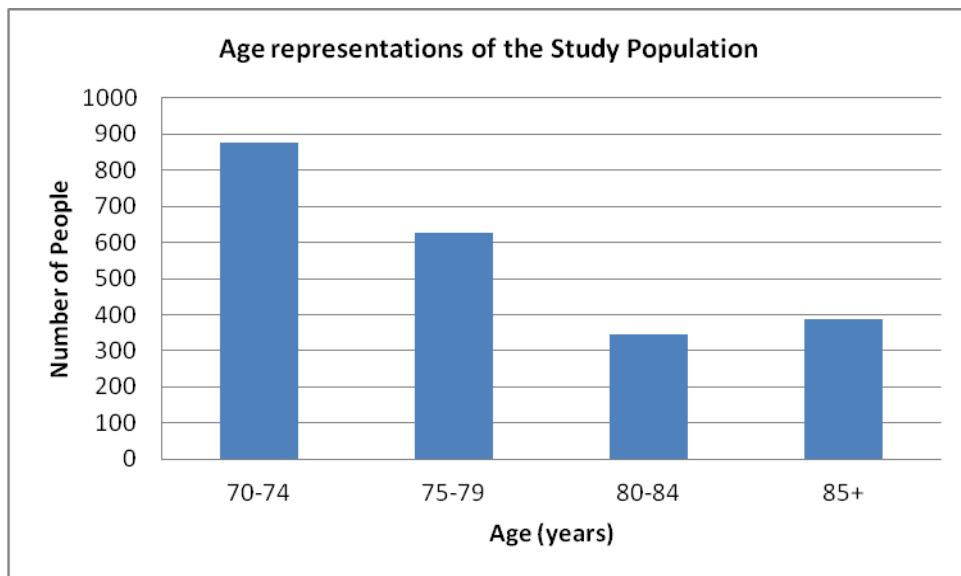
Age

The mean age of 976 men was 77.9 (95% CI 77.4 to 78.3), and of 1256 women was 77.7 (77.3 to 78.1). The proportions of patients aged 70 and over in the different age brackets are demonstrated in the table and graphs below. This is expressed as a percentage of the 70 and over population and as a percentage of the whole Study Population and can be compared to the percentage of people in the age brackets in the overall Hai District DSS. It demonstrates age-wise that the Study Population is representative of the whole DSS population.

Table 6 Demonstration that the age breakdown of the 70 and over population in the study was representative of the whole Hai District DSS population

Age Divisions	People in the Study	Percentage of the 70 and over population in the Study	Percentage of the whole population in the Study	People in the whole Hai District DSS	Percentage of the 70 and over population in the whole Hai District DSS	Percentage of the whole population in the whole Hai District DSS
70-74	877	39.3	1.71	3159	35.62	1.96
75-79	625	28.0	1.22	2531	28.54	1.57
80-84	344	15.4	0.67	1447	16.32	0.90
85+	386	17.3	0.75	1732	19.53	1.07
Total	2232	100.0	4.35	8869	100.0	5.50

Graph 3



Graph 4

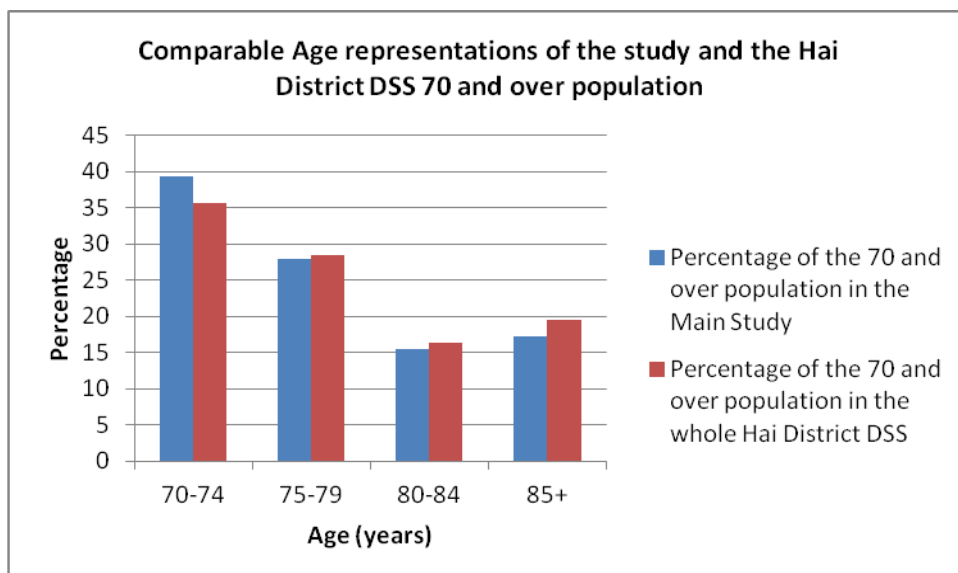


Table 7 Demonstration of the further Divisions of the older age bracket in the Study Population

Age Divisions	Frequency	Percentage
70-74	877	39.3
75-79	625	28.0
80-84	344	15.4
85-89	221	9.9
90-94	89	4.0
95-99	40	1.8
100+	36	1.6
Total	2232	100.0

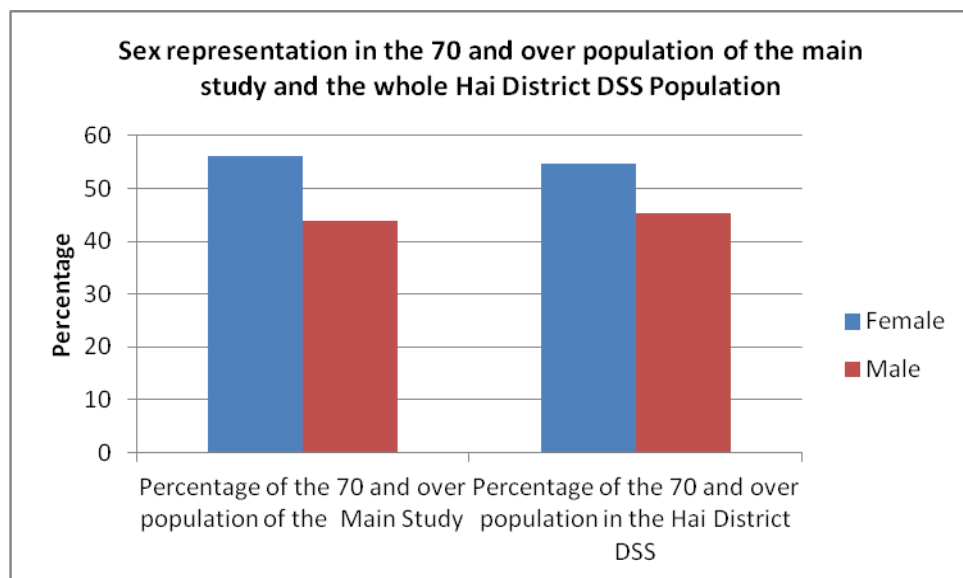
Gender

The proportion of men and women in the Study Population was also representative of the background Hai District DSS population.

Table 8 Demonstration of the comparable breakdown of the 70 and over population by sex in the Study Population and the Hai District DSS population

Sex	People Aged 70 and over in the Study	Percentage of the 70 and over of the Study Population	People Aged 70 and over in the Hai District DSS	Percentage of the 70 and over in the Hai District DSS population
F	1256	56.3	4844	54.6
M	976	43.7	4025	45.4
Total	2232	100.0	8869	100.0

Graph 5



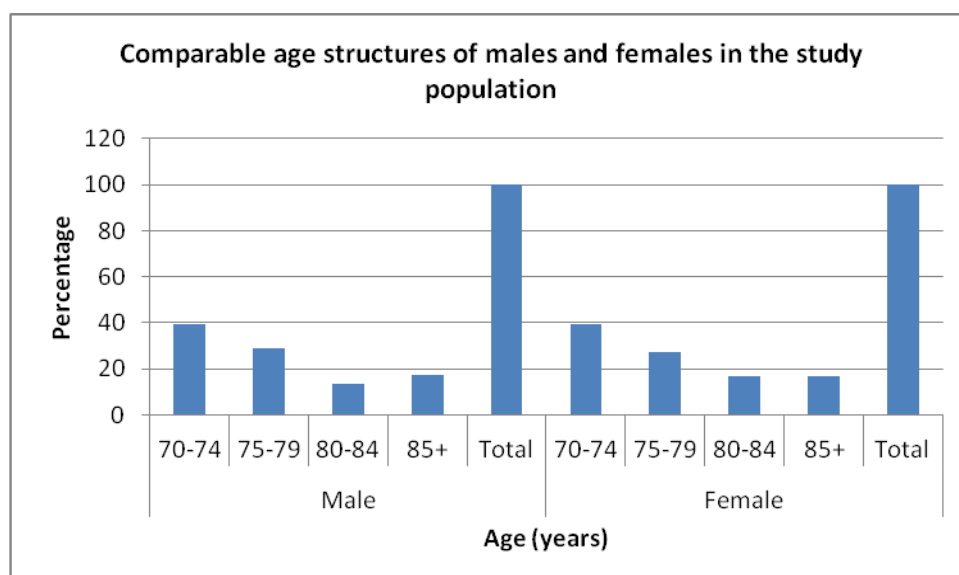
Age structure by Gender

There is no difference between men and women in terms of the age structure of the participants despite there being more women than men in the Study Population.

Table 9 Demonstration of the comparable age structure of males and females in the Study Population

Sex	Age	Frequency of participants in the Study Population	Percentage of the participants in the Study Population
Men	70-74	384	39.3
	75-79	285	29.2
	80-84	135	13.8
	85+	172	17.6
	Total	976	100.0
Women	70-74	493	39.3
	75-79	340	27.1
	80-84	209	16.6
	85+	214	17.0
	Total	1256	100.0

Graph 6



Tribe

The majority of participants were from the Chagga tribe. The Maasai tribe was under-represented in the Study Population as compared to the overall Hai district DSS population but otherwise the tribal breakdown was similar.

Table 10 Tribal representations of the Study Population

Tribe	Number of People in each Tribe aged 70 and over in the study	Percentage in each tribe aged 70 and over in the study
MZARAMO	6	0.3
MNDENGEREKO	4	0.2
MCHAGGA	2033	91.1
MMASAI	7	0.3
MPARE	38	1.7
MNYAMWEZI	7	0.3
MSUKUMA	2	0.1
OTHER	135	6.0
Total	2232	100.0

Religion

The religious divisions were representative. This was particularly important when considering health-seeking behaviour.

Table 11 Religious Representations of the Study Population

Religion	Number of People in each Religion aged 70 and over in the Study Population	Percentage in each Religion aged 70 and over in the Study Population
CHRISTIAN	1763	79.0
MUSLIM	466	20.9
PAGAN	3	0.1
Total	2232	100.0

Marital Status

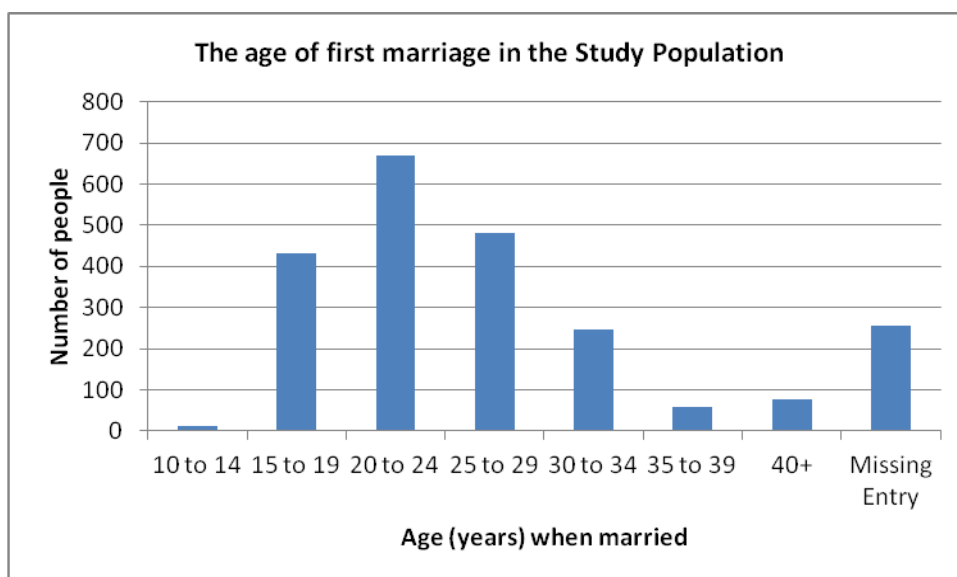
1103 (49.4%) were married, 1050 (47.0%) were widowed, 32 (1.4%) were separated, 27 (1.2%) were single and 20 (0.9%) were divorced. The main reason for divorce was that the woman was unable to have children.

Age When Married

Table 12 The age of first marriage of the Study Population

Age Categories (years)	Number of people aged 70 and over in the Study Population	Percentage of people aged 70 and over in the Study Population
10-14	13	0.6
15-19	431	19.3
20-24	670	30.0
25-29	481	21.6
30-34	246	11.0
35-39	59	2.6
40+	76	3.4
Missing Entry including N/A as the person was not married	256	11.5
Total	2232	100.0

Graph 7



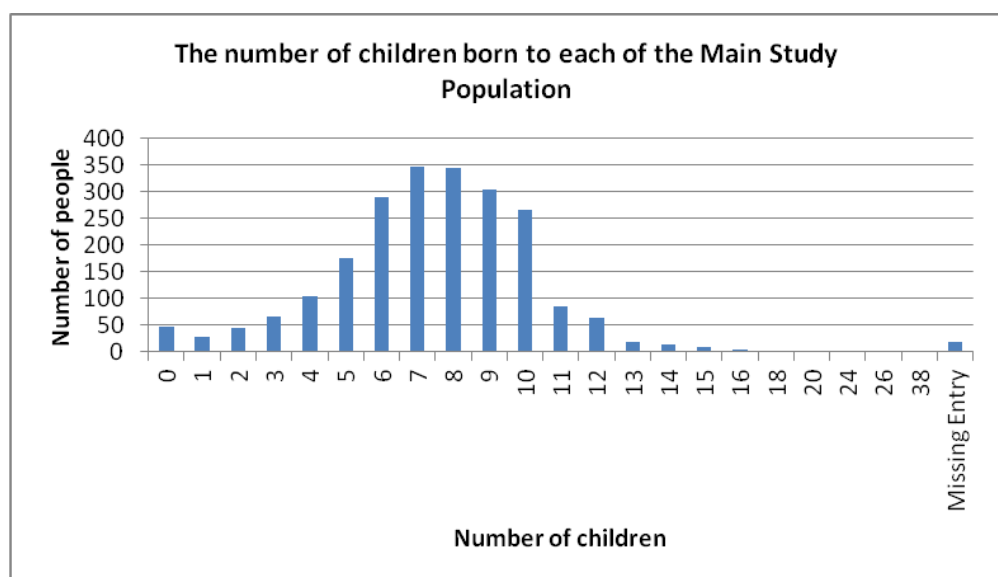
Number of Children

The number of children each study participant had is demonstrated in the table below. Men often had more than 1 wife and therefore the total number of children they fathered with all their wives is recorded.

Table 13 The number of children born to each study participant of the Study Population

Number of children	Number of people aged 70 and over in the Study Population	Percentage of people aged 70 and over in the Study Population
0	46	2.1
1	28	1.3
2	45	2.0
3	66	3.0
4	103	4.6
5	175	7.8
6	290	13.0
7	348	15.6
8	345	15.5
9	305	13.7
10	265	11.9
11	84	3.8
12	63	2.8
13	19	0.9
14	14	0.6
15	10	0.4
16	3	0.1
18	1	0.0
20	1	0.0
24	1	0.0
26	1	0.0
38	1	0.0
Missing Entry	18	0.8
Total	2232	100.0

Graph 8



Mortality level of the children of the Study Population

This data was collected to look at social support and family size of study participants. As can be seen from the table below, only approximately half of the Study Population (n=1078) were asked about how many children they had and also how many of their children were dead (n=1083).

Table 14 The mortality level of the children of the Study Population

Number of children	Frequency in the Study Population	Percentage in the Study Population	Number of children who had died	Frequency in the Study Population	Percentage in the Study Population
0	46	2.1	0	98	4.4
1	32	1.4	1	305	13.7
2	58	2.6	2	271	12.1
3	89	4.0	3	197	8.8
4	157	7.0	4	83	3.7
5	171	7.7	5	56	2.5
6	169	7.6	6	30	1.3
7	139	6.2	7	18	0.8
8	115	5.2	8	13	0.6
9	56	2.5	9	8	0.4
10	26	1.2	10	2	0.1
11	9	0.4	11	0	0.0
12	6	0.3	12	0	0.0
13	1	0.0	13	1	0.0
14	3	0.1	14	0	0.0
15	0	0.0	15	1	0.0
21	1	0.0	21	0	0.0
Total	1078	48.3	Total	1083	48.5
Missing Entry	1154	51.7	Missing Entry	1149	51.5
Total	2232	100.0	Total	2232	100.0

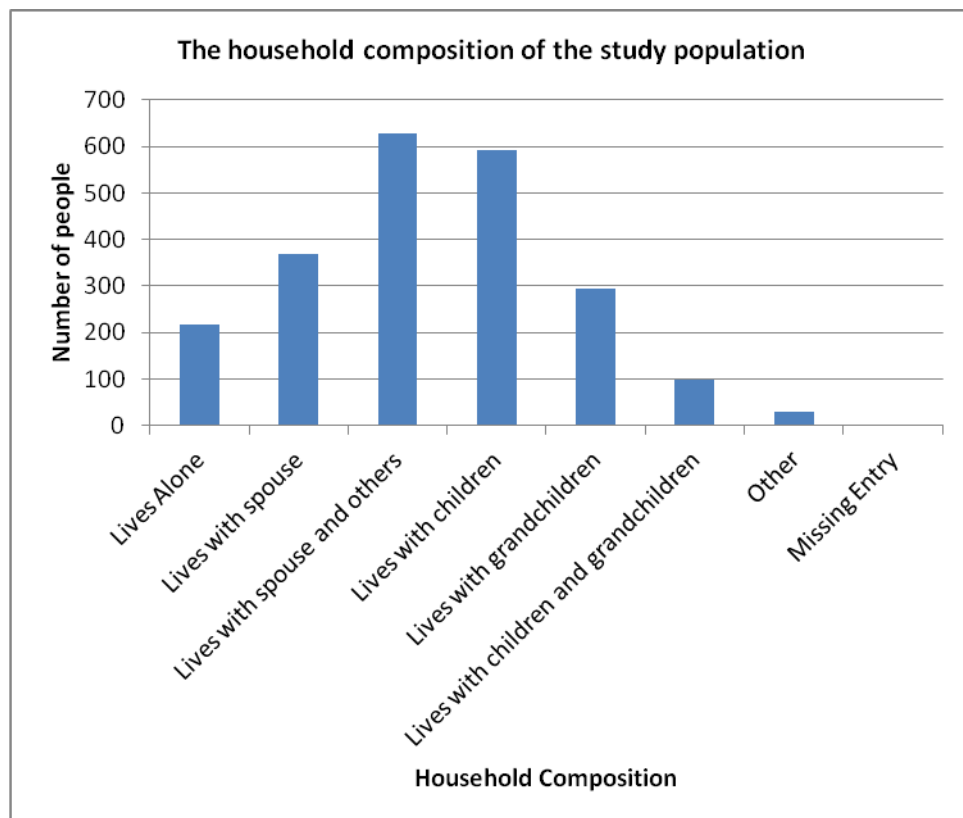
Household Composition

As a further representation of the level of social support for the elderly the participants were asked who they lived with. Their household compositions are demonstrated in Table 16 and Graph 9. In the majority of cases the “other” category represented cohabiting with siblings, with a small minority living with employees.

Table 15 The household composition of the Study Population

Household composition	Number of People in each household situation in the Study Population	Percentage of people in each household situation in the Study Population
Lives Alone	217	9.7
Lives with spouse only	368	16.5
Lives with spouse and others	627	28.1
Lives with children only	593	26.6
Lives with grandchildren	295	13.2
Lives with children and grandchildren	100	4.5
Other	30	1.3
Total	2230	99.9
Missing Entry	2	0.1
Total	2232	100.0

Graph 9



Where the Study Population was seen

I attempted to see participants in a place of convenience for them. In the majority of cases it was possible and practical for them to come to the village health centre or dispensary. When the village was large, people were seen at

other convenient central locations, e.g. a private house or a local church. If the person was unable to travel to a central location they were seen in their own home. The fact that I saw patients in their own home is likely to have increased my case ascertainment and the validity of my conclusions. 1530 (68.5%) people were seen in local health centres, 355 (15.9%) were seen in their own homes, 330 (14.8%) were seen in central large private houses and 17 (0.8%) were seen in a local church.

Distance to the Health Centre

Nearly everyone had to walk to their nearest health centre / hospital and clearly health-seeking behaviour will be affected by a patient's ability to access healthcare and for how long they have to travel. 99 (4.4%) had to travel for 0-29 minutes, 344 (15.0%) travelled for 30-59 minutes, 362 (16.2%) for 60-89 minutes, 100 (4.5%) for 90-112 minutes, 99 (4.4%) for 120-149 minutes, 32 (1.4%) for 150-179 minutes and 61 (2.7%) had to travel for 3 hours or more.

Proportion of the Study Population that was born in and that had ever lived outside the Hai District DSS

The population of the Hai District DSS and the Study Population are fairly static especially with reference to the 70 and over population. The majority of the people (83.9%) in the Study Population were born within the Hai District DSS and only 26.7% had ever lived outside the Hai District DSS.

3.2 Discussion

The census was undertaken by experienced enumerators who had performed several previous censuses in their respective villages in the Hai District. The data were subsequently analysed by analysts in Dar-es-Salaam who again had worked successfully and accurately on previous censuses in the area.

There was a six month time period between completion of the census (end of May 2009) and my point prevalence date (1st January 2010), during which time 301 more people from my surveyed villages turned 70. This was ascertained simply by asking patients their year of birth using memory prompts as for the rest of the census, rather than the exact date, and so may

have introduced a small degree of error with ages. However, this method remains the best validated (173) method in countries where the majority of people do not have birth certificates.

The 12 villages were chosen at random, yet stratified to reflect accurately the spread of upland and lowland villages across the whole Hai District (and thus the tribal mix). The enumerators for each village were residents in their own village and this was beneficial because they spoke both Swahili and the local tribal language, were respected within their village (as they were educated and normally either teachers, nurses or local businessmen/women), and knew the location of houses and inhabitants very well. The benefit to my study was great, as, with these enumerators, my ascertainment was maximised.

The AMOs, supervising the enumerators and co-ordinating data collection, provided intermediary communication between me, the enumerators, and the DMO. They were invaluable not only to relay logistics information but also to act as medical translators during the data collection.

3.3 Conclusions

The census was performed robustly and accurately to allow for precise identification of a proportion of an elderly Tanzanian population to produce accurate results based on reliable methodology. This has allowed me to accurately identify prevalence rates of AF and hypertension in the community-dwelling elderly population.

Chapter 4.

Prevalence of AF and Clinical Correlates - a Case-Control Study

4.1 Methods

In addition to the general methodology mentioned in Chapter 2, the ascertainment of AF cases and controls is described in more detail below.

4.1.1 History Findings

Please see Appendix 2b for full proforma.

4.1.1.1 Presenting Symptoms

Common, important symptoms relating to AF and cardiac problems were recorded in this section. Chest pain was classified as cardiac or non-cardiac, and further delineated if it was thought to be potentially of cardiac origin using the Canadian Cardiovascular Society Angina Classification (176). Breathlessness was graded according to the New York Heart Association Classification of heart failure (177). These scales were chosen for their ease of use and their common acceptance elsewhere in the world. Other symptoms of heart failure and AF were recorded such as orthopnoea and paroxysmal nocturnal dyspnoea, and palpitations, pre-syncope, syncope, tiredness and reduced exercise tolerance.

4.1.1.2 Other History

Other history I felt it was important to record included whether the participants had sought medical help for their symptoms and whether they had been to a health centre / hospital in the previous 12 months or to a traditional healer ever, in order to assess not only health-seeking behaviour, but also the gap in diagnosis and treatment of AF and other conditions such as hypertension. The past medical history concentrated particularly on risk factors for AF and other cardiac conditions, and another assessment (in addition to the Barthel Index (BI) score within the demographics section) of ADLs was made particularly related to stroke.

4.1.2 Examination Findings

4.1.2.1 Cardiac

The examination for AF cases and controls focused mainly on cardiovascular findings, particularly auscultation of the praecordium, assessment of peripheral pulses and systemic stigmata of cardiac disease. See appendix 2b for Proforma.

4.1.2.2 Other

Other important signs related to risk factors for AF were assessed and recorded e.g. fundoscopy was performed for signs of hypertensive retinopathy, lung bases were auscultated for signs of LV failure and pulmonary oedema. Incidental findings that were of interest or cause for concern from a medical perspective were also recorded and appropriate advice or treatment was given (or prescribed if not immediately available).

4.1.3 The Electrocardiograph and standardisation of measurements

The machine used for recording 12-lead ECGs was a MAC 1200™ (GE Healthcare, UK). The study had the use of 2 machines (one of which was already in Tanzania as it was used in a previous study, and one that was purchased with grant money). These machines were introduced to the village enumerators in a 2-hour session, with an initial demonstration of how the machine worked, and then an opportunity to practise recording ECGs on a volunteer and address any queries. The enumerators were provided with a printed sheet, detailing steps in recording ECGs in Kiswahili and a diagram to remind them about electrode placement (see appendix 1). The machines had rechargeable batteries to ensure they were readily usable in health centres / homes without electricity and to minimise AC interference from mains supply. The machines were set-up to record at a paper speed of 50mm/s, with a sensitivity of 10mm/mV, as is standard practice in the UK. The machines were capable of storing up to 40 ECGs digitally, for subsequent download to PC. I aimed to perform 12-lead ECGs on all participants.

4.1.4 Blood Pressure Measurements in AF Cases

Blood pressure was measured as in Section 7.1.1. It is well known that accurate BP measurement in patients with arrhythmias is difficult, particularly if the arrhythmia is irregular and consequently there is beat-to-beat variation in stroke volumes. The current ESC guidelines (178) states:

"Irrespective of what guidelines are agreed upon, blood pressure measurement in atrial fibrillation, particularly when the ventricular rhythm is highly irregular, will at best constitute a rough estimate, the validity of which can perhaps be improved upon only by using repeated measurements or direct intra-arterial measurement".

In following these guidelines, I accept that the BP measurements may not be as accurate as the recordings in the participants in sinus rhythm, but aimed to maximise accuracy by repeating measurements and ensuring that consecutive BPs were within a range of each other (see 7.1.1). Intra-arterial measurements were clearly not an option.

4.1.5 Case definition of AF

AF was diagnosed according to the definitions provided by the ESC guidelines (31). AF is defined as a cardiac arrhythmia with the following characteristics:

- (1) The surface ECG shows 'absolutely' irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern.
- (2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
- (3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm).

Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm strip, should be considered as AF.

For the purposes of this study, cases of atrial flutter (AFI) were included under the umbrella heading of AF. AFI can usually be distinguished from AF on 12-lead ECG, because it tends to be a more organised supra-ventricular arrhythmia, and thus results in characteristic 'saw-toothed' F waves of constant amplitude and frequency, with a cycle length ≥ 200 ms (≤ 300 bpm), and often a regular RR interval. However, as has been mentioned previously, several studies have reported a similar risk profile in Afl patients to that observed in AF patients (131) (179) (132).

4.1.6 Risk stratification for treatment purposes

With regard to persistent / permanent AF, risk stratification has been previously discussed and I employed the CHA₂DS₂-VASc tool. As all of my patients were 70 years of age or older, they all scored at least 1 point with the tool. This meant, as warfarin was not available in this setting, that all of my patients were given aspirin 75mg per day if there was no contra-indication. I did not increase the dose of aspirin in higher risk patients as I did not want to increase bleeding risk. I used EF $\leq 40\%$ or evidence of clinical LVF as a cut-off for deciding whether a patient scored 1 point for 'C', and used the WHO criteria for diagnosis of Diabetes Mellitus (random plasma glucose ≥ 11.1 mmol/L. I did not use fasting glucose due to inability to ask participants to come and see me fasted and did not have the finances to perform HbA1c). I did not test all study participants for Diabetes Mellitus, only patients with AF and the pool of controls, as this was felt to be outside the scope of this study. I may have underestimated risk scores as diagnosis of vascular disease relied solely on symptoms and palpation of peripheral pulses.

With regard to PAF, there is still debate in the literature as to how much PAF is clinically important from the perspective of increasing stroke risk. Please see Chapter 6 for further discussion of the literature

4.1.7 Echocardiography and the contribution of echocardiography to risk stratification

Echocardiography was performed by a trained echocardiographer (MD) using a Sonosite Titan™ (Sonosite Ltd, UK) portable echo machine. Measurements were taken according to European Association of

Echocardiography guidelines as far as was possible given the limitations intrinsic to the setting and the capabilities of the echo machine (180). Importantly with regards to assessing for structural heart disease predisposing to AF, global LV function was noted in addition to LA size and MV structure and function. For the purposes of reporting LV function, EF was normal ($\geq 55\%$), mildly impaired (45-54%), moderately impaired (35-44%), or severely impaired ($< 35\%$) and measured using fractional shortening and visual estimation (as Simpson's biplane method was unavailable on this machine). Other limitations of the echo machine included only being able to record still images and not video loops (meaning function had to be assessed whilst performing the echo), battery life and memory card sufficient to record a maximum of 3 echocardiographs in the field, and lack of Tissue Doppler Imaging (TDI) facility to assess diastolic dysfunction in more detail. Limitations intrinsic to SSA included having to do many of the echos with the patient in a seated position due to lack of beds at health centres / village halls, and that dimmed / dark rooms were not always available for ideal visualisation of images. Having said this, I had to balance limitations with practicality and the machine produced good images for its size and portability, sufficient that following recording in the field, reporting and recording measurements were done the same evening on returning from the field.

It was vital to perform echocardiography on all AF patients and controls. It is well recognised that structural heart disease, particularly LV dysfunction, increased LA size, and MV disease predispose to the development and maintenance of AF (38) (74) (75). In addition to identifying risk factors for development, it was also important to risk stratify patients with AF as to their subsequent risk of stroke. As previously mentioned, LV dysfunction (arbitrarily $\leq 40\%$) is a clinically significant risk factor for stroke in non-rheumatic AF (147), and the identification of a patient with AF and mitral stenosis / rheumatic mitral valve disease immediately places this patient at high risk of thromboembolic problems (31). Therefore, echo was mandatory in order to assess risk in this population and decide on treatment.

4.1.8 Blood Sampling

Blood samples were taken from AF patients and controls for biochemical analyses including urea and electrolytes, liver and thyroid function tests, glucose and lipid profile. These tests were done as they have either implications for the aetiology of AF (e.g. thyroid function tests looking for hyperthyroidism) or contribute to an assessment of overall cardiovascular risk (e.g. lipid profile and random blood glucose). eGFR was calculated and reported using a new equation called the CKD-EPI equation, which is claimed to be as accurate as the more traditional Modified Diet in Renal Disease – 4 (MDRD-4) equation for eGFR <60 ml/min/1.73 m², and 'considerably more accurate' than MDRD-4 in the group with eGFR >60 ml/min/1.73 m² (181). In addition, a recent study by Eastwood et al (182) looked at 944 black Africans from the Ashanti tribe in Ghana, and compared creatinine clearance using 24-hour urine samples to equations for calculating eGFR (Cockcroft-Gault, MDRD-4, CKD-EPI). The study found that the CKD-EPI equation without the adjustment for race was the closest to that of creatinine clearance, outperforming MDRD-4 (with and without adjustment for race) and CKD-EPI (with adjustment for race) which overestimated eGFR and Cockcroft-Gault which underestimated eGFR. The CKD-EPI without race adjustment mirrored decline in GFR in the older age groups better than the other equations (although the study population had a maximum age of 75 years), and therefore is the one I chose to use in my study population. I also calculated eGFR using more traditional measures, the Cockcroft-Gault and MDRD-4 formulae as comparisons. Cockcroft-Gault does not have an adjustment for race in its equation and is known to be inaccurate at both significant overestimation of eGFR in black African patients compared to isotope imaging (183), and significant underestimation compared to creatinine clearance (182). MDRD-4 has an adjustment for race in its equation, but like CKD-EPI, has been shown to be more accurate in black African patients at estimating GFR when using the equation without race adjustment (183). The figures reported therefore are without adjustment for race.

In addition to these traditional tests, other electrolytes such as magnesium and calcium were measured because electrolyte imbalances may contribute to the development of atrial tachyarrhythmias by causing abnormal impulse

generation, which could initiate a re-entrant loop within the atria (184). Hypomagnesaemia was present in 20% of patients presenting with AF in one small study containing 45 patients (185), although it is difficult to estimate the contribution of hypomagnesaemia to AF / AFI given the lack of prospective studies, and the fact that serum magnesium represents only 1% of total body content in general (186). In addition, it is noted that full blood counts (FBC) were not performed in my Study Population despite anaemia potentially contributing to the development of AF through decreasing oxygen delivery to myocardial tissue thus creating an ischaemic substrate. The reason for this was purely economic in that the samples had to be analysed in Moshi and at US\$19 each, were deemed prohibitively expensive.

However, biochemistry samples were spun and frozen at the Duke University laboratory in Moshi on the day of collection, prior to transport on dry ice back to the UK, where they were analysed at North Tyneside General Hospital at a more affordable price. It is not possible to carry out FBC on frozen specimens.

4.1.9 Patient Treatment

AF cases identified were treated with aspirin to lower stroke risk (157) and older rate-control agents (digoxin, atenolol) to reduce symptoms and help improve functional status (187) (in the absence of contra-indication). The agents were chosen based on effectiveness, local availability and cost. Warfarin remains unavailable and unsuitable for stroke prevention in rural Tanzania due to a lack of infrastructure for monitoring INR levels. Potentially promising in the future are the newer anti-coagulants such as rivaroxaban and dabigatran that do not require monitoring, although they are only just beginning to appear on the market (recent FDA licensing in the USA) and are therefore currently very expensive.

In addition to the treatment given for AF, I prescribed treatment to address risk factors such as HTN (bendrofluazide and nifedipine), diabetes mellitus (chlorpropamide) and heart failure (frusemide, captopril). Again, these treatments were chosen for sustainability reasons.

4.1.10 Controls

Controls were selected from the list of those aged 70 years and above within the study villages who were found to have sinus rhythm on their 12-lead ECG. Anyone who had been previously diagnosed with AF or another cardiac arrhythmia requiring treatment was not considered as a potential control. Controls were age- and sex-matched as a group to those identified as having AF. I employed a pragmatic approach whereby a pool of controls was selected by convenience sampling from the background population and controls selected from this pool by use of a random number generator. The reasons for using this approach were multiple:

1. If controls were identified completely at random, they would have been expected to return to the village health centre on a separate occasion, entailing a long walk and preventing them from working which they were often unwilling to do.
2. I found there was more time first thing in the morning for doing more detailed histories, performing echocardiograms etc. before the majority of participants turned up. Often we were seeing >50 participants per day and therefore it was more pragmatic to identify the first 2-3 people per day as controls.
3. Which village I visited on a day-to-day basis depended on accessibility during the prolonged rainy season as well as enumerator availability and it was difficult to plan too far in advance with regard to asking the enumerator to request that specific people return on specific days.

4.1.11 Expected Prevalence Rates

As mentioned previously, the main reason for conducting this study was to accurately document the prevalence of AF in a previously unstudied elderly SSA population. I was expecting prevalence rates to be similar to prevalence rates in African-Americans, with higher rates of rheumatic valvular heart disease in this population compensating for lower rates of IHD (with respect to AF risk factors). I also felt that estimating population risk of AF based on one of the recently published risk prediction algorithms derived from large epidemiological studies in the US would be interesting (188, 189). This was done retrospectively given that the risk prediction tools were published after my data collection had finished and is a rough estimate of predicted

prevalence as these tools are risk prediction tools rather than prevalence prediction tools and risk of incident AF over 5 and 10 years has been estimated from them, rather than prevalence.

I decided to compare my population and risk factors with the African-American cohort in the CHS study, which was analysed using the Framingham risk prediction tool in the Schnabel paper (188). The reason for doing this is that whilst the ARIC prediction tool (189) appeared to predict AF risk with more accuracy than the Framingham AF score (c-statistic 0.76 versus 0.68) in African-Americans, increasing age consistently comes out as the most important risk factor for AF and the ARIC tool has only been validated in a population of 45-64 year olds. It therefore has limited application to my Study Population. In addition, I felt I could be more accurate with the Framingham risk score as the ARIC tool relies on data from clinical examination, smoking status, presence of diabetes mellitus (for example), data which I did not collect. However, I had more risk factors for the Framingham risk score recorded. Unfortunately, the CHS African-American cohort had missing data on valvular heart disease and had consequently been unable to estimate a hazard ratio. Therefore I have not included it in the table below.

Table 16 Risk Factors for AF based on Framingham AF risk prediction tool - a comparison of the Study Population to African-Americans in the Cardiovascular Health Study (CHS AA)

Risk Factor	My Study (n=2232)	CHS AA (n=1552)	
		Risk Factor	Hazard Ratio
Mean Age (years)	77.7	75.3	1.95 (per 10 years)
Gender (% men)	43.7	35.8	1.2 (being male)
BMI (kg/m ²)	21.6	28.5	1.29 (per 5kg/m ²)
SBP (mmHg)	160	141	1.17 (per 20mmHg)
HTN Treatment	94 (4.2%)	58.4%	1.58
PR interval (ms)	152	173	1.12 (per 30ms)
Heart Failure	0	7.8%	3.21

As can be seen, my Study Population was on average older, with more men, a lower BMI, yet a higher mean SBP, a significantly lower percentage of people on anti-hypertensives, a shorter mean PR interval and no-one with significant heart failure (i.e. either EF <45% or clinical heart failure). Therefore, if we look at the risk factors that would increase risk in my Study Population, older age by 2 years would increase risk by approximately 20%, increased mean SBP would increase risk by approximately 17%, and there were 8% more men in my population, increasing risk further. Countering this, it appears that reduced BMI would reduce risk by approximately 30%, PR interval by approximately 10% and my own feeling is that it is incredibly difficult to try to compare the 2 populations in terms of anti-hypertensive treatment (because as will be seen in chapter 7, very few very hypertensive people were on treatment due to under-diagnosis and lack of treatment resource) and heart failure (a value of zero people is likely to be an underestimate and of minimal help given I only had data from 75 'control' echocardiograms). Discounting the final two, and allowing for the fact that the prevalence of valvular heart disease is probably higher in my Study Population than in the CHS AA study, the population risk factor profile suggests I should be expecting a similar prevalence of AF to that seen in an African-American population.

4.1.12 Statistical Analysis

Statistical advice was sought from Dr Keith Gray from Northumbria Health Care Foundation Trust and a calculation of the power of the study performed (based on the Hai DSS study population). Statistical analyses were performed using Statistical Package for the Social Sciences SPSS software, version 17.0, and Microsoft Excel 2007.

Age-standardisation was carried out using the direct method, with standardisation to the WHO world standard (190). Age specific rates for each five year age band were also calculated. Confidence intervals (CIs) for prevalence and for odds ratios were calculated based on the assumptions of the binomial distribution. CIs for continuous variables were calculated from the normal distribution. Due to the small number of AF and PAF cases

identified, significance tests for some data are not presented. Point estimates and proportions are given as appropriate.

4.2 Results

4.2.1 Prevalence of AF

ECGs were performed on 2232 study participants. Of these, 1256 (56.3%) were women and 976 (43.7%) were men. There were 15 cases of AF (14 fibrillation, 1 flutter) giving an overall crude prevalence rate of 0.67% (95% CI 0.33 to 1.01) and an age-adjusted prevalence of 0.64% (95% CI 0.31 to 0.97), as shown in Table 17. Rates were higher in women than men, though not significantly so, as shown in Table 18. There was a general trend towards increased prevalence with increasing age.

Table 17. Age-specific prevalence of atrial fibrillation

Age bands	WHO world population (%)	Combined sexes		
		Cases	Denominator population	Prevalence (%) (95% CI)
70-74	2.21	4	877	0.46 (0.01 to 0.90)
75-79	1.52	2	625	0.32 (0 to 0.76)
80-84	0.91	4	344	1.16 (0.03 to 2.30)
85+	0.635	5	386	1.30 (0.17 to 2.42)
Total	5.275	15	2232	0.67 (0.33 to 1.01)
Age-adjusted*	-	-	-	0.64 (0.31 to 0.97)

* To WHO world population.(190)

Table 18 Age- and sex-specific prevalence of atrial fibrillation

Age bands	Males			Females		
	Cases	Denominator population	Prevalence per 1000 (95% CI)	Cases	Denominator population	Prevalence per 1000 (95% CI)
70-74	2	384	0.52 (0 to 1.24)	2	493	0.41 (0 to 0.97)
75-79	0	285	0	2	340	0.59 (0 to 1.40)
80-84	0	135	0	4	209	1.91 (0.06 to 3.77)
85+	1	172	0.58 (0 to 1.72)	4	214	1.87 (0.05 to 3.68)
Total	3	976	0.31 (0 to 0.65)	12	1256	0.96 (0.42 to 1.49)

4.2.2 Clinical Correlates of AF

Comparison of the clinical characteristics of those with AF and controls is shown in Table 19 for females and Table 20 for males, below. The results are further explained in individual sections below that. Again, data are missing for specific variables in a small number of cases, as detailed in the tables.

Table 19 Comparison of female patients and controls

	Patients (n = 12)	Controls (n= 60)
Mean age (years)	81·5, n = 12	80·3, n = 60
Mean BMI (kg/m ²)	20·9 , n = 9	22·0 , n = 55
Mean pulse rate (beats per minute)	118·7, n = 12	81·6, n = 58
Mean pulse pressure (mmHg)	59·8, n = 12	78·9, n = 60
Mean diastolic BP (mmHg)	105·1, n = 12	91·7, n = 60
Mean systolic BP (mmHg)	164·9, n = 12	170·6, n = 60
BP ≥ 140/90	9 (75·0%), n= 12	48 (80·0%), n = 60
BP > 150/95	7 (58·3%), n= 12	43 (71·7%), n = 60
BP > 160/100	7 (58·3%), n= 12	31 (51·7%), n = 60
Mean serum cholesterol (mmol/L)	4.5, n= 10	4.8, n = 51
Barthel index score	n = 8	n = 31
<i>No disability (19-20)</i>	5 (62·5%)	30 (96·8%)
<i>Moderate disability (15-18)</i>	1 (12·5%)	1 (3·2%)
<i>Severe disability (0-14)</i>	2 (25·0%)	0 (0%)
Palpitations	6 (50·0%), n= 12	5 (8·3%), n = 60
Pre-syncope	6 (50·0%), n= 12	6 (10·0%), n = 60
Shortness of breath	5 (41·7%), n= 12	8 (13·3%), n = 60
Reduced exercise tolerance / tiredness	4 (33·3%), n= 12	5 (8·3%), n = 60
Mean CHA ₂ DS ₂ -VASc risk score	4.27, n = 11	-
Echocardiography		
Left ventricular function	n = 12	n = 60
<i>Normal (EF ≥55%)</i>	7 (58·3%)	54 (90·0%)
<i>Mild impairment (EF 45-54%)</i>	2 (16·7%)	6 (10·0%)
<i>Moderate impairment (EF 35-44%)</i>	2 (16·7%)	0 (0%)
<i>Severe impairment (EF <35%)</i>	1 (8·3%)	0 (0%)
Mean left atrial size (cm)	4·4, n= 12	3.3, n = 49
Left atrial dilation	n = 12	n = 49
<i>Normal</i>	1 (8·3%)	37 (75·5%)
<i>Mild</i>	3 (25·0%)	10 (20·5%)
<i>Moderate</i>	5 (41·7%)	2 (4·1%)
<i>Severe</i>	3 (25·0%)	0 (0%)
Mitral valve stenosis	1 (8·3%), n = 12	2 (3·3%), n = 60
Mitral valve regurgitation	7 (58·3%), n = 12	11 (18·3%), n = 60

Table 20 Comparison of male patients and controls

	Patients (n = 3)	Controls (n = 15)
Mean age (years)	76.7 , n = 3	77.1, n = 15
Mean BMI (kg/m ²)	26.8, n = 3	21.7, n = 15
Mean pulse rate (beats per minute)	105.3, n = 3	69.9, n = 14
Mean pulse pressure (mmHg)	51.7, n = 3	78.1, n = 15
Mean diastolic BP (mmHg)	81.7, n = 3	84.9, n = 15
Mean systolic BP (mmHg)	133.3, n = 3	163.1 , n = 15
BP ≥ 140/90	1 (33.3%), n = 3	11 (73.3%), n = 15
BP > 150/95	0 (0%), n = 3	10 (66.7%), n = 15
BP > 160/100	0 (0%), n = 3	9 (60.0%), n = 15
Mean serum cholesterol (mmol/L)	4.4, n = 3	5.1, n = 12
Barthel index score	n = 3	n = 6
<i>No disability (19-20)</i>	3 (100%)	6 (100%)
<i>Moderate disability (15-18)</i>	0 (0%)	0 (0%)
<i>Severe disability (0-14)</i>	0 (0%)	0 (0%)
Palpitations	1 (33.3%), n = 3	1 (6.7%), n = 15
Pre-syncope	0 (0%), n = 3	0 (0%), n = 15
Shortness of breath	2 (66.7%), n = 3	1 (6.7%), n = 15
Reduced exercise tolerance / tiredness	0 (0%), n = 3	0 (0%), n = 15
Mean CHA ₂ DS ₂ -VASc risk score	1.33, n = 3	-
Echocardiography		
Left ventricular function	n = 3	n = 15
<i>Normal (EF ≥55%)</i>	3 (100%)	13 (86.7%)
<i>Mild impairment (EF 45-54%)</i>	0 (0%)	2 (13.3%)
<i>Moderate impairment (EF 35-44%)</i>	0 (0%)	0 (0%)
<i>Severe impairment (EF <35%)</i>	0 (0%)	0 (0%)
Mean left atrial size (cm)	4.1, n = 3	3.6, n = 9
Left atrial dilation	n = 3	n = 9
<i>Normal</i>	1 (33.3%)	9 (100%)
<i>Mild</i>	2 (66.7%)	0 (0%)
<i>Moderate</i>	0 (0%)	0 (0%)
<i>Severe</i>	0 (0%)	0 (0%)
Mitral valve stenosis	0 (0%), n = 3	0 (0%), n = 15
Mitral valve regurgitation	1 (33.3%), n = 3	2 (13.3%), n = 15

4.2.2.1 Symptoms

The most common symptoms associated with AF in the Study Population were palpitations and pre-syncope, each affecting 6/15 (40%) of those with AF. Next most common was shortness of breath (5/15 – 33.3%), then limited exercise tolerance and tiredness (both 4/15 – 26.7%), and finally cardiac-

sounding chest pain (3/15 – 20%). Of the 5 that had shortness of breath, all of them reported symptoms with moderate exertion and were therefore classified as NYHA class II. This corresponds to high-income country studies where up to 30% of AF patients have symptomatic heart failure of NYHA classes II-IV (191, 192) although it is to be noted that these patients were at the less severe end of the spectrum (NYHA II), as expected for otherwise well community-based patients. In addition, $\geq 20\%$ AF patients have CAD according to these same studies (191, 192) which corresponds well to my study findings of patients with cardiac-sounding chest pain. However, ‘anginal’ symptoms may not necessarily signal large vessel coronary disease and may be as a result of tachyarrhythmia and microvascular coronary perfusion abnormalities associated with AF (193). Interestingly, 5/15 (33%) were completely asymptomatic of their AF, again in keeping with studies in high-income countries that suggest approximately 30% of AF sufferers (particularly the elderly) are unaware of their diagnosis (43). This compared to the control group, whose most common symptom was SOB (19/114 – 22%), followed by pre-syncope (11/114 – 13%) and limited exercise tolerance (9/114 – 10%), then palpitations and tiredness (both 7/114 – 8%). Cardiac-sounding chest pain and syncope were each only present in 2/114 (2%).

4.2.2.2 Signs

Examination findings revealed an average pulse rate of 116bpm (range 60-220) in AF patients. Females had a higher average pulse rate than males (118.7bpm vs. 105.3). This compared to a mean pulse rate of 77.5 in controls, with male controls having higher mean pulse rates than their female counterparts (83bpm vs. 73.4). 2/15 (13.3%) patients had a raised jugular venous pressure (JVP), but no patients had evidence of overt cardiac failure. 2 patients had a raised JVP, and 2 other patients had mild pedal oedema, but the raised JVPs were secondary to tricuspid valve incompetence, and pedal oedema is very common in the elderly and was not considered pathological in these two cases due to the lack of supporting findings. Several AF patients and controls were found to have cardiac murmurs on auscultation of the praecordium but corresponded well with what was subsequently found on echocardiography.

4.2.2.3 Blood Pressure

Mean systolic BP in AF patients was 158.6mmHg and diastolic 100.4mmHg. Females with AF had significantly higher systolic and diastolic BP than their male counterparts (164.9 vs. 133.3 systolic and 105.1 vs. 81.7). Using our pre-determined cut-off points, this equated to 9/12 (75%) female patients with a BP \geq 140/90 but only 1/3 (33%) male. 7/12 (58.3%) female and 0/3 male AF patients had BP \geq 150/95 and 7/12 (58.3%) female patients had BP $>$ 160/100. Overall mean pulse pressure was 58.2mmHg, again with a larger pulse pressure in female AF patients (59.8 vs. 51.7). Comparisons to the control groups can be seen in Tables 19 and 20.

4.2.2.4 Echocardiographic Findings

Left ventricular systolic function was more commonly affected in AF patients than in controls. Overall, 10/15 (66%) AF patients had normal LV function, with 2/15 (13.3%) having mild LV dysfunction, 2/15 (13.3%) moderate LV dysfunction and 1/15 (6.7%) severe LV systolic dysfunction. 3/3 male AF patients had normal LV systolic function meaning female AF patients had lower average ejection fractions.

AF patients had slightly higher mean pulmonary artery systolic pressures (PASP) than controls (25.22mmHg vs. 22.56). Female AF patients had a mean PASP of 25.28mmHg vs. male patients with a very similar mean value of 25mmHg. Whilst male controls were very similar with a mean of 25.86, female controls had much lower mean PASP of 16.37mmHg. None of our patients or controls had significant aortic stenosis.

See Tables 19 and 20 for further echocardiographic indices with comparison to age-and sex-matched controls. No statistical analysis has been performed due to very low numbers of AF patients.

4.2.2.5 Functional Status

Functional status, as determined by the BI score, was lower on average in AF patients (16.9) than in controls (19.4). The mean BI score was significantly lower in 8 female AF patients (16.2) than 3 male AF patients (20), but were fairly similar in 31 female controls (19.5) and 6 male controls (19.3). 5 female patients (62.5%) had mild disability / no disability

(characterised by BI scores of 19-20), 1 (12.5%) had moderate disability (BI 15-18) and 2 (25%) had severe disability (BI <15). All 3 male AF patients scored 19-20 on BI therefore having mild / no reduced functional status. The odds of a female AF patient having severe disability, based on BI score, were 1.31 (95% CI 0.90 to 1.92) those of a man.

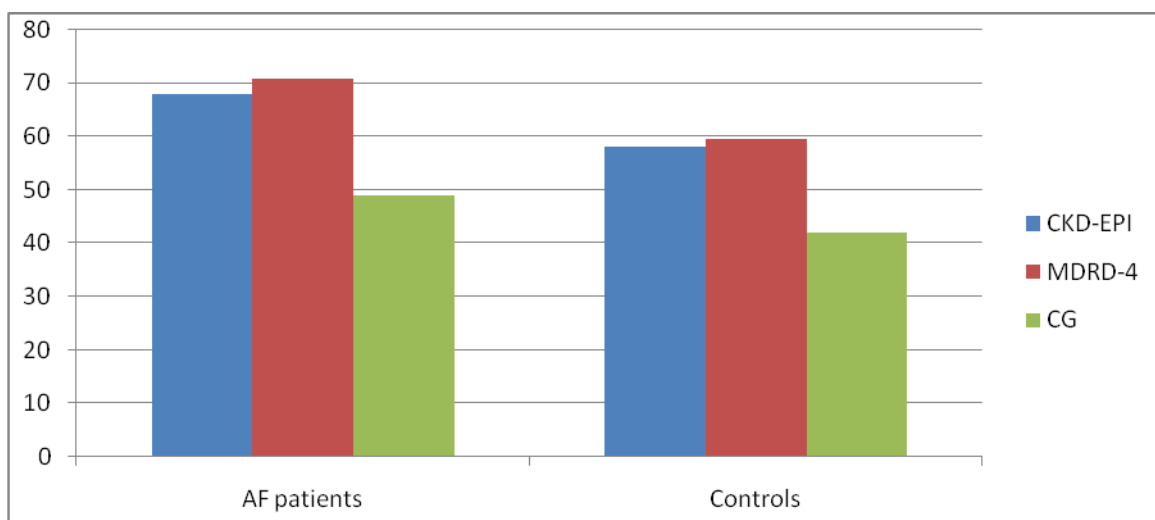
4.2.2.6 Body Mass Index

The mean BMI of AF patients was 22.34, with men having higher values (26.8) than women (20.9). This compares to a mean control BMI of 21.9, with male controls having a very similar BMI (21.7) to female controls (21.9), and to the mean BMI of the background study population of 21.6 (men and women combined), 20.9 (men) and 22.2 (women)

4.2.2.7 Blood Results

AF patients had a mean eGFR of 67.9mL/min/1.73m² using the CKD-EPI equation without adjustment for race, 70.9mL/min/1.73m² using MDRD-4, and 49.1mL/min/1.73m² with the Cockcroft-Gault formula. Male patients had a much higher average eGFR than females (82 vs. 63.7). This was a higher mean eGFR than in controls (see graph below), with mean GFR in controls being 58.1mL/min/1.73m² using CKD-EPI (59.5mL/min/1.73m² using MDRD-4 and 42mL/min/1.73m² for Cockcroft-Gault), and again GFR being better in males than females (78.7 vs. 52.4).

Graph 10 Comparison of eGFR (mL/min/1.73m²) in AF patients and controls, using 3 different equations



With regards to electrolytes, AF patients had K⁺ (4.3mmol/L), Ca²⁺ (2.33) and Mg²⁺ (0.84) values that were well within the normal ranges, and this compared similarly to control patients with mean values of K⁺ (4.4mmol/L), Ca²⁺ (2.35mmol/L) and Mg²⁺ (0.86mmol/L).

Two female controls were biochemically hyperthyroid yet clinically euthyroid, and no AF patients had significant thyroid abnormalities.

With respect to risk factors for CVD, AF patients and controls had fairly similar mean total cholesterol (TC) and glucose levels. AF patients had a mean TC of 4.45, with controls being slightly higher at 4.69. Mean glucose levels were 5.18 (AF patients) and 5.22 (controls). No AF patients had a random blood glucose \geq 11.0, but 2 male controls did (11.7 and 12.9).

4.2.2.8 Risk Stratification for Stroke

Mean CHA₂DS₂-VASc score was 3.64 (excluding 1 patient with rheumatic mitral valve disease). Female AF patients were at higher thromboembolic risk than their male counterparts, with a mean score of 4.3 (range 3-7) compared to 1.33 (range 1-2). Nevertheless, there were only 2/15 (13.3%) patients, both male, that scored 1 (and who would therefore be classified as intermediate risk). The other 13/15 (86.7%) would be classified as high thromboembolic risk (12 patients with a risk score >1, and 1 other patient with rheumatic MS classified as high risk).

4.2.2.9 Sequelae at Follow-up

1/15 AF patients had died at follow-up but the village enumerator did not know any more details and it was felt inappropriate at that time to enquire further. Another patient had been hospitalised with symptoms and signs of heart failure after discussion with the village enumerator (who was also a nurse at the village health centre). There are therefore missing data with regard to follow-up and blood results on these 2 cases.

4.2.3 Treatment and Advice for AF

Patients were given an information sheet regarding AF in Swahili (see appendix 5) and advised of symptoms, signs and potential sequelae. They were also given advice and education regarding the medication I prescribed for them. All 15 AF patients were prescribed aspirin 75mg od, given that they were all classified as at least intermediate risk of stroke sequelae. With regard to rate control, 9/15 (60%) were prescribed digoxin (125mcg or 250mcg depending on size and frailty), 3/15 (20%) were prescribed propranolol (40mg bd or 80mg bd depending on BP and pulse rate), 2/15 (13.3%) did not require rate control as their ventricular rate was adequate, and 1/15 (6.7%) was previously aware of her diagnosis of AF and was taking 500mcg od of digoxin – this was halved by me to 250mcg as she was bradycardic. Digoxin was prescribed in the majority due to the fact that it was often the only rate-control drug available at the village dispensary, and was significantly cheaper than propranolol. Propranolol was the most widely available beta-blocker and was prescribed in 1 case where the patient was having frequent paroxysms of AF and in 2 cases where the patients had either accompanying angina or were quite symptomatic from AF with a fast ventricular response and therefore rapid ventricular rate control was important.

Concomitant anti-hypertensive medications were prescribed in 5 patients, in the form of nifedipine (1/15), bendrofluazide (3/15) and lisinopril (1/15). Nifedipine and bendrofluazide were chosen primarily as they were most widely available and most effective. Bendrofluazide was the cheapest medication but I tried to avoid prescribing it with digoxin due to the risk of hypokalaemia and subsequent digoxin toxicity / proarrhythmia, and in these

patients we gave nifedipine instead. In the case of lisinopril, the patient was already on this relatively expensive drug, yet his hypertension was not adequately controlled and therefore the dose was increased, with advice regarding re-checking of renal function given.

4.2.4 Follow-up

2 patients were not seen at follow-up; 1 had died and 1 had been admitted to hospital. Of the remaining 13 AF patients, 2 had reverted to sinus rhythm and therefore their digoxin was stopped and 1 continued to have a fast ventricular response and therefore their digoxin was increased. Of the 8 patients that were followed-up and originally symptomatic, 4 (50%) had noticed an improvement in their symptoms since the commencement of treatment. Unfortunately, other than the patient who was previously aware of her AF diagnosis and already on treatment, not one of the patients had returned to the health centre for a repeat prescription, although 4/13 followed-up still had medication remaining from my initial prescription. Reasons cited for this included not having enough money, being too busy with work and having forgotten. Repeat education, advice and shorter prescriptions were given.

4.3 Discussion

4.3.1 AF Prevalence Data

4.3.1.1 Comparison to Other Populations

There have been a limited number of studies in SSA looking at AF (59, 60, 62, 63). Most have looked at the incidence of AF (59, 60) and mortality due to AF (63) in hospital populations, or at stroke risk factors in the community (62). The study by Connor et al (62) in South Africa was based on a questionnaire sent to 200 general practices recruiting 9133 patients (mean age 50.7 years), of whom 23% were black. The reported prevalence rate of AF in black patients was 2%, although this is likely to be an overestimate given that patients with an irregular pulse were classified as having AF.

Table 1 summarises AF prevalence from elsewhere in the world. All of the studies report a much higher prevalence of AF in equivalent age groups. In the UK, Majeed et al (194) looked at 1.4 million people on a GP research database, and found a prevalence of AF in the 70-74 age group of 4.6% in men and 3.3% in women, rising to >10% in both men and women aged 85+.

In Europe, Heeringa et al (37) found even higher rates, reporting a prevalence of 6.9% in men and 5.4% in women aged 70-74, rising to almost 1 in 5 in both men and women aged 85+. Whilst ethnicity was not stated in either study, it is likely that the populations did not contain many black people of African origin. Go et al (39) reported on 1.89 million adults in the USA, with 3.6% (68,040) being African-American. This study reported similar rates in white patients to Majeed's study (194), but lower rates in black patients (4.4% 70-79 age group, 7.7% 80+). However, these rates were still 11 times (70-79 age group) and 6 times (80+) higher than those found in my study. Upshaw et al (40) found similarly lower rates in black patients presenting to a US hospital. Lower rates are also found in studies from Japan (49, 50), Korea (54) and China (52), although the only instances where these low rates truly compare to my data is in the female 80+ group in the study by Iguchi et al from Japan (50) (2.5% versus our 1.89% for the same age band) and in the Jeong study from Korea (54) in the female 75-79 age group (0.5% versus 0.59% in my study).

Most of the above studies are epidemiological studies from high-income countries where data is available on the prevalence of PAF and consequently added to prevalence estimates. This study has primarily estimated prevalence rates solely from the findings of a 'one-off' 12-lead ECG, and consequently is likely to have under-estimated the prevalence of AF in a rural elderly SSA population. Having said this, as will be seen in chapter 6, there also appears to be a low prevalence of PAF in this population. Even if we use a generous definition of PAF of only 1 episode of irregular NCT >30 seconds in duration, the prevalence would only be 0.64% + 2.6% = 3.24% in total, and thus still significantly lower than other populations studied.

4.3.1.2 Reasons for Low Prevalence Rate

Contemporary data are building up regarding the influence of genetic polymorphisms on the susceptibility of certain populations to AF. In a recent review, it has been suggested by Xiao et al (195) that 2 chromosomal loci and 17 causal genes had been identified in familial AF, with an additional 7 common variants and single-nucleotide polymorphisms in 11 different genes indicated in non-familial AF. These mutations occur in genes coding for

potassium channels, sodium channels, connexins, atrial natriuretic peptides, calcium handling proteins and nucleoporins. In the 1st genome-wide association study (GWAS) of AF (196) a strong association between AF and 2 single-nucleotide polymorphisms (SNPs) on chromosome 4q25 was identified. Approximately 35% of those of European descent have at least one of the DNA sequence variations and the risk of AF increases by 1.72 and 1.39 per copy. Both SNPs are adjacent to the PITX2 gene, essential for cardiac development (in knockout mice, PITX2c is responsible for extension of left atrial myocardium into the pulmonary veins (197) and thus may be a candidate gene (198). Interestingly, in preliminary results from the Vanderbilt-Meharry registry, only 17.1% of African-American controls carried the common 4q25 variant (72). This suggests significant racial differences in polymorphisms, and either protective genetic factors in African-Americans or predisposing factors in Caucasians. Whilst African-Americans are predominantly of West African descent and again are likely to be genetically very different from the East African population that I studied, I feel the same underlying principles with regard to genetic differences are applicable, and it is likely that there are protective factors, either genetic factors, or novel environmental factors, present in my Study Population. In further support of the argument for a genetic basis/novel environmental factors for protection against AF is my initial attempt at a comparison with the CHS African-American cohort with regard to population risk. From examining identified risk factors, whilst they differ to some degree in both studies, the population risks appear to be approximately the same yet, as has been explained above, the prevalence of AF in my Study Population is significantly lower than African-American populations, thereby suggesting an unmeasured risk (in the CHS AA population) which may well be a genetic difference in susceptibility to AF.

Another reason for a lower AF prevalence in my Study Population is it is likely that there is a much lower contribution of ischaemic heart disease (IHD) to AF causation in blacks in SSA than in Western countries, given it accounts for <1% of deaths (80) (versus 20% deaths in other high-income countries (81)). This idea is supported by the lower prevalence of AF seen in Japan in combination with previously known lower prevalence of IHD (199) when compared to Western countries. One potential contributor to putative

lower rates of IHD in the Study Population could be the low mean serum cholesterol levels seen in patients (Tables 19 and 20).

In addition, it has been noted previously that increased BMI and obesity increases risk of AF (90), possibly because of an associated increase in atrial volume. The mean BMI of the Study Population was low, being 20.9 in men and 22.2 in women. These BMI levels compare similarly to an elderly Chinese population, which were noted to be much lower than a Western Caucasian population (200), and tallies with lower AF prevalence rates found by Zhou et al (52).

Patients with significant rheumatic valvular disease (which I initially hypothesised would increase prevalence rates in this population) and AF may die earlier because of AF or valve sequelae and this may, in part, explain the low mean age of people with AF from other studies in SSA (60, 63). This idea is supported by the high 1-year mortality rate (29.5%) of AF patients from a study based in Cameroon by Ntep-Gweth *et al* (63) and by the fact that only one of my AF patients was felt to have rheumatic heart valve disease on echocardiography.

It is also possible that AF may manifest differently in black Africans compared with other populations. It has been suggested that African-Americans may have more paroxysmal AF, rather than persistent AF seen in Caucasians (153), and thus partially explain their increased stroke burden (201) despite the lower prevalence of AF in epidemiological studies (39). As black Africans share this increased stroke burden, the same suggestion may be made regarding paroxysmal AF in this population.

Finally, there was a shortfall between census number and people screened and I cannot exclude the possibility that AF was over-represented in people who refused to be screened. However, access to healthcare in Tanzania is limited and it seems unlikely that people with chronic ill-health would ignore the opportunity to be assessed.

4.3.1.3 Gender and Age Differences

I found AF to be more prevalent in women than men, supporting the findings of previous hospital-based studies in SSA (59, 60) and studies from Iran (55) and Turkey (56), although numbers were small and so drawing firm conclusions is difficult. In the Heart of Soweto study in South Africa, Sliwa *et*

a/(60) suggested the higher prevalence in women was due to higher levels of obesity, with the real risk factor for AF being obesity rather than female gender *per se*. In my study, female patients had a mean BMI (20.9) less than the study population in general, although mean BMI in women was significantly higher than in men overall. Previous studies in high-income countries show that men are 50% more likely than women to develop AF (38) yet it has been shown to be a more common hospital presentation in women than men in South Africa (59, 60). It has previously been shown that the prevalence of IHD in Iran is higher in women than men (202) and that the prevalence of ischaemic ECG findings in Turkish adults is higher in women than men (203). This may explain in part reasons for higher AF prevalence in women in these populations and the Study Population. Other potential reasons for the majority of our AF cases being women include the larger overall female numbers in the study, and that the background population of women had significantly higher systolic, diastolic, and pulse pressure than men. The reasons for the gender differences in BP are not entirely clear, given that there was no difference in anti-hypertensive use between sexes in the background population, but it has been noted in Western populations that prevalence rates of hypertension are higher in women than men over the age of 70 (204).

In my study of those aged 70 years and over there was a trend towards higher prevalence of AF with age, as noted in studies from other countries (all studies in Table 1). Again, I recognise that the small number of cases limits the generalisability of my findings.

4.3.2 Clinical Correlates

HTN has previously been shown to be the single biggest risk factor for AF, responsible for 14% of all cases (38). Systolic pressure (74) and pulse pressure (205) have been suggested as the driving factors behind AF development rather than diastolic pressure. However, these studies contained very few, if any, black patients and it has been noted that increased rates of HTN do not always translate into an increased incidence of AF in an African-American population (75). In my Study Population 60.0% of AF cases had a BP greater than or equal to 140/90, and 46.7% had a BP greater than 160/100. Surprisingly, mean systolic BP and pulse pressure

were higher in the control group than in those with AF. However, AF cases had significantly higher diastolic BP than controls. This could simply be a consequence of higher mean heart rates in AF patients. Alternatively, it could be that diastolic hypertension is more important than systolic BP in this population in relation to AF. A third and more likely explanation is the one alluded to in the methods, that of difficulties in accurate BP measurements in patients with irregular arrhythmias and as previously stated, whilst I tried to be as accurate as possible with measurements, the BP recordings in AF patients are likely to be less accurate than those of the control group in sinus rhythm.

LV systolic dysfunction, increased left atrial size and mitral regurgitation were significantly more common in AF patients than in controls, in-line with other studies (38) (74) (75).

4.3.3 Functional Status and Stroke Risk

AF cases had lower Barthel Index scores reflecting reduced functional status and higher levels of disability. This may be due to the fact that AF patients not only had significantly more cardiac-related symptoms, but in addition one patient had a dense hemiparesis following stroke and was severely disabled (Barthel Index score 4). However, even after exclusion of this patient, mean BI scores remained lower in AF patients than controls (17.9 vs. 19.4).

Overall, CHA₂DS₂-VASc scores were higher in women than in men. Even after adjustment for the extra point gained for being female, the thromboembolic risk remains higher, in keeping with the Heart of Soweto study findings (60). I feel this reflects not only increased average age and BP of female patients but also supports the idea that women with AF are at increased risk of thromboembolic disease (206).

4.4 Conclusions

I have shown that the prevalence of AF in elderly black Africans is strikingly low in comparison with elderly populations from other regions (even accepting a slightly higher rate with the addition of the prevalence of PAF), and in particular is up to 11 times lower than in a comparable elderly black American population (39), itself thought to have a lower prevalence than a matched Caucasian population.

Only one of 15 AF cases was previously aware of their diagnosis, and patients with AF need to be identified earlier in order to reduce the risk of serious medical complications arising from AF, such as stroke.

In a country where rheumatic fever (and thus rheumatic valve disease) remains common and HTN is reaching epidemic proportions, we would expect AF prevalence to be high. The low prevalence of AF in elderly Tanzanians is likely to be multifactorial, with both genetic and environmental differences.

Whilst currently the reasons for these differences are incompletely understood, the data suggests significant differences, both in a genetic sense (with the potential for protective polymorphisms) and an environmental sense, combining to lead to these differences in disease occurrence. Further work is needed to elucidate novel protective factors, and genetic sequencing in this population.

Chapter 5. Electrocardiographic P wave Indices

5.1 Methods

5.1.1 *Electrocardiograph Analysis and Quality Control*

This was conducted at the medical physics department of Freeman Road Hospital, Newcastle upon Tyne and is detailed below.

5.1.1.1 *P wave indices*

All study participants underwent 12-lead (ECG), performed according to the Society for Cardiological Science and Technology Guidelines (207). The standard 10-second, 12-lead ECG was acquired and processed using GE Medical Systems® CardioSoft™ and 12-SL™ analysis programs. The ECG data were sampled at 500 samples/s with an amplitude resolution of 5 μ V. The raw ECG data were stored together with the ECG measurements provided by the software, for further offline processing. The detection and analysis systems used on the GE MAC 1200 machines have been well validated, and median beats across the 12-leads are used to minimise artefact and noise, and maximise accuracy in measurement (208-210), a key feature in the machines use when in a challenging environment in a rural community in SSA.

Digital records were visually assessed for technical errors and inadequate quality and, following exclusion of these records (n=198) along with those without P wave annotations (n=27) from the 12-SL program (including patients with AF), the number of ECG records suitable for further analysis totalled 2007.

The P wave annotations (P onset, P offset and QRS onset) of signal-averaged beats produced by 12-SL™ were adopted for further offline P wave parameter computation.

P onset (P_{ON}) was automatically annotated as the earliest across the twelve leads, P offset (P_{OFF}) as the latest. The QRS onset (QRS_{ON}) was also automatically annotated as the earliest across the twelve leads.

Based on the fiducial point markers (P_{ON} , P_{OFF}) for each lead, P wave amplitude (P_{AMP}) and area (P_{AREA}) were computed. P_{AMP} was calculated as

the peak-to-nadir amplitude difference on individual leads. Mean P_{AMP} across 12 leads ($P_{AMP} (avg)$) and P_{AMP} in lead II ($P_{AMP} (II)$) were considered for statistical analysis. Defining a baseline reference as the horizontal line intercepting the ECG at P_{ON} , P_{AREA} was computed on individual leads as the area underneath the curve with respect to the baseline, as shown in Figure 5 (grey area). Mean P_{AREA} across 12 leads ($P_{AREA} (avg)$) and P_{AREA} in lead II ($P_{AREA} (II)$) were considered for statistical analysis. If the P wave was biphasic (Figure 5.d) the positive and negative contributions to the area were summed. In lead V1, the P wave terminal negative force (P_{TNF}) was also computed as the product between the (right-most) negative lobe amplitude (Figure 5.d, dotted vertical line) in units of μV and its time interval (Figure 5.d, dotted horizontal line) in units of seconds between the (right-most) negative zero-crossing of the baseline and P_{OFF} .

P wave duration (P_D) was computed as the time interval between P_{ON} and P_{OFF} . P wave dispersion was not calculated due to the global definition of P_{ON} and P_{OFF} by the 12-SLTM program. The PR interval was calculated as the time interval between P_{ON} and the annotated QRS_{ON} . RR interval was also calculated and thus a normalised PR interval was calculated as $PR / RR * 100$ and reported as a percentage of RR (PR%).

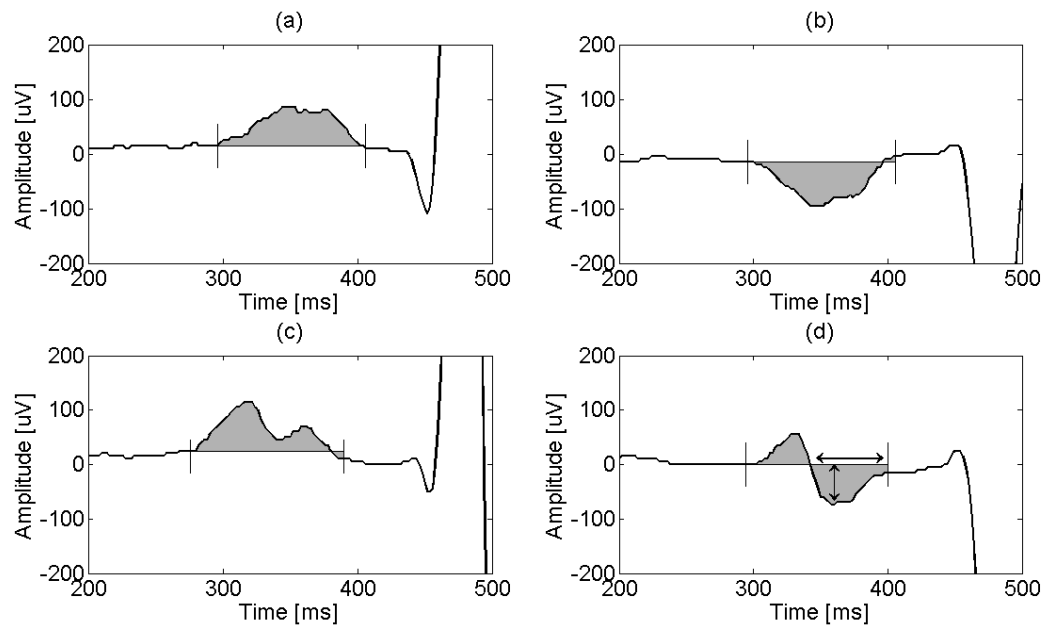


Figure 5: P wave area computation for different P wave morphologies: positive (a), negative (b), positive notched (c), biphasic (d). P wave area is total shaded area. Arrows in (d) show duration and amplitude for P_{TNF} computation. Solid vertical lines show P_{ON} and P_{OFF} .

5.1.2 P wave Indices Analysis

Statistical advice was obtained from Dr. Luigi DiMarco and Dr. Philip Langley in the Medical Physics department of Freeman Road Hospital. PWI were computed for each record and statistical analysis was carried out according to the age and gender groupings, with median and interquartile ranges reported. Further, *Lilliefors* test was performed on all age-gender groups to test the null hypothesis of normal data distribution. The test rejected the null hypothesis in a substantial number of cases therefore a non-parametric test was adopted to perform the one-way analysis of variance (ANOVA). The *Kruskal-Wallis* (KW) rank-sum test (an extension of the Wilcoxon rank-sum test for more than two groups) was employed, setting a confidence level of 95% ($\alpha=0.05$), and *post hoc* analysis for multiple comparisons was then carried out according to Tukey's honestly significant difference (HSD) criterion.

5.2 Results

5.2.1 Description of P wave Indices

Table 21 summarises the record count and the age-gender grouping.

Table 21 – Age-gender grouping of records

Gender \ Age	70-74 years	75-79 years	80-84 years	85+ years	Unknown	Total
Male	346	261	116	160	4	887
Female	437	310	184	171	18	1120
Total						2007

Effects of Age

PWI statistics with respect to age-bands are reported in Table 22, with p values representing a difference between two age groups for each PWI. Figure 7 displays the box-plot of the indices (first quartile, median, third quartile and whiskers representing the farthest sample from the box within a distance equal to the inter-quartile range) by age-band, showing multiple group comparisons for each PWI. P_{AMP} (lead II and average) was significantly lower in the 85+ age group than in the other 70-74, 75-79, and 80-84 age groups. P_{AREA} (lead II and average) was significantly higher in the

70-74 age group compared to the other 3 age groupings. Both P_{AMP} and P_{AREA} suggested a decrease in value with age. Normalised PR interval was significantly higher in the 85+ than the 70-74 and 75-79 age groups suggesting an increase with age, and RR interval significantly lower in the 85+ than 70-74 and 75-79 age groups. There were no significant differences in P_D or P_{TNF} across age groups.

Table 22 – PWI for each age-band. Median (inter-quartile range) reported

Parameter	Age Group				<i>p</i> value (*)
	70-74 Years (n=783)	75-79 Years (n=571)	80-84 Years (n=300)	85+ Years (n=331)	
P_D [ms]	112 (104-120)	112 (104-120)	111 (102-120)	110 (102-122)	N.S.
$P_{AMP}(avg)$ [μ V]	115 (97-140)	113 (92-137)	111 (93-135)	103 (87-124)	$p < 0.001$
$P_{AMP}(II)$ [μ V]	195 (155-250)	185 (145-240)	180 (143-235)	165 (125-210)	$p < 0.001$
$P_{AREA}(avg)$ [mV*ms]	4.92 (3.86-6.04)	4.60 (3.72-5.83)	4.60 (3.72-5.43)	4.26 (3.36-5.33)	$p < 0.001$
$P_{AREA}(II)$ [mV*ms]	8.97 (6.71-11.36)	8.38 (6.59-10.49)	8.18 (6.21-10.06)	7.39 (5.56-9.49)	$p < 0.001$
$P_{TNF}(V1)$ [μ V*s]	1.25 (0.53-2.16)	1.28 (0.34-2.55)	1.25 (0.47-2.14)	1.62 (0.93-2.89)	N.S.
RR [s]	0.76 (0.69-0.87)	0.76 (0.67-0.86)	0.75 (0.66-0.84)	0.74 (0.63-0.84)	$p < 0.01$
PR [ms]	150 (138-166)	152 (138-168)	154 (142-168)	158 (142-173)	$p < 0.01$
Normalised PR [%]	19 (17-22)	20 (17-23)	21 (18-24)	21 (18-25)	$p < 0.001$

(*) *p*-value from KW test, referring to null hypothesis of all samples drawn from same population

Abbreviations: P_D = P duration, P_{AMP} = P amplitude (avg=average, II=lead II), P_{AREA} = P area, P_{TNF} = P terminal negative force in lead V1. N.S. = not significant.

Effects of Gender

Table 23 details background characteristics of mean age, BP and BMI in addition to gender-specific PWI. Women had a significantly higher systolic and diastolic BP and BMI than men ($p < 0.001$). There was no significant difference in age between genders. Men had significantly greater P_D , P_{AREA} (average and lead II), RR and PR interval ($p < 0.001$) (yet the difference in

normalised PR interval between genders was not significant). Women had a significantly greater P_{TNF} than men ($p=0.030$).

Table 23 – P wave indices and background clinical characteristics (Median (Inter-quartile Range)) for male vs. female patients. Statistical significance (*p value*) of group difference (KW test, $\alpha = 0.05$) reported.

Parameter	Male (n = 887)	Female (n = 1120)	<i>p value</i>
Mean Age (years)	77.9	77.5	
Blood Pressure	N=884	N=1116	
Systolic [mmHg]	151(132 - 175)	162(141 - 190)	M<F ($p<0.001$)
Diastolic [mmHg]	82(73 - 93)	88(79 - 99)	M<F ($p<0.001$)
Body Mass Index	N=824	N=1020	
BMI [Kg/m ²]	20.0(18.0-23.0)	21.0(19.0-24.0)	M<F ($p<0.001$)
P Wave Indices	N=887	N=1120	
P_D [ms]	112(104 - 122)	110(102 - 118)	M>F($p<0.001$)
P_{AMP} (avg) [μ V]	113(95 - 136)	111(93 - 136)	N.S.
P_{AMP} (II) [μ V]	185(145 - 235)	185(145 - 240)	N.S.
P_{AREA} (avg) [mV*ms]	4.89(3.97 – 6.00)	4.52(3.59 – 5.51)	M>F($p<0.001$)
P_{AREA} (II) [mV*ms]	8.65(6.70 – 11.13)	8.21(6.08 – 10.25)	M>F($p<0.001$)
P_{TNF} (V1) [μ V*s]	1.19(0.35 - 2.13)	1.49(0.79 - 2.42)	M<F($p=0.030$)
RR [s]	0.80(0.71 – 0.90)	0.73(0.64 – 0.82)	M>F($p<0.001$)
PR [ms]	156(144 - 172)	150(136 - 164)	M>F($p<0.001$)
Normalised PR [%]	20(17 - 22)	20(18 - 24)	N.S.

Abbreviations: BP = blood pressure, BMI = body mass index, P_D = P duration, P_{AMP} = P amplitude (avg=average, II=lead II), P_{AREA} = P area , P_{TNF} = P terminal negative force in lead V1. N.S. = not significant. M>F = median value in Male population significantly higher than in Female population.

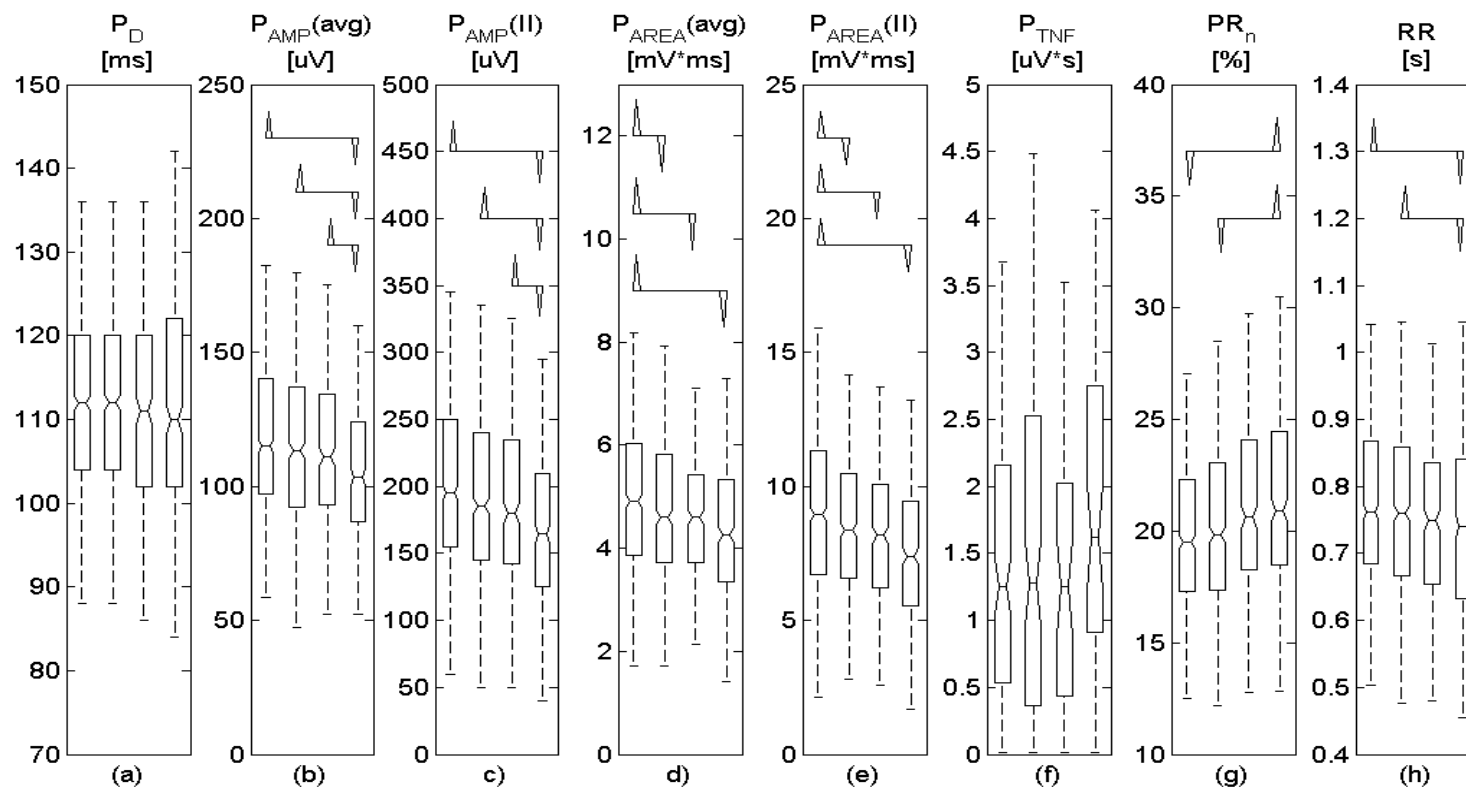


Figure 6 – Multiple comparison (Tukey HSD criterion) *post hoc* analysis of P wave indices, normalised-PR interval, and RR interval with respect to age band, combined for male and female subjects. Box-plot represents median (notched), 1st and 3rd quartile. Whiskers represent the farthest sample from the box within the inter-quartile range. Horizontal lines connect groups with significant difference ($p < 0.05$). Triangle pointing up (Δ) at the end of the line indicates group whose median is significantly higher, and down if group median significantly lower.

5.3 Discussion

5.3.1 ECG P wave Indices Descriptors / Predictors of AF

5.3.1.1 Effect of Age

P_{AREA} and P_{AMP} in both men and women exhibit a significant decrease in value with age. It has been previously suggested that autonomic tone may be related to P wave area and that during periods of sleep when autonomic tone is reduced, this is reflected by decreased P wave area (151). Autonomic tone is known to reduce with age (211) and this would be a potential explanation for a decrease in P wave area seen with age in our population. Age-related loss of atrial myocytes and thus decreased volume of electrically-active atrial tissue, reflected in smaller velocity P waves may further explain the decline in values with age.

With the knowledge that advancing age (37, 39) and increased P wave area (153) increases the risk of AF, it seems paradoxical that P wave area decreases with age in the Study Population. However, it should be remembered not only that P wave area predicted AF in a population of 45-64 year olds in a high-income country (153) and therefore may not be applicable to our population, but also that age and PR interval (which increases with age and is also known to increase risk of AF (156)) are likely to be more potent risk factors in the Study Population.

Normalised PR interval increases in both men and women with age in my study and this is likely to be because of gradual fibrosis of intra- and inter-atrial conduction fibres. It has previously been noted that the prevalence of 1st degree heart block increases with age (212). The prevalence of 1st degree heart block (PR >200ms) in the Study Population was 3.6% (73/2007), similar to another community-based study in the elderly (75-85 years) in the US (213) reporting a prevalence of 2.1%, but lower than a hospital-based elderly (70+ years) population (11.7%) (212).

In the Study Population, P duration did not change significantly with age. Previous work has suggested an increase in P_{D} with age when looking at a broader age range in smaller numbers of people (214), although examining this data more closely reveals that in similar age groups (i.e. 66-75 and 76-85 year olds) there was no significant change in P_{D} , as in my study.

5.3.1.2 Effect of Gender

My study also demonstrates significant differences in PWI with respect to gender. Men had higher values than women for P duration and P area. Men are known to have larger atrial diameters than women (215). Furthermore, median BMI was lower in men (20.0 (18-23) kg/m²) than women (21.0 (19-24) kg/m²) in my study overall, potentially reflecting lower impedance of body mass between electrodes and cardiac signals, and these are potential reasons for larger PWI in men.

The finding of generally larger PWI in men provokes discussion around the effect of hypertension on PWI, given the fact that women had a higher mean BP than men. Hypertension has been shown to increase P_D (216), yet women had a smaller P_D than men. However, P_{TNF} was greater in women than men, and is likely to be a more sensitive predictor of systemic hypertension, having been well-validated for inclusion in criteria for assessing left ventricular hypertrophy (217).

Median PR interval was longer in men than women, consistent with a previous large multi-centre study (218), although, unlike in my study, that study did not normalise PR for heart rate. In doing so, I found that, because women had higher heart rates than men overall, when PR was normalised for RR interval, there was no gender difference.

5.3.1.3 Comparison with Other Populations

I have not directly compared my numerical data to other studies, either because of a lack of age-specific data, or a difference in measurement methodology, particularly with regards calculating P wave area (153). The latter point has been noted as a particular problem in comparing studies (219), and I have focused on presenting new data from elderly Tanzanians and, in comparing to other studies, looked simply at trends with respect to age and gender. What is clear is that my Study Population is different genetically and environmentally from other populations studied and further work is needed to look at 'normal values' in my Study Population. It is known that factors such as chronically elevated atrial pressure, ischaemia and metabolic stress lead to atrial remodelling and thus changes in atrial conduction and P wave morphology on the surface ECG (219). It is also known that ischaemic heart disease is less common in black Africans in SSA

than in high-income countries (80). Furthermore, hypertension prevalence rates are approaching that of high-income countries and yet detection, treatment and levels of control are much lower (220). These points suggest the prevalence of factors influencing PWI in an elderly SSA population are likely to be very different from those of other populations already studied and thus that reference ranges for PWI derived from other populations are not valid for my Study Population.

5.3.1.4 Strengths and Limitations

My study has several strengths. It contains a large sample size that has been randomly selected within a rural African community-based population. All study variables were ascertained uniformly, and of particular note, the ECGs were analysed with computer assistance, thus minimising intra- and inter-observer variability. My analysis did not exclude outliers and thus gives a more balanced overall picture of PWI.

There are also several limitations noted. Specifically with regard to my study, as I only surveyed approximately 25% of the 70+ population, there is a possibility of sample bias, despite the randomly-selected nature of the Study Population.

The measurement method meant my data produced PWI calculated from a median P wave, rather than each individual P wave on the 12-lead ECG. The reason for doing this is that P_{ON} and P_{OFF} were more reliably identified as the production of a median beat eliminates a significant amount of baseline 'noise'. This comes at the expense of data from each individual lead and the ability to calculate PWI such as maximum and minimum P_D and P wave dispersion.

The median differences with age and gender were all fairly small in a clinical sense. Whilst many were statistically significant, it should be remembered that the differences are unlikely to be clinically significant. However, my primary aim for this study was not to look at clinical impact of the changes, but simply initially to report them. I foresee that these results will be the precursor to the production of reference ranges for an elderly SSA population and in the future be used to predict disease states such as AF.

5.4 Conclusions

To my knowledge, this will be the first published report of PWI in a large community-based elderly population in SSA. There are significant differences in PWI with gender and age in my study. This population is geographically and genetically different from other populations studied and thus it will be interesting to note whether PWI predict diseases such as AF and stroke in this population. However, in a low-income country such as Tanzania, where healthcare resources are limited, yet the number of elderly with chronic disease continues to grow exponentially, measurement of PWI may form an important, accessible and ultimately affordable part of risk assessment for these diseases in the future.

Chapter 6. Ambulatory Monitors

6.1 Methods

6.1.1 Longer-term Cardiac Monitoring

For the purposes of ambulatory ECG monitoring, the study used 2 Holter (full-disclosure, 24 hour) monitors, and 10 event (selective disclosure with limited memory, up to 7 day) recorders. The first Holter monitor was a Mortara H-Scribe™ (Mortara Instruments, Milwaukee, US) 12-lead Holter monitor, and the second a Darwin Medilog AR12 HRV™ (Schiller, Australia) 3-lead Holter monitor. The longer-term event recorders were Novacor R-test Evolution™ (Novacor, France) monitors. The recorders were chosen as they have been shown to be superior to 24-hour monitors in identifying episodes of PAF (221) over longer periods, are automated and therefore particularly useful in identifying asymptomatic episodes of PAF (222) and have been shown to have good accuracy at detecting episodes of PAF (223), with a sensitivity of 96.1% and specificity 92.6%. The monitors have a total recording time of 20 minutes and were programmed to store irregular R-R intervals that could correspond to paroxysms of AF. The parameters for event-triggered recordings were: 50 s for absolute pauses (RR interval >2.5s); 175s for relative pauses (RR interval >150% previous RR interval); 500s for premature beats (RR interval <[mean RR-12.5% x mean RR]); 60s for bradycardia (R frequency <50 minutes⁻¹); 250s for runs (RR interval <RR-12.5% x RR] for > 3 beats); and 30s for ST shift (<1mm or >3mm). 120s were devoted to patient-triggered recording but as the majority of patients were asymptomatic this was under-utilised. These settings have been previously validated for the detection of PAF (224). The enumerators were given an introduction to these ambulatory monitors and were shown how to do basic troubleshooting such as changing electrode stickers that may become detached during monitoring. Whilst the event recorders have been previously shown to increase AF detection rates, they do not have full disclosure as with the 24-hour tapes. The memory of the event recorders extends to 20 minutes for the purposes of recording arrhythmias. If the memory becomes full, then the most recent arrhythmias (i.e. later in the

recording) will be stored. However, whilst the recorder may not formally 'record' an arrhythmia, it can give an idea of arrhythmia burden as it will record the number of arrhythmia events 'seen' in each category. Because the recording strips are of 30 seconds length, if the arrhythmia is longer than that, it will not necessarily trigger a further 'seen event', so may underestimate arrhythmia burden. Of course the arrhythmia may well last less than 30 seconds but there is no way of analysing this from the recordings. Because I cannot say exactly how long each person had arrhythmia for, I feel the most useful way of presenting the results is to say how many 30 second periods per 24 hours of recording had arrhythmia present, and in this context I will focus mainly on irregular narrow complex tachycardia (NCT) i.e. PAF and PAFI. Whilst I will be unable to document an accurate delineation of how much PAF each person has, this will not be the primary aim of this section. This will be to further examine whether P wave indices influence / predict occurrence of PAF in these patients. From a clinical importance perspective, as I am adopting a conservative time of 5 minutes in any 24 hour period being clinically important (as delineated from the literature, see introduction), this will equate to anyone who has more than 10 thirty-second periods with irregular NCT per 24 hours.

6.1.2 Choice of Participants

The study aimed to perform ambulatory monitoring in a sub-group of the Study Population. With regard to 24-hour monitoring, participants were chosen primarily on a pragmatic basis using convenience sampling. It was not possible to choose these patients entirely at random given the logistics of being in different villages on a daily basis, and participants' reluctance not only in wearing the monitors but also coming back to the health centre to have the monitor detached when they often lived long distances from the health centre and were busy with work. With regard to the R-test monitors, I produced a scoring system for P wave predictors, meaning each ECG could be classified as having a low, intermediate or high number of P wave predictors for subsequent AF development. The scoring system was based primarily on the paper by Soliman et al (153) in Stroke, with scores for each P wave predictor weighted according to their hazard ratio in that paper. In addition to these measurements, I also included PDISP (225) and PR

interval (156) in the scoring system. The table below shows which P wave measurements were used and their weighted scoring.

Table 24: Scoring System for P wave Indices

P wave Predictor	Weighted Scoring
P wave duration lead II	4
P wave terminal force V ₁	2
Maximum P wave duration	4
P wave dispersion (maximum – minimum P wave duration)	3
Maximum P wave area	2.5
PR duration	1.5
Max Total	17

This scoring system enabled me to divide the ECGs into low, intermediate and high numbers of P wave predictors. The divisions were arbitrary, with <6 points scoring low, 6-12 points intermediate and >12 points high. The idea behind this scoring system is that P wave predictors are on a continuum, rather than being absolute values and if I split the ECGs up solely into those with and those without P wave predictors, I would have been likely to miss out on a lot of detail within the group with P wave predictors. The other idea behind the system was to enable me to try and perform equivalent numbers of event recordings on those in all 3 groups. I did not however have the luxury of taking ECGs back from the field and analysing them on the computer prior to putting the event recorders on because of the aforementioned problems of getting participants back to the health centre on more than one occasion. Therefore, the initial screen of the ECG was an examination by me in the field for known P wave predictors.

6.1.3 Case definition of PAF

Short runs of regular and irregular narrow-complex tachycardia are common in the elderly, and hence the suggested cut-off for describing AF of a minimum of 30 seconds continuous irregular narrow-complex tachycardia. Paroxysmal AF is self-terminating, usually within 48 hours. Although AF paroxysms may continue for up to 7 days, the 48-hour time point is clinically

important—after this the likelihood of spontaneous conversion is low and thromboembolic risk rises substantially. In the results and discussion I use the terms ‘irregular NCT’ and ‘AF’ interchangeably, acknowledging the fact that according to the strict definition, the irregular NCT has to be >30 seconds in length to be classified as AF, yet the episodes that I will be discussing are often <30 seconds in length. This is due to the generally smaller burden of AF seen on ambulatory monitoring.

6.1.4 How Much PAF is Clinically Important?

Data from the Italian AT500 registry looking at PAF detected by anti-tachycardia pacemakers and the subsequent risk of thromboembolism in 725 patients (226) suggest that episodes of AF lasting >24 hours increase risk of arterial embolism by 3.1 times in elderly patients. Episodes >5 minutes and <24 hours made no difference to risk. This concurs with data from the AIDA study (227). Data from the more recent TRENDS study (228) looking at 2486 patients with dual-chamber pacemakers and at least 1 risk factor for stroke, found that a burden of atrial tachycardia or AF \geq 5.5 hours per 24-hour period doubled risk of thromboembolism. The 5.5 hours was cumulative and did not have to occur in 1 single episode.

However, 2 further trials have demonstrated much lower levels of detected atrial tachycardia are needed to increase stroke risk. In the Mode Selection Trial (MOST) (229), atrial high rate episodes (AHREs) detected by pacemaker in 312 patients with sinus node dysfunction were looked at in correspondence with the subsequent risk of stroke and death. Of the 312 patients, 160 (51.3%) had at least 1 AHRE >5mins over a median 27 months of follow-up. The presence of 1 AHRE >5mins increased risk of mortality by 2.48 times and stroke 2.79 times. In the Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT) (230), 2580 patients were followed-up for a mean of 2.8 years. AHREs were common, occurring in 36% overall. AHREs >6 minutes were associated with a 2.5-fold increase in the risk for stroke and systemic embolism. It should be noted that whilst numbers in the MOST trial were fairly small, the number in ASSERT and length of follow-up was much better.

The reason for use of 5 and 6 minutes cut-off is that these are the accepted cut-off values for the respective pacemakers in accurately detecting AHREs. Suggestions arising from these study results include whether even shorter episodes may predispose to arterial embolic events and that AHREs appear to be an appealing surrogate for PAF to facilitate such studies (231).

6.1.5 Treatment Decisions for PAF

Based on the above data, I decided that a pragmatic cut-off for treatment with aspirin for PAF would be >5minutes in every 24-hour period, and the treatment dose was 75mg od.

6.1.6 Analysis

As previously mentioned, the 24-hour monitors were full-disclosure, whilst the event recorders had a finite memory for automatic arrhythmia detection. Manual analysis of the recordings was combined with automatic reports generated by the recorders themselves, and the results are presented below, with mean values and 95% confidence intervals reported for the more important results.

6.2 Results

3 different ambulatory monitors were used to collect data on longer term cardiac rate and rhythm monitoring in a sub-set of patients chosen during the main study, as detailed in the methods. They were mainly used to identify the burden and prevalence of paroxysmal AF in the background population and this results section will concentrate mainly on that, but will also report other interesting findings.

6.2.1 24-Hour Tapes

47 patients, chosen on a pragmatic basis, underwent Holter recording with the Mortara H-Scribe™ (H-Scribe) and 49 with the Medilog Darwin AR12 HRV™ (Medilog). With regard to the H-Scribe, 35 patients were women and

12 were men, with a mean age of 77.7 years. With regard to the Medilog, 34 patients were men and 15 were women, with a mean age of 79.6 years. This totalled 50 women and 47 men undergoing full disclosure Holter monitoring. The table below details mean recordings for duration, heart rate, supra-ventricular ectopics (SVEs) and ventricular ectopics (VEs) and pauses.

Table 25 Overall Averaged Results of Holter monitoring

Recorder	Number of Records	Duration	Heart Rate (bpm)			SVEs			VEs		
			minutes	Min	Mean	Max	Runs <3	Runs ≥3	Max Run	Runs <3	Runs ≥3
H-Scribe	47	1282.7	52.5	78.3	128.7	869.1	20.7	108.4	678.4	0.17	2.42
Medilog	49	1701.2	51.2	77.7	137.7	513.1	5.9	8.2	203.1	0.14	1.75

Of the patients undergoing monitoring with H-Scribe, 5 patients had evidence of irregular runs of narrow-complex tachycardia (NCT) that looked like AF. However, the burden of this arrhythmia was low, as detailed in the table below.

Table 26 Burden of irregular NCT in individual patients undergoing H-Scribe monitoring

Patient (gender + age)	Recording Duration minutes	Heart Rate (bpm)			SVEs			Pauses
		Min	Mean	Max	<3 beats	≥3 beats	Max run (beats)	seconds
1 (F 71)	1390	40	65	136	40	3	11	1.7
2 (F 73)	1293	46	70	127	66	3	5	1.47
3 (M 84)	1318	58	78	132	3418	6	23	1.34
4 (M 76)	1440	42	69	135	87	3	4	1.84
5 (F 86)	1440	48	70	131	1163	48	33	1.64

Patient 5 appeared to have the heaviest burden of irregular NCT, but whilst her longest run of NCT was 33 beats (15 seconds), the remaining 47 runs ≥3 beats were all <5 secs, meaning she had <5 minutes in total of irregular NCT over a 24-hour period.

Of those undergoing Medilog monitoring, there were also 5 patients who suffered irregular NCT, details of which are in the table below.

Table 27 Burden of irregular NCT in individual patients undergoing Medilog monitoring

Patient (gender + age)	Recording Duration minutes	Heart Rate (bpm)			SVEs		Pauses	
		Min	Mean	Max	<3 beats	≥3 beats	Max run (beats)	seconds
1 (F 72)	1390	46	72	143	148	6	40	0
2 (M86)	1279	57	83	137	110	1	15	0
3 (F 76)	2487	46	90	170	2553	147	101	1.45
4 (F 72)	1605	66	98	164	327	41	13	0
5 (F 83)	2206	51	73	127	167	7	11	0

As can be noted, again the burden of irregular NCT was light, apart from for patient 3, who had a significant burden of paroxysmal AF. Whilst it should be noted that her recording was longer than others (totalling over 41 hours) the 147 runs of AF were mostly up near the max run of 101 beats (approx 40 secs at a rate of 150 bpm), thus giving her a burden much higher than our proposed cut-off of 5 minutes in 24 hours.

In addition to the irregular NCTs, there were 4 cases with regular runs of NCT in the H-Scribe group (none in the Medilog group), although none of which resembled atrial flutter. The burden is detailed in the table below.

Table 28 Burden of regular NCT in individual patients undergoing H-Scribe monitoring

Patient (gender + age)	Recording Duration minutes	Heart Rate (bpm)			SVEs			Pauses seconds
		Min	Mean	Max	<3 beats	≥3 beats	Max run (beats)	
1 (F 86)	1349	45	82	163	7420	526	13	2.34
2 (F 80)	1440	49	105	159	79	75	157	1.6
3 (F 101)	1440	50	82	163	15277	195	51	1.39
4 (F 70)	1440	68	106	203	49	41	4628	1.22

Whilst trying to classify further the regular NCT, it appeared patient 1 had multi-focal atrial tachycardia, patients 2 and 4 appeared to have AV nodal re-entrant tachycardia and it was difficult to further classify patient 3 due to

quality of recording. Clearly, patient 4 appears to have the heaviest burden of SVT, and she was the only one of the 4 to be symptomatic from her arrhythmia.

6.2.2 Event Recorders

137 event recordings were performed on 75 men and 62 women with an average age of 77.0 years. The following table shows mean values for recording time, total number of SVEs and VEs (isolated, short runs 2-5 beats and longer runs >5 beats) recorded AND seen (see methods) and longest pause.

Table 29 Overall mean values for event recordings

Number of recordings	Length of recording (hours)	SVEs isolated	SVE short runs	SVE long runs	VEs isolated	VE short runs	VE long runs	Pauses (seconds)
137	90.03	1410	296	34	1073	167	6	1.20

Of the 137 recordings performed, 29 (21.2%) showed evidence of irregular NCT (including Atrial Flutter) of which 17 were men and 12 were women. The table below shows further details of this group.

Table 30 Characteristics of group with irregular NCT on event recording, mean values

Recording number	Recording Length (hours)	SBP	DBP	BMI	BI	SVEs isolated	SVEs short run	SVEs long run	No. 30 sec periods containing AF (total)	No. 30 sec periods containing AF / 24 hours	Longest Pause (secs)
29	104.25	166.4	89.1	21.5	19.6	3050	969	131	130.7	23.25	1.55

It should be noted that only 5 (3.6%) recordings had a potential burden of PAF >5 minutes / 24 hours i.e. 10 thirty-second periods that contained irregular NCT. These 5 recordings are responsible in the main for the relatively high mean value of 23.25 for number of 30 second periods containing AF / 24 hours. Without these 5 recordings, the mean values for

total number of 30 second periods containing AF and number per 24 hours would reduce dramatically to 5.96 and 0.82 respectively.

Further details of these 5 patients are contained in the table below.

Table 31 Patients with >10 thirty-second periods containing AF in 24 hours

Patient (Gender / Age)	Recording Length (hours)	SBP	DBP	BMI	BI	SVEs isolated	SVEs short	SVEs long	No. 30 sec periods containing AF (total)	No. 30 sec periods containing AF / 24 hours	Max Pause (secs)
1 (M77)	141.52	147	74	17.6	20	3851	363	115	115	19.4	2.0
2 (F80)	138.24	221	125	26.6	19	655	380	104	104	18.06	1.76
3 (M73)	134.56	120	72	20.2	20	25877	14476	1481	1481	264	2.08
4 (F85)	142.4	156	104	23.3	20	7282	6896	1307	1307	220.4	5.2
5 (M77)	136	130	66	18.8	20	15986	3023	640	640	112.86	1.44

As previously mentioned, I attempted to put event recorders on patients with an even spread of degree of P wave ‘predictors’ of AF. This was initially done fairly crudely in the field as specified in the methods section, with subsequent manual measurement on a computerised screen with a cursor through the Cardiosoft V4.2™ program. Of the 137 recordings, 100 were manually measured, with 29 considered to have a high score on the P wave predictors scoring system (methods), 39 a medium score and 32 a low score, which provides an even spread given the limitations of the initial method of visual measurement. Reasons for non-measurement via Cardiosoft™ were either that the ECG was not stored digitally, the quality was not deemed sufficient for accurate measurement, or the digital ECG file was corrupt at the time of attempted measurement.

6.2.3 Overall Prevalence of PAF

The prevalence of PAF, using a definition of ≥1 episode of irregular NCT >30 seconds in length, in this study would be 5/137 (3.6% (95% CIs 0.5 to 6.7)) for the event recorders and 1/96 (1% (95% CIs -2.1 to +3.1)) for the Holters. If we combine these numbers then the overall prevalence of PAF in this

study totals 6/233 which is 2.6% (0.6 to 4.6). The percentage of people with no PAF therefore is 227/233 which is 97% (94.8 to 99.2) of the cohort.

6.2.4 Relationship of P wave Indices to Ambulatory Monitor Findings

Subsequent to the 'rough' delineation of 'P wave predictors' in the field, the ECGs of patients undergoing both Holter and Event Recorders were analysed digitally through Cardiosoft™ and 12-SL™ to look more closely at P wave indices. A comparison was made between the P wave indices of those patients with evidence of irregular NCT (i.e. AF) and those without, on both Holter and Event recorder, as shown in the tables below. Records with missing P wave annotations have been excluded, as detailed in the tables.

Table 32 – P wave parameters (Median (Inter-Quartile Range)) for patients undergoing Holter monitoring with and without evidence of AF.

Parameter	Irregular NCT N = 9	Others N = 79	<i>p value</i>
Pd [ms]	112(107 - 129)	112(102 - 122)	N.S.
Pamp(avg) [μV]	115(94 - 134)	113(98 - 144)	N.S.
Pamp(II) [μV]	170(150 - 228)	190(135 - 240)	N.S.
Parea(avg) [μV*ms]	4978(3699 - 5957)	4898(3988 - 5955)	N.S.
Parea(II) [μV*ms]	8380(6435 - 9820)	8480(6575 - 11225)	N.S.
Ptnf(V1) [μV*s]	1.76(0.00 - 0.00)	1.37(0.42 - 2.39)	N.S.
PR [ms]	142(129 - 156)	158(142 - 179)	N.S.
RR [ms]	807(682 - 921)	770(689 - 899)	N.S.
Norm. PR [%]	18(16 - 20)	20(17 - 24)	N.S.

Pd = P duration, Pamp(avg) = mean P wave amplitude (across 12 leads), Parea(avg) = mean P wave area (across 12 leads), Ptnf = P wave terminal negative force, PR = PR interval (Pon to QRson). P value reported for KW test ($\alpha=0.05$), N.S. = not significant.

Table 33 – P wave parameters (Median(Inter-Quartile Range)) for patients undergoing Event Recording with and without evidence of AF

Parameter	Irregular NCT N = 26	Others N = 104	<i>p value</i>
Pd [ms]	117(106 - 130)	112(105 - 122)	N.S.
Pamp(avg) [μV]	119(82 - 153)	119(100 - 151)	N.S.
Pamp(II) [μV]	208(120 - 275)	210(160 - 273)	N.S.
Parea(avg) [μV*ms]	5245(3535 - 6164)	5224(4111 - 6991)	N.S.
Parea(II) [μV*ms]	9485(6030 - 11830)	9770(7275 - 12325)	N.S.
Ptnf(V1) [μV*s]	0.87(0.39 - 2.44)	0.98(0.19 - 2.96)	N.S.
PR [ms]	158(146 - 170)	158(146 - 170)	N.S.
RR [ms]	736(637 - 841)	759(674 - 843)	N.S.
Norm. PR [%]	22(18 - 27)	21(18 - 24)	N.S.

Pd = P duration, Pamp(avg) = mean P wave amplitude (across 12 leads), Parea(avg) = mean P wave area (across 12 leads), Ptnf = P wave terminal negative force, PR = PR interval (Pon to QRson). P value reported for KW test ($\alpha=0.05$), N.S. = not significant

As can be seen from the tables, none of the P wave indices appeared to be significantly different between the group suffering from irregular NCT and those without.

However, if we look in more detail at those patients undergoing event recordings and divide the group having irregular NCT (n=26) into those with >5 minutes of PAF / 24 hours (n=4 as 1 ECG not analysable) and those with <5 minutes PAF / 24 hours (n=22), then, comparing the group with clinically significant PAF to those with <5minutes per 24 hours (Table 33) or those without any evidence of irregular NCT (Table 34), it can be seen that the group with >5 minutes of PAF per 24 hours has a significantly longer P_D than the other 2 groups, and a non-significant increased PR interval. In comparison to the group with <5 minutes PAF, there is also a significantly larger P_{TNF}, and a significantly smaller P_{AMP} and P_{AREA} in lead II. In comparison with the group with no irregular NCT, there is a significantly smaller P_{AMP} average and in lead II, and significantly smaller P_{AREA} in lead II.

Table 34 PWI (Median (Inter-Quartile Range)) for patients undergoing event recorders with >5minutes PAF / 24 hours of recording versus those <5 minutes / 24 hours

Parameter	<5mins PAF / 24 hours N = 22	>5mins PAF / 24 hours N = 4	p value
Pd [ms]	113(105 - 125)	134(127 - 136)	NCT<NCT5+(<i>p</i> =0.027)
Pamp(avg) [μV]	121(86 - 155)	74(58 - 111)	N.S.
Pamp(II) [μV]	213(143 - 280)	80(68 - 155)	NCT>NCT5+(<i>p</i> =0.028)
Parea(avg) [μV*ms]	5344(3829 - 6483)	3655(2347 - 5338)	N.S.
Parea(II) [μV*ms]	9710(7255 - 11995)	4525(3170 - 6925)	NCT>NCT5+(<i>p</i> =0.016)
Ptnf(V1) [μV*s]	0.63(0.39 - 1.20)	2.97(2.44 - 0.00)	NCT<NCT5+(<i>p</i> =0.017)
PR [ms]	156(146 - 168)	184(155 - 212)	N.S.
RR [ms]	736(637 - 841)	732(594 - 836)	N.S.
Norm. PR [%]	22(18 - 25)	29(22 - 31)	N.S.

Pd = P duration, Pamp(avg) = mean P wave amplitude (across 12 leads), Parea(avg) = mean P wave area (across 12 leads), Ptnf = P wave terminal negative force, PR = PR interval (Pon to QRson). P value reported for KW test ($\alpha=0.05$). NCT= <5minsPAF/24hours. NCT5+= >5minsPAF/24hours

Table 35 PWI (Median(Inter-Quartile Range)) for patients undergoing event recorders with >5minutes PAF / 24 hours of recording versus those with no irregular NCT

Parameter	Clinically Significant PAF N = 4	No Irregular NCT N = 104	<i>p value</i>
Pd [ms]	134(127 - 136)	112(105 - 122)	NCT5+>NC T-(<i>p</i> =0.007)
Pamp(avg) [μV]	74(58 - 111)	119(100 - 151)	NCT5+<NC T-(<i>p</i> =0.037)
Pamp(II) [μV]	80(68 - 155)	210(160 - 273)	NCT5+<NC T-(<i>p</i> =0.014)
Parea(avg) [μV*ms]	3655(2347 - 5338)	5224(4111 - 6991)	N.S.
Parea(II) [μV*ms]	4525(3170 - 6925)	9770(7275 - 12325)	NCT5+<NC T-(<i>p</i> =0.011)
Ptnf(V1) [μV*s]	2.97(2.44 - 0.00)	0.98(0.19 - 2.96)	N.S.
PR [ms]	184(155 - 212)	158(146 - 170)	N.S.
RR [ms]	732(594 - 836)	759(674 - 843)	N.S.
Norm. PR [%]	29(22 - 31)	21(18 - 24)	N.S.

Pd = P duration, Pamp(avg) = mean P wave amplitude (across 12 leads), Parea(avg) = mean P wave area (across 12 leads), Ptnf = P wave terminal negative force, PR = PR interval (Pon to QRson). P value reported for KW test ($\alpha=0.05$). NCT- = no NCT, NCT5+ = >5minsPAF/24hours

6.2.5 Other Findings of Note

With respect to the Holter monitors, there was 1 patient who had Wenkebach (Mobitz type I) and 2 patients with Mobitz type II. There was also 1 patient who had ventricular standstill (i.e. non-conducted P waves with no escape rhythm) for 9.9 seconds. Surprisingly, particularly with the last case, the patients were asymptomatic and the bradyarrhythmias were mainly nocturnal. This clearly raises ethical issues in a resource-poor country about doing Holters on asymptomatic patients and this is discussed in section 2.10. With respect to the Event Recorders, 1 patient had Wenkebach and 1 patient had complete heart block. Latterly, the patient had a regular ventricular escape rhythm of 32 bpm. Again, the patients both denied having any symptoms and were given advice as in section 2.10.

6.3 Discussion

The two main reasons for performing ambulatory monitoring in a subgroup of my Study Population was to document the prevalence of PAF (i.e. that which is not picked up on 12-lead ECG), and also to look at P wave indices in the ambulatory monitor group to see if there were any PWI that might predict PAF. I will focus on the former in this section and the latter is discussed below in section 6.3.2.

The first thing to say about reporting prevalence of PAF is that it is difficult. Up to 90% of episodes of PAF may be entirely asymptomatic (232) (233), including some lasting >48 hours (233), yet PAF may be responsible for up to 25% of all AF (234). Thus the patient is unaware of the episode and therefore does not present for 12-lead ECG. In addition, no single ambulatory monitor, be it internal or external, is perfect. There is a trade-off between length of recording and disclosure i.e. a full disclosure monitor, when examined by a trained operator, is more likely to be able to detect all episodes and be able to quantify AF burden over a 24 hour – 7 day period whereas, if it is not full-disclosure, it becomes more difficult to quantify exact amounts of PAF. However, we also know that the longer the recording, the greater the chance of actually detecting some PAF in the first place, usually requiring a monitor that does not provide full disclosure and relies upon computer algorithms to ‘detect’ and record PAF. Neither method is perfect and it has been estimated that PAF may be documented in ~70% of patients suffering from the arrhythmia with ambulatory monitoring, with a fairly poor negative predictive value (for the absence of AF) of 30-50% (32).

Despite these problems and the fact that performing ambulatory monitoring tends to be time-consuming and expensive with regard to resources, there are several epidemiological studies reporting on PAF but mainly in smallish numbers and reporting mainly on general ambulatory monitor findings rather than specifically on PAF.

6.3.1 Comparison to other populations

A study from Greece (235) looked at AF incidence in patients presenting to hospital with AF that lasted <7 days and was not associated with any acute illness. They found an incidence of 7.2/10,000/year in men and 5.3/10,000/year in women. There were more incident cases in men and they

occurred at a younger age on average. The incidence increased with age. It must be pointed out that this is likely to be a significant under-estimation given they only included patients who were symptomatic and therefore presented to hospital.

A UK study (236) looking at almost 2000 patients aged 40-89 years with AF in a GP research database, found that 525 (27.8%) on further classification had PAF. The authors calculated this to be equivalent to an incidence rate of 1.0 per 1000 patient years.

A study looking at the prevalence of PAF post-acute stroke using different methods of detection looked at 149 patients (224). AF was detected in 22 patients overall (14.8%), with 12 (8% of total stroke patients) of these having PAF and thus only being identified using either Holter (7 patients – 4.7%) or external loop recorder (5 patients – 3.3%). A further study looking at 413 stroke / TIA patients undergoing Holter monitoring (237) found that PAF occurred in 39 (9.2%) patients, but only lasted >30 seconds in 11 (2.5%) patients, with the remaining 26 having PAF <30 seconds over a mean recording length of 22.6 hours.

A study in *Chest* in 1982 (238) looked at 98 healthy elderly patients aged 60-85 undergoing 24-hour Holter recording. They noted that paroxysmal atrial tachycardia occurred 22 times in 13 (13%) patients, with only 1 patient showing a 2 second run of atrial flutter and no observed PAF.

The Bronx Aging Study (213) looked at 423 independent, community-dwelling subjects aged 75-85 undergoing 24-hour ambulatory cardiac monitoring. They noted 17 patients (4%) with evidence of AF on their recording, although 14 subjects had evidence of AF on their 12-lead ECG and therefore only 3 patients (0.6%) of the sample had PAF unidentified on 12-lead ECG. The authors do not further describe the burden of that PAF.

A community-based study from Finland (239) performed ambulatory monitoring on an elderly population (aged 65+) of 162 subjects and found AF in 5 (3.1%) but it is not clear how many patients were known to have AF on 12-lead ECG and therefore how much of the AF was paroxysmal, as the focus of the paper was more towards general findings on ambulatory monitoring and risk of death.

The Cardiovascular Health Study (240) looked at 1512 randomly selected 24 hour monitors in participants aged 65+. Sustained AF (i.e. already identified

on 12-lead) was present in 1.7% of women and 2.5% of men, whilst intermittent AF (just picked up on 24 hour monitoring) was present in 1.1% of women and 0.8% of men.

It is difficult to compare my Study Population directly to these other studies given differences in methodology, particularly with respect to ambulatory monitors used and background characteristics of the populations studied. Having said this, it would appear that my results are fairly similar to these other studies when comparing Holter monitors, given 1/96 (1.0%) of patients undergoing 24-hour recording demonstrated runs of irregular NCT >30 seconds in length that would be classified as PAF.

There are very few studies in the literature reporting prevalence of PAF using non-invasive event recorders such as the ones I used (Novacor R-test EvolutionTM) and, again, it is therefore difficult to see how my results compare to other populations. However, the majority of studies are in post-stroke patients and have reported an increased prevalence / detection rate of PAF in event recorders over 24 hour monitors (224). It would therefore stand to reason that the prevalence of PAF in patients undergoing event recordings is higher, at 3.6% (5/137), than those undergoing Holter. Obviously my results are limited to a degree by the low overall number of recordings. With regard to how much PAF is clinically significant from the point of view of increasing stroke risk sufficiently that formal anticoagulation should be considered, again it is difficult to say. Studies come mainly from cohorts of patients with permanent pacemakers (226, 228-231, 233) with AF detection algorithms, using a surrogate of atrial high rate episodes (AHRE) for AF, shown to be 'tantamount' to AF (231). These cohorts are by nature a fairly specific, self-selecting group with known cardiac conducting disease, and there have been no community-based studies looking at PAF and stroke risk in the general population. In addition, these studies differ with how much PAF they consider to be clinically important. The range is from 5 minutes in a 24 hour period (i.e. 1 AHRE detected) (229) up to >24hours continuous paroxysm (226) (227). I decided beforehand to adopt the more conservative estimate from the MOST trial of 5 minutes in a 24 hour period as a treatment threshold for aspirin, given the fact that my patients were elderly and the majority were hypertensive, and thus at high risk of stroke (anti-hypertensives were also prescribed in patients with BP>160/100). As

mentioned previously, because the event recorders were not 'full disclosure', the 5 minute period was estimated from the number of 30 second periods in 24 hours that irregular NCT was observed. If there were >10 periods, they received treatment if there were no contraindications. I aim to follow up my ambulatory monitor patients as currently I have no data on how much PAF increases stroke risk in the Study Population and, as mentioned above, it may be that elderly black Africans are more susceptible to a lower burden of PAF.

Comparing the results of the two Holter monitors, the mean recording length was 419 minutes (33%) longer with the Medilog monitor than H-Scribe. The mean heart rates were very similar, yet there were many more SVEs (isolated and runs) and VEs (runs <3 beats) in the H-Scribe population. It is noted that there were more women than men in this group and this is one potential reason for the difference but it is probably more likely to reflect the differences in the detection algorithms for each monitor.

6.3.2 P wave Indices and PAF

It is interesting to note that in the group of patients with evidence of >5mins in 24 hours of PAF, that P wave duration was significantly longer than in the groups with <5mins/24 hours (21ms) and also those without evidence of NCT (22ms). It is also interesting to note that only the group with >5mins PAF per 24 hours had a median value >120ms (134ms). The other 2 groups had median values <120ms (113ms for the group <5mins PAF per 24 hours and 112ms for group without PAF). It has been previously noted by Soliman et al (153) that maximum P_D and P_D in lead II are the strongest predictors of incident AF (HR 4.07 and 3.90 respectively) in their study looking at PWI and prediction of PAF and stroke. There are several other papers (225, 241, 242) that agree with my finding of an increased P_D being more common in patients with evidence of PAF. The DeBacquer study notes, similarly to mine, that a cut-off of 120ms seems to separate patients with AF ($P_D \geq 120ms$ present in 71%) and without (present in 41%). However, they also note that this is only when combined with morphologic changes such as notched or deflected P waves, whereas other studies (153, 225, 241) comment on the effect of P_D alone. It is also worth making clear at this stage that the other studies have used maximum P_D and P_D in lead II, whereas in my study it was

a signal averaged- median beat averaged over the 12 leads that predicted PAF, not previously noted in the literature.

With regard to PR interval, it was noted there was a longer PR interval in the group with >5mins PAF per 24 hours by 28 ms over the group with <5mins PAF per 24 hours (184 vs 156ms), and 26ms over the group with no PAF (184 vs 158ms). The differences did not reach statistical significance in either group comparison but again these results agree with other suggestions from the literature indicating an increased risk of PAF with prolonged PR interval (153, 156). In the Cheng study (156) a 20ms increase in PR interval resulted in an 11% increase in risk of AF.

Interestingly, with regards P wave amplitude and area, the patients with >5mins per 24 hours of NCT had significantly lower values in lead II than the group with <5mins PAF per 24 hours (P_{AMP} 80 vs. 213 μ V, P_{AREA} 4525 vs. 9710 μ V*ms) and the group with no PAF (P_{AMP} 80 vs. 210 μ V, P_{AREA} 4525 vs. 9770 μ V*ms). This suggests a difference from the Soliman study (153) and is likely to be a result of small numbers in each group rather than a true difference.

When discussing these differences, it is important to maintain a clinical perspective. Realistically speaking, it will be difficult in routine clinical practice, without the aid of callipers etc., to accurately measure differences in PWI and determine an individual's potential risk. The concept of a cut-off point, such as is suggested by 120ms for P_D , may be useful but these PWI must be used in conjunction with other clinical variables when assessing risk.

6.4 Conclusions

My findings show a similar burden of PAF in a sub-group of my Study Population to that in other populations studied in high-income countries. It suggests either that PAF does not appear to be a major contributory factor to the increased stroke burden seen or that, potentially, black Africans are more susceptible to a lower burden of PAF than other populations.

P wave duration and PR interval may be predictive factors for PAF in my Study Population, but should be taken in context of the patient's overall risk factor profile.

Chapter 7. Hypertension

7.1 Methods

7.1.1 Blood Pressure and standardisation of measurements

I had 2 BP machines available for use. Both were newly calibrated A&D UA-767™ (A&D Instruments Ltd, UK) automated monitors, that conform to the accuracy standards of the British Hypertension Society and have been previously validated for use as automated monitors (243). The enumerators were given a further session with initial demonstration and then subsequent practice, with instruction sheet as *aide memoire* given. In accordance with the World Health Organization (WHO) STEPS protocol (244) and similar to protocols used in large hypertension trials (229, 230), BP was performed 3 times in the right arm with the arm supported at the level of the heart with the participant in the sitting position after at least 5 minutes of resting quietly, and then once after standing for 3 minutes in a similar fashion. The participant's sitting BP was recorded as an average of the 2nd two recordings. An appropriately sized cuff was employed and the participant was given a full explanation as to the procedure in order to try and allay anxiety and potential 'white-coat' hypertension (noted to be a particular problem in the elderly, but also in elderly that may well never have had their BP taken before). If there was a greater than 10mmHg difference in either systolic +/- diastolic BP between the 2nd and 3rd recordings, then further recordings were taken until 2 consecutive readings were concordant within this range. The study performed sitting and standing BP readings in all study participants (disability allowing).

7.1.2 Case Definition of Hypertension

HTN was defined as BP $\geq 140/90$ mmHg for the purposes of reporting prevalence. I further classified hypertensives according to suggested treatment guidelines for SSA of BP $>150/95$ mmHg (245), my own pre-determined cut-off for immediate commencement of treatment for HTN of $>160/100$ mmHg, and those with severe (Grade 3) HTN of $\geq 180/100$ mmHg. Isolated systolic hypertension (ISH) was defined as a systolic BP 140-

159mmHg (Grade 1) or ≥ 160 mmHg (Grade 2) with a diastolic BP < 90 mmHg. Pulse pressure (systolic minus diastolic) was also recorded.

7.1.3 *Electrocardiographic criteria of left ventricular hypertrophy*

As with the measurement of P wave indices in Chapter 5, this was performed digitally using 12-SL analysis software available on the GE MAC 1200TM machines I was using to look at participants with ECG LVH and how well this correlated with whether they were found to be hypertensive. In addition, I also looked at how well ECG LVH correlated with echo LVH in the participants that underwent an echocardiogram (i.e. cases and pool of controls from the AF prevalence study). With the 12-SL system, median beats are produced to help eliminate noise, and the Sokolow-Lyon index is reported. This index measures the product of the S wave in lead V1, added to the larger of the R waves in either V5 or V6. The cut-off for ECG LVH is ≥ 3.5 mV. All electrocardiographic criteria for LVH have been shown recurrently to be specific but not overly sensitive with regard to true LVH (when compared to imaging such as echo or MRI). However, according to a recent study comparing multiple ECG LVH criteria to CMR findings, the Sokolow-Lyon index is the best performing criteria overall, with a sensitivity of 26% and specificity of 92.6% (246). In the significant percentage of the total overall study population that was African-American (25.7% - 1241 participants), the sensitivity of Sokolow-Lyon increased to 36.7%, at the expense of the specificity which dropped slightly to 86.8%. This therefore seemed the most suitable and appropriate ECG criteria to report. Of 2130 digital ECG records, 1350 (63.4%) had ECGs suitable for calculation of Sokolow-Lyon index, after exclusion of records without annotation and visually inadequate quality. Basic statistics were applied to the results, including 95% CIs for percentages and p values for differences between some groups using the Mann-Whitney test. Of the AF case-control group, 53 had all three of

1. an ECG with LVH index annotation
 2. echocardiographic measurement of septal and posterior wall thickness and LA diameter
 3. BP recording
- and were compared in a sub-group analysis.

7.1.4 Echocardiographic criteria for left ventricular hypertrophy

LV wall thickness and left atrial diameter were measured and classified according to British Society of Echo guidelines (247), such that normal LV wall thickness was defined as 0.6-1.2cm, with mild, moderate and severe hypertrophy defined as wall thicknesses 1.3-1.5cm, 1.6-1.9cm, and ≥ 2.0 cm respectively. LA diameters were gender specific.

7.2 Results

7.2.1 Prevalence of Hypertension

Of the 2223 participants able to have their BP taken, only 670 (30.1%) people had an average BP of $<140/90$ (i.e. were normotensive), 1553 (69.9%) had an average BP $\geq 140/90$, 1289 (58.0%) had an average BP over 150/95 and 993 (44.7%) had an average BP over 160/100. Therefore, more than 2 out of every 3 study participants were hypertensive with a BP $\geq 140/90$, and almost 2 of every 3 hypertensives identified had BP $>160/100$ (993/1553 or 63.9%). 653 participants (29.4%) had Grade 3 'severe' HTN ($\geq 180/110$). It was not possible to take 9 people's BP. This was either because they refused to have it done, stated that it was painful or they were felt to be too physically or mentally unwell for it to be appropriate.

Table 36 Frequency and Crude Prevalence of hypertension at varying diagnosis and treatment cut-offs

Blood Pressure	Frequency	Crude Prevalence (95% CI)
$< 140/90$	670	30.1 (28.2 – 32.1)
$\geq 140/90$	1553	69.9 (68.0 – 71.8)
$>150/95$	1289	58.0 (55.9 – 60.0)
$>160/100$	993	44.7 (42.6 – 46.7)
$\geq 180/110$	653	29.4 (27.5 – 31.3)

The following table reports age-adjusted (to WHO world population) prevalence rates (95% CI) for $n=2196$ because 27 patients had missing data for age, as I was unable to establish accurately enough their year of birth beyond saying they were over the age of 70 and are therefore excluded from analysis.

Table 37 Age-adjusted prevalence rates for hypertension bands

Blood Pressure	Age-Adjusted Prevalence (95% CI)
< 140/90	30.7 (28.8 – 32.6)
≥140/90	69.7 (67.8 – 71.6)
>150/95	57.7 (55.6 – 59.8)
>160/100	44.3 (42.2 – 46.4)
≥180/110	29.0 (27.1 – 30.9)

7.2.2 Gender and Age Differences

The mean pulse pressure and diastolic and systolic blood pressures of the Study Population are described in the table below, according to sex category. As can be noted, all 3 measures were significantly higher in women than men in the Study Population. In fact, despite making up only 56% of the total study population, almost 2 out of every 3 hypertensives (61%) were women.

Table 38 Mean BP results of the Study Population by Gender

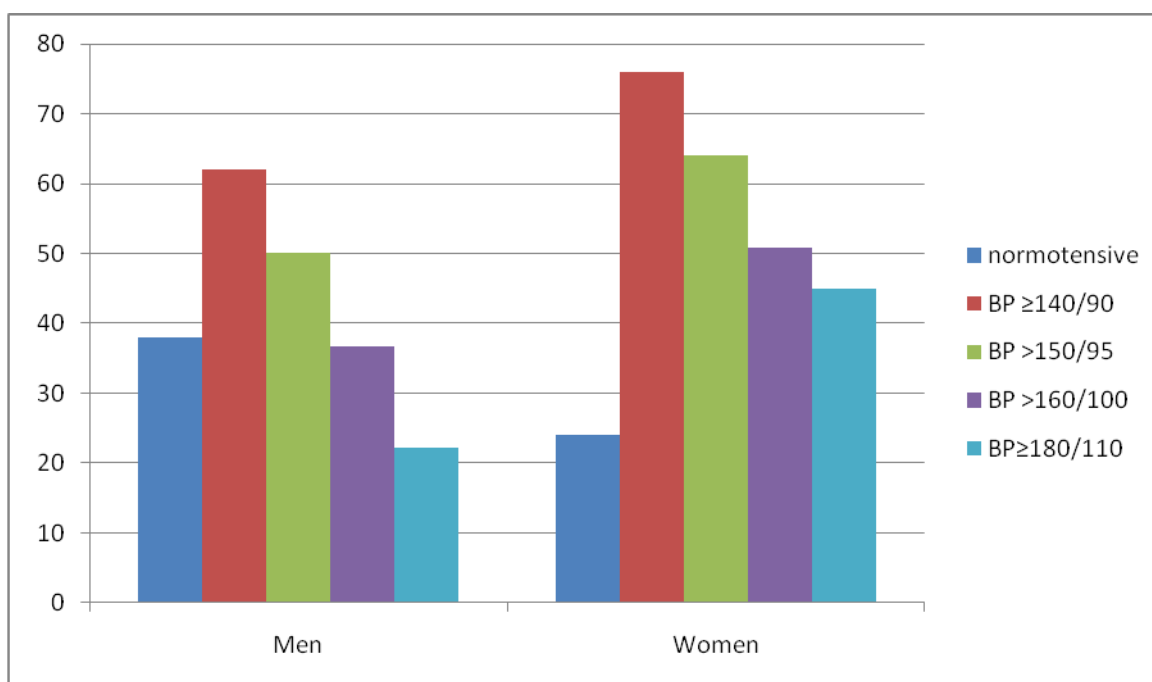
	Males (n = 972)	Females (n= 1251)
Mean pulse pressure (95% CI)	71.3 (69.9 to 72.7)	76.6 (75.3 to 78.0)
Mean diastolic BP (95% CI)	83.1 (82.1 to 84.0)	89.3 (88.4 to 90.2)
Mean systolic BP (95% CI)	154.3 (152.3 to 156.4)	166.0 (164.1 to 167.9)

When each hypertensive band was broken down by gender, there were a significantly higher number of women than men in each band, as can be seen in the table and graph below. What can also be noted, particularly in the graph, is that there was a higher percentage of women that were hypertensive overall and an increased percentage of women making up the group with very high BPs i.e. ≥180/110.

Table 39 Number of study participants in each hypertensive band by gender (percentage is of total hypertensive population for each band)

BP	Men (95%CI)		Women (95% CI)		Total	
	Frequency	%age	Frequency	%age	Frequency	%age
≥140/90	603	39 (36.4 – 41.3)	950	61 (58.8 – 63.6)	1553	100
>150/95	487	38 (35.1 – 40.4)	802	62 (59.6 – 64.9)	1289	83
>160/100	357	36 (33.0 – 38.9)	636	64 (61.1 – 67.0)	993	64
≥180/110	216	33 (29.5 – 36.7)	437	67 (63.3 – 70.5)	653	42

Graph 11 Percentage of study participants in each hypertensive band by gender (percentages are of total study population by gender with available BPs i.e. 972 men and 1251 women)



With respect to HTN prevalence and age, the following tables and graph illustrate the frequency and prevalence in men and women by 5-year age bands. The total population with age and BP recorded is 2196 (965 men and 1231 women).

Table 40 Frequency of hypertension by gender and age-band

Age	70-74		75-79		80-84		85+	
	Men	Women	Men	Women	Men	Women	Men	Women
Sex								
Normotensive	147	129	112	75	48	48	59	44
BP ≥140/90	233	355	170	258	85	156	111	166
BP >150/95	190	295	131	227	66	127	96	142
BP >160/100	147	224	91	183	50	101	65	117
BP ≥180/110	84	146	62	130	38	63	30	87
Total Population	380	484	282	333	133	204	170	210

Table 41 Prevalence (95% CI) of hypertension by gender and age-band

Age	70-74 (95% CI)		75-79 (95% CI)		80-84 (95% CI)		85+ (95% CI)	
Sex	Men	Women	Men	Women	Men	Women	Men	Women
Normotensive	38.7 (33.8 – 43.6)	26.7 (22.8 – 30.6)	39.7 (34.0 – 45.4)	22.5 (17.6 – 27.4)	36.1 (27.9 – 44.3)	23.5 (17.7 – 29.3)	34.7 (27.6 – 41.9)	21 (15.4 – 26.5)
BP ≥140/90	61.3 (56.4 – 66.2)	73.3 (69.4 – 77.3)	60.3 (54.6 – 66.0)	77.5 (72.6 – 82.4)	63.9 (55.7 – 72.0)	76.5 (70.6 – 82.3)	65.3 (58.1 – 72.4)	79 (73.5 – 84.6)
BP >150/95	50 (45.0 – 55.0)	61 (56.6 – 65.3)	46.5 (40.6 – 52.3)	68.2 (62.7 – 73.6)	49.6 (41.1 – 58.1)	62.3 (55.6 – 68.9)	56.5 (49.0 – 63.9)	67.6 (61.3 – 73.9)
BP >160/100	38.7 (33.8 – 43.6)	46.3 (41.8 – 50.7)	32.3 (26.8 – 37.7)	55 (49.1 – 60.8)	37.6 (29.4 – 45.8)	49.5 (42.6 – 56.4)	38.2 (30.9 – 45.5)	55.7 (49.0 – 62.4)
BP ≥180/110	22.1 (17.9 – 26.3)	30.2 (26.1 – 34.3)	22.0 (17.2 – 26.8)	39.0 (33.8 – 44.3)	28.6 (20.9 – 36.2)	30.9 (24.5 – 37.2)	17.6 (11.9 – 23.4)	41.4 (34.8 – 48.1)

Table 42 Levels of hypertension by age band and gender (M=male, F=female), by percentage of each age band

Age band	70-74		75-79		80-84		85+	
Gender	M	F	M	F	M	F	M	F
BP <140/90	38.7 (33.8 – 43.6)	26.6 (22.8 – 30.6)	39.7 (34.0 – 45.4)	22.5 (17.6 – 27.4)	36.1 (27.9 – 44.3)	23.5 (17.7 – 29.3)	34.7 (27.6 – 41.9)	21 (15.4 – 26.5)
BP 140-149/90-95 (Grade 1)	11.3 (8.2 – 14.4)	12.4 (9.5 – 15.3)	13.8 (9.8 – 17.8)	9.3 (6.2 – 12.4)	14.3 (8.3 – 20.3)	14.3 (9.4 – 19)	8.8 (4.6 – 13.1)	11.4 (7.1 – 15.7)
BP 150-159/95-99 (Grade 1)	11.3 (8.2 – 14.4)	14.7 (11.6 – 17.8)	14.2 (10.1 – 18.3)	13.2 (9.6 – 16.8)	12 (6.5 – 17.5)	12.7 (8.1 – 17.3)	18.2 (12.4 – 24.0)	11.9 (7.5 – 16.3)
BP 160-179/100-109 (Grade 2)	16.6 (12.9 – 20.3)	12 (9.1 – 14.9)	10.3 (6.7 – 13.8)	15.9 (12.0 – 19.8)	9.0 (4.1 – 13.9)	18.6 (13.3 – 24.0)	20.6 (14.5 – 26.7)	14.3 (9.0 – 19.6)
BP ≥180/110 (Grade 3)	22.1 (17.9 – 26.3)	30.2 (26.1 – 34.3)	22.0 (17.2 – 26.8)	39.0 (33.8 – 44.3)	28.6 (20.9 – 36.2)	30.9 (24.5 – 37.2)	17.6 (11.9 – 23.4)	41.4 (34.8 – 48.1)

Graph 12 Levels of hypertension by age band and gender (M=male, F=female), by percentage of each age band

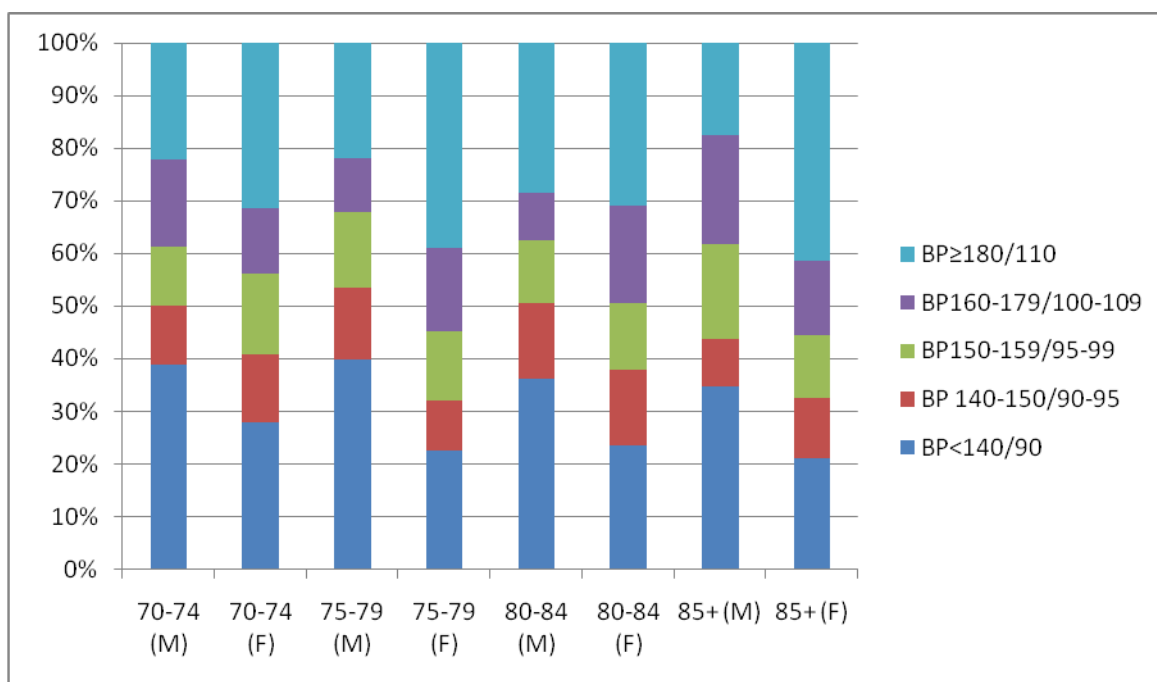


Table 43 Age-adjusted prevalence rates (95% CI) by age band (male and female combined) and level of hypertension

	70-74 years	75-79 years	80-84 years	85+ years
BP 140-149/90-95	12.7 (10.5 – 14.9)	11.7 (9.2 – 14.2)	16.0 (12.1 – 19.9)	7.1 (4.5 – 9.7)
BP 150-159/95-99	14.1 (11.8 – 16.4)	14.1 (11.3 – 16.9)	14.0 (10.3 – 17.7)	10.2 (7.2 – 13.2)
BP 160-169/100-109	17.4 (14.9 – 19.9)	13.7 (11.0 – 16.4)	16.7 (12.7 – 20.7)	11.8 (8.6 – 15.0)
BP ≥180/110	28.4 (25.4 – 31.4)	32.2 (28.5 – 35.9)	33.7 (28.7 – 38.7)	21.3 (17.2 – 25.4)
BP ≥140/90	72.6 (69.6 – 75.6)	71.7 (68.1 – 75.3)	80.4 (76. – 84.6)	50.4 (45.4 – 55.4)
OVERALL				

Isolated Systolic Hypertension

733 of 1553 hypertensives (47.2%) had isolated systolic hypertension (ISH). This works out as an overall crude prevalence rate of 33.0% (733/2223) and an age-adjusted prevalence rate of 31.6%. The table below shows the frequency breakdown by gender and SBP band. 411 (52.6% women) had Grade 1 ISH (SBP 140-159) and 322 (61.5% women) had Grade 2 ISH (SBP ≥160). The crude prevalence rates of Grade 1 and 2 ISH were therefore 18.5% (411/2223) and 14.5% (322/2223) respectively.

Table 44 Levels of systolic BP by gender

Gender	SBP ≥ 180	SBP ≥ 160 but < 180	SBP ≥ 140 but < 160	Total
Male	41	83	195	319
Female	76	122	216	414
Total	117	205	411	733

7.2.3 Participant Awareness of Hypertension, Treatment and Adequate Control

586 (26.3% of total and 37.7% of the hypertensive group) of the Study Population (189 (32.3%) men, 397 (67.7%) women) were aware that they had HTN but only 94 of these (16% of participants aware of their hypertension, 6.1% of total who were hypertensive) were on regular treatment (48 (51%) men, 46 (49%) women).

Of the 94 people on treatment for HTN, 14 (11 (79%) men, 3 (21%) women) had controlled blood pressure of $< 140/90$, 21 had an average blood pressure of less than or equal to $150/95$ and 34 had an average blood pressure of less than or equal to $160/100$. Therefore 60 had an average blood pressure of $> 160/100$, and 80 still had uncontrolled blood pressure, i.e. a blood pressure of $\geq 140/90$. Therefore, of the hypertensive population overall, only 0.9% (14/1553) had adequately controlled BP.

To suggest a rough pattern for HTN in this population therefore would be as follows – a ‘rule of sixths’:

- 4/6 of the total Study Population (1553/2232) were hypertensive
- 2/6 of the total Study Population (653/2232) had Grade 3 (severe) HTN
- 2/6 of the Study Population had ISH
- 4/6 of the hypertensive group (950/1553) were women
- 4/6 of the hypertensive group (993/1553) had moderate/severe HTN with BPs $> 160/100$
- 4/6 of the group with moderate/severe HTN (636/993) were women
- 2/6 of the hypertensive group (586/1553) were previously aware of their HTN
- 1/6 of the group previously aware of their HTN (94/586) were on current treatment
- 1/6 of the group on current treatment (14/94) were adequately controlled

7.2.4 Functional Status and Co-morbidities

As noted previously, functional status in women overall is worse than men, with an OR of 1.31 of being severely disabled (BI <15) if female. This is reflected in the BI scores for the different bands of HTN between the genders, with women having lower BI than men in each BP band. However, there appears to be little difference in levels of disability between BP bands, as shown in the table below.

Table 45 Barthel Index scores by gender and BP level

Blood Pressure	Barthel Index Score		
	Male	Female	Overall
<140/90	19.35	19.12	19.27
≥140/90	19.37	19.22	19.28
>150/95	19.32	19.23	19.26
>160/100	19.27	19.12	19.18

7.2.5 Advice and Treatment

Of 1553 hypertensive subjects, 993 had a BP >160/100, my cut-off for commencement of treatment. Of these 993, 855 (86.1%) were given a prescription for bendroflumethiazide, 21 (2.1%) a prescription for nifedipine, and 25 (2.5%) a prescription for propranolol (usually due to concomitant angina or benign essential tremor). Of 52 patients (5.2%) taking medication in this BP band already, 38 (3.8%) were asked to continue their current medication (and usually reminded of the importance of taking on a daily basis), 10 (1.0%) were asked to increase their current medication, and 4 (0.4%) were changed to more effective agents. Of the remaining 40 patients (4.0%), 26 patients (2.6%) refused to take medication and 14 (1.4%) were considered too frail. The 560 participants that had a BP between 140-160/90-100 were given detailed advice regarding diet and lifestyle and it was recommended to them that they returned to their local health centre for BP monitoring on a regular basis. All patients with HTN were given education regarding non-pharmacological intervention such as stopping smoking and reducing salt and alcohol intake. Physical activity was discussed but I quickly realised that participants spent the majority of the day either working in their 'shamba' / cleaning the homestead, or were too frail / disabled to work.

7.2.6 Electrocardiographic criteria of left ventricular hypertrophy

Of the 1350 ECGs with digital Sokolow-Lyon index annotations, 576 were men and 774 women. The number with LVH criteria was 342 in total (25.3% (95% CI 22.9-27.7)). As a percentage, there were more men with ECG LVH (29.2%(25.1-33.3)) than women (22.5%(19.6-25.4) (see Table 45). This was statistically significant with a p value <0.001.

Table 46 Distribution of LVH Index

	Sokolow-Lyon Index		Total
	<3.5mV	≥3.5mV	
Male	408	168	576
Female	600	174	774
Total	1008	342	1350

On comparing ECG LVH to systolic and diastolic BP, I found that both systolic and diastolic BP was significantly higher in participants with ECG LVH criteria, and BMI was significantly higher in participants without ECG LVH criteria, as in Table 47 below.

Table 47 Descriptive statistics of LVH Covariates (mean +- SD)

Covariate	No. Recordings	Sokolow-Lyon Index		P value (*)
		<3.5mV	≥3.5mV	
BMI	1237	22.2±4.7	20.8±3.5	<0.005
Systolic BP	1344	156±32	175±35	<0.0001
Diastolic BP	1344	85±16	91±17	<0.0001

(*) Mann-Whitney test, α=0.05

When I looked at the sub-group of 53 participants (23 men, 30 women) who had undergone echocardiography, only 9 (17%) fitted criteria for ECG LVH. Covariate analysis in Table 47 shows again a significantly higher SBP in those with ECG LVH, and whilst there is a suggestion that septal and posterior wall thicknesses are higher in the ECG LVH group, these results do not reach significance.

Table 48 Subgroup analysis of LVH covariates for those undergoing echocardiography (mean±SD)

Covariate	Sokolow-Lyon LVH index		P value (*)
	<3.5mV (n=44)	≥3.5mV (n=9)	
BMI	20.6±6.7	19.1±2.1	0.144
SBP	162±33	199±34	0.007
DBP	91.7±20	104±18	0.080
Septal wall thickness (cm)	1.27±0.25	1.34±0.34	0.699
Posterior wall thickness (cm)	1.15±0.18	1.29±0.34	0.218
LA diameter (cm)	3.62±0.7	3.58±0.44	0.89

* Mann-Whitney test, $\alpha=0.05$

On examining the ECG LVH group, only 4 of 9 (44%) had echocardiographic evidence of LVH. Of these 4, 2 had concentric hypertrophy (1 mild, 1 severe), with the other 2 being isolated septal hypertrophy (mild) and asymmetric hypertrophy (moderate septal and mild posterior wall hypertrophy). Of the group without ECG LVH, 18/44 (41%) had evidence of some degree of LVH. Of those with concentric hypertrophy, 5 had mild and 1 had moderate. 3 had asymmetric hypertrophy, with moderate septal and mild posterior wall hypertrophy. 9 had evidence of isolated septal hypertrophy, with 6 measured as mild, 2 as moderate and 1 as severe. Therefore, the sensitivity of the Sokolow-Lyon index in my population is 18% (identifying 4/22 with LVH) and the specificity 59% (identifying 26/44 without LVH either on ECG or echo).

7.3 Discussion

7.3.1 Comparison of Prevalence Rates to Other Populations

HTN prevalence (BP ≥140/90) from the National Health Survey of England in 1998 (204) examined 11,529 adults ≥16 years old, finding an overall prevalence of 37%. This rate increased with age, and HTN was more common in men than women up until the age of 70, when it became more prevalent in women. The prevalence in men aged 70-79 was 77.6%, and 81.8% in the 80+ group, compared to 82.7% and 83.8% respectively in women.

An overview of HTN trends in the USA (248) found a prevalence rate of 28.9% in 2004, with ethnic and gender differences. Prevalence was highest

in non-Hispanic black women at 40.8%, and was lowest in Mexican-American men at 26.2%. In those aged ≥ 70 years, the prevalence was 63.3% in white men and 78.8% in white women. This compared to 83.4% in black men and 83.1% in black women, and 69.1% in Hispanic men and 78.8% in Hispanic women.

There are more data in SSA regarding HTN than there are for AF, although it has been noted that very few studies provide age-standardised data and thus comparison of studies is more difficult (220). Also, there are no studies dedicated to HTN in the elderly, with most studies containing small numbers of over 70s. Cut-off values for HTN are taken as $\geq 140/90$ unless mentioned otherwise, as these values differ in SSA studies.

It is helpful to begin by mentioning data from Tanzania. A study by Swai et al from almost 20 years ago (249) looked at 8581 adults (aged 15+) in 3 distinct regions in rural Tanzania. Prevalence was low at 10.9%, 3.6% and 2.3% for men in the regions of Kilimanjaro, Morogoro and Mara respectively, and 9.6%, 5.2% and 3.6% for women in the same regions. In the 65+ group, prevalence was higher in women than men in all three regions and again highest in Kilimanjaro region in both men and women at 27.2% and 27.3% respectively. The mean BPs in the 65+ group in Kilimanjaro were 141/83 for men and 142/84 for women. Another study by Edwards et al published 11 years ago (250) looked at HTN prevalence in rural (Kilimanjaro region) versus urban (Dar-es-Salaam) Tanzania. The prevalence in older men (>54 years) was 77.8% in the urban area and 54.0% in rural area, versus 69.0% and 61.0% in women in these respective areas. The mean BPs were 149.3/89.3 and 143.2/88.5 for urban and rural men >54 years, and 148.6/92.0 and 144.1/88.1 for urban and rural women in the same age group. It is interesting to note from this not only that average mean BP is higher in urban versus rural, that HTN prevalence appears to be higher in more affluent / 'less poor' rural areas (i.e. Kilimanjaro) but also how difficult it is to look at temporal trends in the prevalence of HTN, given that in the Swai study the BP cut-off for hypertension was $\geq 160/95$, and in the Edwards study was $\geq 140/90$.

Elsewhere in SSA, a review by Opie et al (251) suggests that the prevalence of HTN in the 65+ age group is ~30-40% in rural West Africa, ~50% in semi-urban West Africa and 50-60% in a mixed South African population. At the

time (2005) these compared to slightly higher rates of 60-70% for black Americans of a similar age (252).

A more recent review by Addo et al (220) found difficulty comparing temporal trends in BP due to differences in methodology. However, picking out studies in the review that have been mentioned to have data on elderly patients, prevalence of HTN in those aged 65+ was ~60% (men and women) in a Liberian study (253) and ~70% (men) to ~80% (women) in a study from Senegal (254).

Summarising these prevalence rates in comparison to my Study Population, it would appear that prevalence rates in both elderly men (27.2% rising to 62%) and elderly women (27.3% rising to 76%) in Kilimanjaro region have increased significantly since 2000 when the study by Edwards et al was performed, although it is noted that the population is not exactly the same because their rates are in the 65+ age group and mine are in the 70+. In addition, mean systolic BPs in both men and women have increased significantly, from 143.2 in men and 144.1 in women to 154.3 in men and 166.0 in women. In the same period, diastolic BP has stayed fairly level in women (88.1 in 2000 versus 89.3 in 2010) and has actually decreased in men (88.5 in 2000 versus 83.1 in 2010). Compared to other populations in SSA, it would appear that my prevalence rates are on the higher side, being similar to rates reported from Senegal (254) and significantly higher than from other parts of West Africa (255) or South Africa (256). These rates are approaching HTN prevalence rates in the 70+ age group reported from high-income countries, from ~75-85% for a mainly Caucasian / Asian population in England, to >80% in black Americans.

With regard to isolated systolic hypertension (ISH), there are few data from SSA (251) and yet it is known to be an important problem in the elderly and in my Study Population ISH comprised almost half (47.2%) of all hypertension seen. This is similar to prevalence rates from the UK, where 46.1% of men and 57.3% of women aged 70-79 with HTN had ISH, and 49.8% and 53.1% for men and women in the 80+ age group (204).

7.3.2 Reasons for Prevalence Rates

There are many proposed ethnicity-related causes of HTN. These include low plasma renin values in blacks, increased intracellular sodium levels with

depression of sodium pump, and genetic differences in epithelial sodium channels and the renin-angiotensin-aldosterone system (251). In addition, it has been noted that black Americans have increased peripheral vascular resistance(251), and in a South African study (257), low birth weight and thus an 'underweight phenotype' has been associated with increased BP in adult life.

In addition to the above factors, there is also a link between socioeconomic status and BP in SSA (258). The general trend appears to be that as socioeconomic status increases, so do obesity and BP. The Kilimanjaro region is a 'relatively affluent' rural area due to its favourable climate and proximity to major tourist attractions such as Mount Kilimanjaro and the Serengeti National Park which may be why HTN may be similarly prevalent to urban African areas and increasing at such a rapid rate. This is linked to the idea of increasing 'Westernisation', meaning a change in lifestyle to more sedentary and the increase in availability (geographically and economically) of unhealthy foods.

The prevalence of HTN in the elderly in Tanzania is yet to reach levels seen in high-income countries, and certainly in black Americans. This may be due to the fact that people in SSA who develop HTN earlier in life remain undetected and untreated for much longer than in high-income countries, and thus are more likely to suffer hypertensive sequelae such as strokes, and die earlier. Consequently, proportionately more people with less severe HTN would make it to old age and into our demographic population studied.

7.3.3 Gender and Age Differences

BP is known to increase with age in high-income country studies (204) (248). Proposed mechanisms in the elderly include increased sodium sensitivity, increased aortic stiffness due to loss of elasticity, increased atherosclerosis, endothelial dysfunction and reduced organ perfusion (particularly renal) (259). There is a general trend in my Study Population population in both men and women of an age-related increase in BP. The percentage of hypertensive patients in the Study Population rises between the ages of 70-74 to 85+ from 61.3% to 65.3% in men and 73.3% to 79.0% in women (although these changes do not reach statistical significance).

It is noted in the Study Population that BP in women is greater than that in men. This correlates to high-income country studies showing both that HTN is more prevalent in women overall in the USA (248), and particularly in the elderly in England (204).

7.3.4 Participant Awareness of Hypertension, Treatment and Adequate Control

Detection, treatment and adequate control of HTN in SSA, and particularly the Hai District of northern Tanzania, remain poor. In my study, 37.7% of hypertensives were aware of their diagnosis, 6.1% were treated and 0.9% were adequately controlled. In the study by Edwards et al (250) in the Hai District in 2000, 17% were aware, 11% treated and 0.7% controlled. It should be remembered that the latter study included all adults, not just the elderly. These results suggest either that there has been very little improvement in detection, treatment and control of HTN in the Hai District in the last 10 years, or that there may have been an improvement in the adult population overall but that the elderly population has been neglected. Both possibilities are equally feasible but the results are even more surprising and disappointing given the fact that the same research group instituted several health interventions at the time to improve detection, control and treatment of NCDs, specifically hypertension, diabetes, asthma and epilepsy (260). These interventions included development of local treatment guidelines, sustainable local clinics for detection and treatment and health promotion at a national level.

Elsewhere in Africa, a study from Ghana in West Africa (261) found in an adult population with a prevalence of hypertension of 29.4% overall, only 34% were aware of their HTN, but 28% were receiving treatment and 6.2% were adequately controlled. Clearly this is not ideal, but it is slightly better than in Tanzania. The authors interestingly found that, whilst knowledge of one's own HTN increased with age, treatment and adequate control was worse than in younger age groups. It was felt that, whilst older people may be more interested in looking after their health, they were less likely to have the financial means with which to finance long-term treatment.

A study from South Africa (256) reported much better levels of detection, treatment and control from a demographic and health survey in 1998. Using

a BP cut-off of 160/95, they reported 41% of men were aware of their hypertension, 39% were on treatment and 26% had their BP controlled. The figures for women were 67%, 55% and 38% respectively. This is just inferior to rates found in the USA (248) with overall awareness at 71.8%, treatment 61.4% and control 35.1%, although it should be remembered that the cut-off for the US study was 140/90mmHg. In the 65+ age group in the UK, only just over half of cases were being identified in 1998 (56.5%), of whom 45.6% were treated and 11% were adequately controlled (204).

Most of these figures are inferior even to Wilber and Barrow's classic suggestion of a 'rule of halves' (262) in that only half of the hypertensives were being detected, and only half of those were treated, of which only half were adequately controlled (N.B. using a cut-off of 160/95mmHg). My figures equate more to a rough 'rule of sixths', with only 2 sixths of hypertensives aware, 1 sixth of those aware treated, and 1 sixth of those treated adequately controlled.

It has previously been suggested that adult women in SSA (and high-income countries) have been reported to have better detection, treatment and control rates than men (220). The authors suggest this may be due to increased contact with health services when of child-bearing age. It is clear from my study of the elderly that men have better rates of treatment and control than women. Elderly women do not have the same reasons as younger women to seek healthcare services and from my experience it tended to be men that travelled around more as women who tended to stay around the homestead, with men having a more important status in society. Thus men are more likely to come into contact with health services through word-of-mouth, advertising etc., and have their health valued more than female members of the family.

Overall, the low levels of detection, treatment and control emphasise the challenges of non-communicable disease management in SSA from the perspectives both of difficulty in accessing healthcare in a resource-poor country and also ensuring patients are aware of the dangers of undetected / untreated diseases (such as hypertension) that are asymptomatic in the majority of cases and yet require lifelong treatment.

7.3.5 Hypertension and AF

One of my most interesting and surprising findings is that my Study Population had such a high prevalence of HTN, yet such a low prevalence of AF. The two conditions are intrinsically linked, given a pathophysiological mechanism of sustained high BP increasing LA pressure and thus encouraging LA stretch over time, leading to heterogeneity of atrial conduction and encouragement of multiple re-entrant wavelets, a substrate primed for AF development. As has been mentioned previously in section 1.3.1, HTN is the most common condition associated with AF in population-based studies (73) and has been said to be the single biggest risk factor for AF, responsible for 14% of all cases (38). However, it has also been shown that increased rates of HTN do not always translate into increased incidence of AF (188). With HTN prevalence rates similar to high-income countries, my study suggests that HTN in itself may not be such a risk factor for the development of AF, as in other populations or that other influencing factors such as ischaemic heart disease (which may well be subclinical in high-income countries and thus prevalence under-estimated) are often overlooked when considering causative risk factors in other populations. There is also the potential for genetic polymorphisms in this East African population that are as yet undiscovered, that may protect against AF.

7.3.6 Treatment and Advice

The vast majority (86.1%) of my hypertensive patients were given bendrofluazide, the cheapest, most readily available, and one of the most effective agents in lowering BP in the elderly. They were also advised of side-effects and recommended they have their renal function checked within a month of starting the drug (whilst accepting that the majority will not). Thiazide diuretics (hydrochlorothiazide, chlorthalidone, and bendrofluazide) are recommended by the American College of Cardiology for initiating therapy. They cause an initial reduction in intravascular volume, peripheral vascular resistance, and BP, and are generally well tolerated (259). The price per 5mg tablet was 35TzS (i.e. 1.75 pence) and therefore a patient on 2.5mg bendrofluazide could be treated for a month for <30 pence. Those with contraindication to bendrofluazide were given nifedipine, slightly more expensive and less available, but the calcium channel blocker of choice in

this part of Africa. Results of controlled trials have demonstrated the safety and efficacy of calcium antagonists in elderly patients with HTN. They appear well suited for elderly patients, whose hypertensive profile is based on increasing arterial stiffness, decreased vascular compliance, and diastolic dysfunction (259). The price per 10mg tablet was 45TzS (2.25 pence) and therefore a patient on 10mg bd of nifedipine could be treated for a month for £1.50. After this, the price of anti-hypertensives rose fairly rapidly, and combined with lower levels of effectiveness / more side-effects, meant our treatment policies and guidelines were confined mainly to bendrofluazide and nifedipine. ACE-Inhibitors were not used by me given their reduced effectiveness in elderly black people (259), their lack of availability in many of the villages and their price making them prohibitively expensive for most patients.

With respect to the 38 patients who said they were actually taking anti-hypertensive medication regularly, it transpired that in a significant number of cases this did not mean on a daily basis. What it often meant was that the patient had been prescribed medication at one point after presenting with some likely unrelated symptom such as headache, been prescribed bendrofluazide as they had concomitant HTN, and taken a tablet subsequently only when they felt unwell or had a headache. They were reminded of the importance of taking daily tablets and educated as to why this was the case.

Only 1.4% of patients with a BP >160/100 were considered too frail for treatment. It would be interesting to know similar levels of frailty in high-income countries but this seems to be a fairly low figure in an over-70s population. When we look at levels of disability, a marker of frailty, we can compare BI scores with a European population. Using the BI, 4.3% and 6.9% of the Study Population were severely and moderately disabled respectively, compared to 9% and 26% in an equivalent European population (263). This supports the idea that the Study Population had fewer patients who were too frail to be treated than may be found in other populations.

During my time in Tanzania, I produced HTN guidelines to try and standardise treatment across the district (see Appendix 6). There was a huge disparity with regard to the quality of health assessment and the availability of drugs across the district, generally showing a trend to increased quality of

assessment and drug availability with size of health centre and accessibility by road. The guidelines were produced using a combination of best evidence, local availability of drugs and Tanzanian national guidelines in conjunction with the District Medical Officer.

7.3.7 Electrocardiographic criteria of left ventricular hypertrophy

The main findings from this section are that the prevalence of ECG LVH in this elderly population is 25%, ECG LVH correlates well with both systolic and diastolic BP readings, but doesn't appear to correlate particularly well with echo findings, providing a sensitivity and specificity of 18% and 59% respectively when compared to the 'gold standard' for measuring LVH of echocardiography. ECG LVH is more common in men and also in those with a lower BMI.

ECG LVH has previously been shown to be an ominous sign. It is associated with an 8-fold increase in cardiovascular mortality and has been shown to be more common in stroke and MI patients. Hypertension predisposes, and at systolic pressures >180mmHg evidence of ECG LVH is seen in 50 percent in other studies (264). However, the precise pathologic and anatomic meaning of ECG LVH remains unclear, as it is only modestly related to actual findings on echo and MR. It has been suggested that the ECG 'aberrations' are as much to do with myocardial damage as hypertrophy itself (264). The fact that 1 in 4 of this elderly population has evidence of ECG LVH suggests that there is a significant number at risk of cardiovascular sequelae.

Whilst there is a good correlation between ECG LVH and SBP, this relationship is not so good for echo parameters of hypertrophy. The numbers in this section of the study were small and thus make it more difficult to comment confidently but may suggest that LV geometric patterns in elderly black Africans, particularly those that are hypertensive, may be different from other populations studied i.e. this population does not see classic hypertrophied myocardium as a result of hypertension and may see myocardial 'damage' as previously mentioned but with normal wall thicknesses. In retrospect, what would have been enlightening would have been to measure troponin and BNP levels to look for chronic myocardial damage and wall stretch.

It is little surprise that the ECG LVH group had a lower mean BMI, and contained more men as a percentage. The sensitivity of ECG LVH criteria is known to be reduced in obese patients, thought to be because of attenuating effects of increased tissue mass between praecordial electrodes and the heart itself (265). My study cohort revealed women to have a higher BMI than men, and with extra breast tissue in a significant number of patients, it stands to reason that men would have a greater percentage fitting criteria for ECG LVH.

With regard to numbers of ECGs with an LVH index annotation, 1350 is lower than I was expecting, particularly when compared to the number of ECGs with P wave annotations. However, LVH index relies on specific leads (V1, V5/V6) for its measurement, whereas the P wave is a 'global' measurement, taken over 12 leads. This may explain this fact to a degree, but on visual inspection of ECGs without LVH index annotations, whilst some display a sub-optimal baseline, one would be confident of measuring LVH index manually and reliably. This has not been done on the remainder as I felt it would give more accurate results just using one analysis technique and not to introduce measurement bias between techniques.

7.4 Conclusions

My results suggest that HTN prevalence rates are high in the elderly in Tanzania and are approaching (if not having caught up with) rates seen in high-income countries, having rapidly increased in recent years.

Despite this, the rates of detection, treatment and control remain very low and rather than the classic 'rule of halves', my study conforms more to a 'rule of sixths', despite attempts at education, community awareness programs and increased availability of medication over recent years.

My findings of a very low prevalence of AF and a high prevalence of HTN suggest that HTN remains overwhelmingly the largest risk factor for stroke, and poor rates of detection and control the reason for increased incidence rates in the Study Population compared to Caucasian populations in high-income countries.

ECG LVH correlates well with BP, particularly SBP, but this does not always translate into true ventricular hypertrophy.

Chapter 8. Overview of Discussion

8.1 Strengths

Overall strengths of the project are that I have collected a large amount of data from an elderly African cohort. Methodologically robust in the random choice of villages to reflect the population spread across the whole district, with the use of census data collected by experienced enumerators and a sound infrastructure, my study has enabled the collection of important NCD data in an elderly population.

Specifically with respect to AF, I used the gold standard of 12-lead ECG to identify my cases and, likewise with respect to HTN, I used an automated machine minimising inter-observer variability and validated to British Hypertension Society standards (243).

With respect to PWI, all study variables were ascertained uniformly and, of particular note, the ECGs were analysed with computer assistance, thus minimising intra- and inter-observer variability. My analysis did not exclude outliers and thus gives a more balanced overall picture of PWI.

8.2 Limitations

The study was limited by a number of factors. I was expecting to find a similar AF prevalence rate to that found in elderly African-Americans but the low overall numbers of patients with AF made it difficult for me to comment confidently on different sub-groups. It is possible but unlikely that people with AF were under-represented in the 25.1% of the 70 and over population that I screened, given the random choice of villages accurately reflecting topographic and demographic differences within the DSS. There is a mismatch in numbers from the census and those I actually saw and it is also possible that AF was over-represented in those who refused to be screened. Again, this is unlikely given poor access to healthcare and thus patients with chronic ill health are unlikely to pass up the opportunity to see a doctor. The use of historical events to determine participants' year of birth reduces the reliability of the ages quoted and there is a possibility that the population was younger than quoted. However, this is a well recognised problem of research in SSA and the techniques I used are well-validated. Whilst I had excellent

interpreters who were medically trained, it was difficult at times to ascertain the finer points of a patient's symptom burden, given the lack of medically descriptive words in Swahili and other local tribal languages spoken by village elders.

With respect to PWI, the measurement method meant my data produced PWI calculated from a median P wave, rather than each individual P wave on the 12-lead ECG. The reason for doing this is that P_{ON} and P_{OFF} were more reliably identified as the production of a median beat eliminates a significant amount of baseline 'noise'. This comes at the expense of data from each individual lead and the ability to calculate PWI such as maximum and minimum P_D and P wave dispersion.

The median differences with age and gender were all fairly small in a clinical sense. Whilst many were statistically significant, the differences are unlikely to be clinically significant. However, my primary aim for this part of the study was not to look at clinical impact of the changes but simply initially to report values and trends. I foresee that these results will be the precursor to the production of reference ranges for an elderly SSA population and in the future be used to predict disease states such as AF.

With respect to the ambulatory monitors, there was no truly random choice of patients. With respect to the Holter monitors, if I was in a certain village for several consecutive days, it was often the patients that turned up earlier in the morning who were asked to wear the monitors. This allowed them to wear them for as close to 24 hours as possible, return them and for me to download the data to a laptop and then place them on someone else the following day. Thus, truly random choice was sacrificed for extra patient numbers and may well have biased the results in favour of patients who were fitter and more mobile (and less likely to have cardiac problems?) and thus likely to get to the health centre earlier, or patients who live closer to the health centre and thus possibly look after their health more closely. With respect to the event recorders, again it was not a truly random choice given I looked at the ECG to attempt a rough calculation of P wave 'predictors' for the purposes of getting an even spread of patients in each group. All 10 (or 8 following 2 having malfunctioned!) monitors were put on patients in 1 village on a Tuesday with the aim of returning to that village the following Monday to collect the recorders to allow the data to be downloaded on a Monday night

and recorders placed back on patients the following day in a different village. It was sometimes the case that I struggled to find 10 patients willing to wear the monitor in one village and other participants aged over 70 were therefore selected.

With respect to the HTN data, there are obvious limitations inherent in epidemiological surveys with assessing BP on only one visit. This has been shown previously to overestimate prevalence and underestimate those adequately controlled on treatment (266). In addition, there are problems inherent to BP measurement in the Tanzanian elderly. Firstly, most will never have had their BP taken before, and this will exacerbate anxiety levels and 'white-coat hypertension', already known to be a significant issue in the elderly. Secondly, there is the idea of 'pseudohypertension', a problem whose prevalence is not really known, but suggested to be an issue in the elderly due to stiffening of the arteries and thus decreased compliance. Both of these problems are likely to have overestimated prevalence, despite my trying to minimise effects of the former with a clear explanation of what having BP recorded involved and discarding the first measurement of three. Another issue with my HTN data is the fact that I found it very difficult to assess dietary and social contributory factors. The rural Tanzanian diet is very healthy in that it consists of a lot of rice and vegetables but also often lacking in taste for the same reason. There is a liberal usage of salt therefore to flavour food but I found it very difficult to quantify exact amounts and felt my data may suffer due to the inaccuracies of this and therefore I made a conscious decision to stop collecting this data. Likewise, estimating alcohol intake proved beyond our means, as most elderly people enjoy social drinking, where they will pass around a container of 'mbege', or local brew, and each person will imbibe in turn. Therefore, when I asked about alcohol, the reply came 1 or 2 litres per night, but as this was shared often between several people and the exact percentage of alcohol was unknown as it had been brewed locally, I could not estimate number of units drunk. I did not collect data on smoking as very few elderly people smoked as they could not afford it. The data comparing ECG and echo LVH is limited due to small numbers that had a complete data set for comparison.

8.3 What does this study add?

I began with the hypothesis that AF would be more common in the elderly population of Tanzania, primarily because of rheumatic mitral valve disease, and was keen to perform a robust community-based prevalence study of AF in the elderly, given its causal link with stroke and the substantially increased stroke burden seen in Tanzanians (267). What is clear from this study is that elderly Tanzanians appear to have a strikingly low prevalence of persistent / permanent AF and a similar prevalence of PAF to other populations, suggesting that the increased burden of stroke is either due to other risk factors such as hypertension, or that black Africans are more susceptible to smaller amounts of PAF. It tells us that AF does not appear to be a large health burden in elderly Tanzanians and is thus important when assessing healthcare planning for NCDs in this area in the future.

What is particularly interesting is the finding of HTN prevalence rates similar to high-income countries in the setting of such low prevalence rates of AF. Currently this is difficult to explain but suggests that HTN does not predispose to AF in black Tanzanians as it does elsewhere in the world. However, it also tells us that HTN is likely to be the major risk factor for the increased stroke burden seen in Tanzanians and that, whilst the elderly population are particularly at risk, detection, treatment and control rates remain dangerously low.

8.4 What further research does it suggest?

It will be interesting to know whether the low prevalence of AF is confined to the elderly, or whether this phenomenon extends across all adult age groups, and prevalence in young and middle-aged adults needs to be determined. Future research into whether genetics play a role in the low prevalence of AF despite the high prevalence of HTN will be important. Studying AF candidate gene differences between this population and other populations, both in other areas of Africa and in high-income countries will be interesting. Is there some degree of genetic 'protection' from developing AF, or the myocardial substrate that predisposes to AF in this population? Further research may even be directed towards developing a novel risk prediction algorithm for AF in this population, thereby identifying those at highest risk for monitoring / treatment.

Further confirmation of HTN prevalence rates and the effects of 'white-coat hypertension' and arterial stiffness will ideally be determined in future studies using 24-hour ambulatory BP monitoring and assessing pulse wave velocities. In addition further work is needed, particularly in the elderly, to look at reasons for such low levels of detection, treatment and control of hypertension and identify possible solutions.

With respect to PWV, rural elderly Tanzanians appear to have different 'normal' values to other populations studied. Hopefully, work done here will lead on to identification of reference ranges in this population and may be of some use clinically, in the future (with some refinement) in order to identify people at risk of NCDs such as AF and stroke.

Appendix I: Information sheet for recording a 12-lead ECG


Jinsi Yakupima Shinikizo La Damu (Presha)

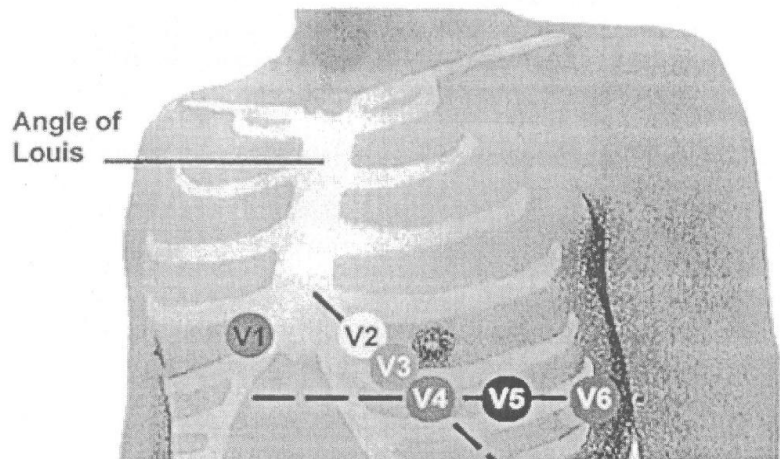
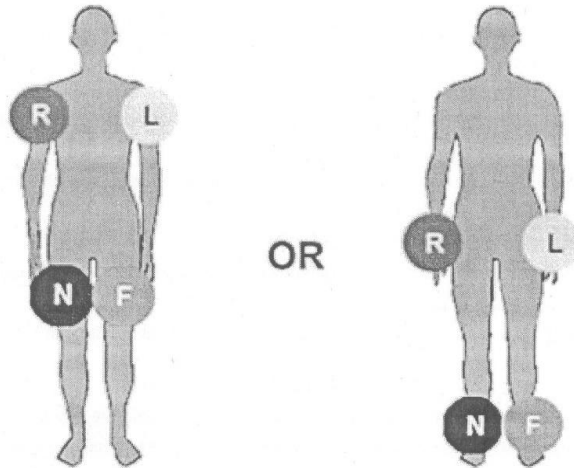
1. Mweleze mgonjwa nini kitafanyika, mwakikishie kuwa hamna madhara/maumivu na ujitahidi kumweka kwa hali ya amani (iwapo anawasiwasi presha/shinikizo la damu litakuwa juu)
2. Mgonjwa akae kwa utulivu kwa dakika tano (hii ni nafasi nzuri ya kufanya ECG/kupima mapigo ya moyo yasiyo ya kawaida)
3. Weka mashine kwenye mkono wowote (maana vipimo vya shinikizo la damu havina tofauti kwenye mkono wowote ule, ila epuka mkono ambao umeshawahi kuumia au uliyo na ulemavu)
4. Kamba ya mashine inatakiwa iwe upande wa mbele ya mkono mshipa unapopita-brachial artery.
5. Hakikisha mkono umelegezwa na umeshikiliwa au umezuwiwa (Na anayepima au kitanda)
6. Hakikisha mkono umezuwiwa panapolingana na moyo
7. Hakikisha mashine iko kwenye alama ya 240
8. Bonyeza kitufe cha buluu (samawati) kuwasha (pia kuzima au kufuta kwa mfano kama mashine haijawekwa mkononi kwa usahihi)
9. Vipimo vitatu vya kwanza vipimwe mgonjwa akiwa amekaa au amelala (zingatia unapima akiwa vipi, amekaa, amesimama au amelala)
10. Subiri dakika moja kabla ya kila kipimo
11. Mwombe mgonjwa asimame, mpime tena mara moja (Hakikisha mkono umezuwiwa panapolingana na moyo)
12. Hakikisha mgonjwa anasimama angalau kwa dakika 2 kabla ya kupima kipimo cha kusimama.

Jinsi Ya Kupima Mapigo Ya Moyo Yasiyo Ya Kawaida

1. Mgonjwa akae au alale mwambie awemtulivu na umhakikishie kwamba kipimo hakina madhara wala hakiumi kwa jinsi yoyote (iwapo mgonjwa ametulia, punguza mitingishiko isiingiliane na rekodi za mashine)
2. Mgonjwa avue nguokuanzia kwenye kiuno kwenda juu, na akunje suruali
3. Weka electrodes kumi za ECG kama ilivyoonyeshwa hapo chini (6 kwenye kifua na 2 kwenye mikono na 2 nyingine kwenye miguu)
4. Ambatisha ECG leads kwenye electrodes
5. Washa mashine kwa kutumia kitufe cha kuwasha au kuzima, itachukua kama sekunde 20 kuwaka ①
6. Subiri hadi screen/mashine ionyeshe mistari, alafu bonyeza kifungo/kitufe kilicho andikwa (Pat)
7. Hii itakuwezesha kuingiza taarifa za mgonjwa.
8. Chagua 'yes' kwa 'mgonjwa mpya?' Tumia mshale wa kushoto ← alafu bonyeza (↓)
9. Ingiza jina la ukoo kwa kutumia vifungo vya herufi alafu bonyeza (↓)
10. Andika jina au majina ya kwanza alafu bonyeza (↓)
11. Iwapo umekosea, futa kwa kutumia..... X
12. Bonyeza kitufe (Pat) kurudi kwenye screen au kioo cha ECG
13. Hakikisha kwamba mistari ya chini imenyooka kukata kwenye screen/kioo, na inamistari ya ECG kwa juu



14. Kama kunatatizo kwenye viunganishi vyovyote vya lead vitatoa sauti na electrode ambayo inatatizo itaonyesha chini ya screen/kioo. Sauti ikiisha baada ya sekunde chache na mistari imenyooka-
15. Bonyeza kitufe cha 'acquire' 
16. Baada ya sekunde chache, karatasi iliyo na maandishi ya ECG itatokea kwa upande wa mwisho wa mashine
17. Baada ya mashine kumaliza kuchapa, angalia screen/kioo kwa sekunde chache hadi uone maandishi haya 'Saving ECG' na '10 ECGs stored'.
18. Hii inamaanika kwamba vipimo vimeifadhiwa kwenye kumbukumbu na unaweza kuondoa leads/electrodes kwa mgonjwa na kuzima mashine.



Namba ya simu ya mkononi ya daktari Mathayo (iwapo tatizo lolote limejitokeza kwenye mashine) - 0755987287

Appendix II: a. Demographic Data Collection Proforma

KIBALI CHA KUTAFITI MATATIZO YA MISHIPA YA FAHAMU NA KUCHUNGUZA KISABABISHI KATIKA WILAYA YA HAI

Tarehe ya uchunguzi _____ Eneo la uchunguzi _____
 Date of assessment: ___/___/___ Assessment site: _____

DEMOGRAPHIC DETAILS/TAARIFA ZA WATU

Jina _____ Tarehe ya kuzaliwa _____ Umri _____ Miaki _____ Jinsia: Me/Ke
 Name: _____ DOB: ___/___/___ Age: |_|_|_| Yrs Sex: M / F
 (Jina) _____ (kijiji (Jina) _____
 Balazi (name) : _____ Tawi/Village(name): _____
 (nyumba 10) _____ No. yanyumba _____ No. yasimu _____
 Shina (10 cell no.)|_|_|_| House code |_|_|_| Cell phone no.: _____
 Mgonjwa anaweza kutembea _____ Umbali/muda wa kwenda kwenye kituo cha afya _____
 Ambulant: Yes/Ndiyo No/Hapana Distance/Time to Health Centre: _____

HISTORIA YA ZIADA INAHITAJIKA **Yes/Ndiyo** **No/Hapana**

FURTHER DEMOGRAPHIC DETAILS/ TAARIFA ZA ZIADA ZA WATU

Tribe/kabila|_|_|_| Religion/Dini |_|_|_| Marital status/Hali ya ndoa |_|_|_| Household comp'n/Muundo wa kaya |_|_|_|
 1. Mzaramo 1. Christian/Mkirsto 1. Married/Ameoa/olewa 1. Lives Alone/Anaishi mwenyewe
 2. Mndengereko 2. Muslim/Mwislam 2. Widowed/Mjane 2. With spouse/Anaishi na mwenza
 3. Mchagga 3. Hindu/Mhindi 3. Divorced/Mtalikiwa 3. Spouse/others/ Na mwenza na wengineo
 4. Mmasai 4. Pagan/Mpagani 4. Single/Kapera 4. W son/daughter/ Na watu wazima
 5. Mpare 5. Other – state 5. Separated/Ametengana 5. W grandchildren/ Na watoto wengine
 6. Mnyamwezi Nyingine – taja _____ 6. Other state Nyingine - taja _____
 7. Msukuma _____
 8. Other – state/ Nyingine - taja _____

Age when married/Umri alipoowa/olewa |_|_|_| YRS Number of children/Idadi ya watoto |_|_|_|

Patient born in Hai/Mgonjwa mzawa wa Hai: Yes/Ndiyo No/Hapana Details/Maelezo _____

Ever lived outside Hai/Alishawahi kuishi nje ya Hai: Yes/ Ndiyo No/Hapana Details/Maelezo _____

BLOOD PRESSURE/ SHINIKIZO LA DAMU Tulia kwa dakika 5 kabla ya kusoma kipimo na dakika 1 kati ya kila kipimo, kasha simama kwa dakika 3 kabla ya kusoma kipimo cha mwisho **AKIWA AMESIMAMA/ STANDING**

Systolic				
Diastolic				

Kimo/Height/demispan (cm) _____ **Uzito/Weight(measured/estimate)(kg)** _____

SCREENING QUESTIONNAIRE Answered positively/ **DODOSO LA UCHUNGUZI/Lililojibiwa kwa mtazamo chanya**

Swali	Mtazamo Chanya	Mtazamo Hasi	Elezea
1			
2			
3			
4			
5			
6			
7			
8			

9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Kazi za kila siku (za maisha)

Question no	Alama/Score	3	2	1	0
1	Kula		Anajilisha	Anahitaji msaada wa kula	Analishwa
2	Kuoga			Anajitegemea	Anategemea mtu
3	Kujiweka katika hali ya usafi kwa mfano kusugua meno			Anajitegemea	Anategemea mtu
4	Kuvaa		Anajitegemea	Anahitaji msaada mdogo	Anategemea mtu
5	Kinyesi		Anaweza kuzuia kinyesi	Kinatoka mara moja moja kwa bahati mbaya	Kinyesi kinatoka bila kufahamu (hawezi kuzuia)
6	Mkojo		Havuji mkojo	Unavija mara moja moja kwa bahati mbaya	Anavuja mkojo
7	Kutumia choo		Anajitegemea	Anahitaji msaada mdogo	Anategemea mtu
8	Anahamishwa na watu wangapi? Kwa mfano kutoka kitandani kwenda kwenye kiti	Anajitegemea	Anahitaji msaada mdogo	Anahitaji msaada mkubwa/sana	Anategemea mtu
9	Kutembea	Anajitegemea	Anatembea kwa msaada wa mtu mmoja	Anajitegemea wheelchair	Hawezi kutembea
10	Anatembea kilimani		Anajitegemea	Anahitaji msaada mdogo	Anategemea mtu
	Vifaa vya kutembelea?	Ndio Elezea	Hapana	Angetumia kama ingekwepo/ ingepatikana	
	Anamatatizo ya kuona?	Ndio	Hapana		
	Umeambiwa kwamba una kisukari?	Ndio	Hapana		

HAI ATRIAL FIBRILLATION PREVALENCE STUDY (2009/2010)

STUDY SELECTION.

DETAILS OF AF

History: 1. Totally from patient
 2. Patient with collateral help (specify who) _____
 3. Totally from collateral (specify who) _____

Symptoms	yes	No	Details
Palpitations			
SOB			
NYHA I (no Sx / limitation)			
NYHA II (mild Sx)			
NYHA III (mod Sx)			
NYHA IV (severe /rest Sx)			
PND			
Orthopnoea			
Pedal Oedema			
Chest Pain			
CCSAC 0 (asymptomatic)			
CCSAC I (strenuous)			
CCSAC II (moderate)			
CCSAC III (mild)			
CCSAC IV (rest)			
Pre-syncope			
Syncope			
Tiredness			
Limited ET			
Other please specify			

When did symptoms start? Year: _____ Age: _____

Details: _____

Any event illness prior to first Sx? Yes No Details _____

History: Free Text (please continue on reverse as required)

D: TREATMENT HISTORY

Help Sought for Cardiac Symptoms: Yes No Age/Year when help sought _____

- | | | | |
|--------------------------------------|--------------------------|--------------------------|--------------------------|
| 1. Self-medication using modern drug | <input type="checkbox"/> | 7. Government hospital | <input type="checkbox"/> |
| 2. Family members or friends | <input type="checkbox"/> | 8. Private dispensary | <input type="checkbox"/> |
| 3. Traditional healers/medicines | <input type="checkbox"/> | 9. Private health centre | <input type="checkbox"/> |

- | | | | |
|-----------------------------|--------------------------|----------------------------|--------------------------|
| 4. Village health worker | <input type="checkbox"/> | 10. Private hospital | <input type="checkbox"/> |
| 5. Government dispensary | <input type="checkbox"/> | 11. Private Pharmacy, shop | <input type="checkbox"/> |
| 6. Government health centre | <input type="checkbox"/> | | |

Details: _____

Known AF/Reason Given for the Symptoms? Yes No

Diagnosis/Reason? _____ By Who? _____ When? _____

Follow up? Yes No Details _____

Treatment for AF symptoms

Treatment	Drug	Dose/ Freq	From who	Since when	Compliance	Afford Reg	Effective	Side Effects	Why stopped
Current					Daily From time to time When available	Y / N	Very Good Good No effect Bad Very Bad	Dizziness Tiredness Headache Nausea Rash Other	N/A
Y / N									

Traditional Healer Intervention?: Yes No Length of trad. Healer treatment:

- | | | | |
|---------------------------------------|--------------------------|------------------------|--------------------------|
| 1. Oral medication | <input type="checkbox"/> | 1. Less than one week | <input type="checkbox"/> |
| 2. Bath | <input type="checkbox"/> | 2. 1 – 2 weeks | <input type="checkbox"/> |
| 3. Inhalation | <input type="checkbox"/> | 3. 2 weeks – 1 month | <input type="checkbox"/> |
| 4. Topical | <input type="checkbox"/> | 4. More than one month | <input type="checkbox"/> |
| 5. Roots/leaves (state type if known) | <input type="checkbox"/> | | |
| 6. Scarification | <input type="checkbox"/> | | |
| 7. Other (state): _____ | <input type="checkbox"/> | | |

Effective? Yes No Cost _____

Explanation/Diagnosis _____

Details: _____

Other Medications? Yes No

Details: _____

PAST MEDICAL HISTORY

Any current/past severe/chronic illnesses Yes No

- | | | | |
|--------------------------|--------------------------|-------------------------------|--------------------------|
| 1. Angina / IHD | <input type="checkbox"/> | 6. Rheumatic Fever | <input type="checkbox"/> |
| 2. Hypertension | <input type="checkbox"/> | 7. Heart Failure | <input type="checkbox"/> |
| 3. Stroke | <input type="checkbox"/> | 8. Hyper/Hypothyroidism | <input type="checkbox"/> |
| 4. Diabetes | <input type="checkbox"/> | 9. Congenital Cardiac Problem | <input type="checkbox"/> |
| 5. Hypercholesterolaemia | <input type="checkbox"/> | 10. Other (state) | <input type="checkbox"/> |

Details _____

If Stroke, impaired ADLs? Yes No

- | | | | |
|---------------|--------------------------|-------------------|--------------------------|
| 1. Mobility | <input type="checkbox"/> | 6. Toilet Use | <input type="checkbox"/> |
| 2. Continence | <input type="checkbox"/> | 7. Feeding | <input type="checkbox"/> |
| 3. Washing | <input type="checkbox"/> | 8. Transfer | <input type="checkbox"/> |
| 4. Dressing | <input type="checkbox"/> | 9. Walking Aids | <input type="checkbox"/> |
| 5. Grooming | <input type="checkbox"/> | 10. Other (state) | <input type="checkbox"/> |

Details: _____

In the previous twelve months:

Admitted to: hospital? Yes No

Attended health centre/dispensary? Yes No

- 1. Once
- 2. Twice
- 3. More than twice (state) _____

- 1. Once
- 2. Twice
- 3. More than twice (state) _____

Details/diagnosis: _____

FAMILY HISTORY

Is there a family history of Cardiac disorders? Yes No

- | | | | |
|-------------|--------------------------|--------------------|--------------------------|
| 1. Brother | <input type="checkbox"/> | 7. Grandmother | <input type="checkbox"/> |
| 2. Sister | <input type="checkbox"/> | 8. Grandfather | <input type="checkbox"/> |
| 3. Father | <input type="checkbox"/> | 9. Maternal aunt | <input type="checkbox"/> |
| 4. Mother | <input type="checkbox"/> | 10. Paternal aunt | <input type="checkbox"/> |
| 5. Son | <input type="checkbox"/> | 11. Maternal uncle | <input type="checkbox"/> |
| 6. Daughter | <input type="checkbox"/> | 12. Paternal uncle | <input type="checkbox"/> |

State what _____

SOCIAL HISTORY

- Alcohol Intake** Yes No
- | | |
|------------------------|------------------------------------|
| 1. Mainly local brew | 1. Light (weekends and on holiday) |
| 2. Mainly bottled beer | 2. Average (<4 days/week) |
| 3. Mainly spirits | 3. Heavy (4 + days/week) |

More heavily in the past? Yes No

Details: _____

Occupation Past/Present: _____

Had to stop because of symptoms? Yes No

Details _____ **Smoking /**

Snuff / Chewing Tobacco Yes No **Pack Years** _____

Caffeine (>4 cups / day) Yes No **Amount** _____

CLINICAL EXAMINATION

General Inspection

Comfortable at Rest Yes No

Details _____

Pedal Oedema Yes No

Details _____

Other Obvious Diagnoses / Signs Yes No

Details _____

Pulse

Rate _____

Regular Yes No

Details: _____

Normal Character Yes No

If No, Details: _____

JVP

Raised Yes No

Description: _____

Facial Features

Arkus	Yes	No
Xanthelasma	Yes	No
Anaemia	Yes	No
Malar Flush	Yes	No
Cyanosis	Yes	No
Angular Stomatitis	Yes	No

Fundoscopy

L Eye	Normal	Abnormal	Impossible
R Eye	Normal	Abnormal	Impossible

Details: _____

Chest Inspection

Scars	Yes	No
-------	-----	----

Details: _____

Deformity	Yes	No
-----------	-----	----

Details: _____

Chest Palpation

Apex Beat	Normal	Abnormal	Impalpable
-----------	--------	----------	------------

Details: _____

RV Heave	Yes	No
----------	-----	----

Thrill	Yes	No
--------	-----	----

Details: _____

Chest Auscultation

S1 + S2 Normal	Yes	No
----------------	-----	----

Details: _____

Murmurs	Yes	No
---------	-----	----

Systolic	Yes	No
----------	-----	----

Diastolic	Yes	No
-----------	-----	----

Details: _____

Added Sounds	Yes	No
--------------	-----	----

Details: _____

Basal Creps	Yes	No
-------------	-----	----

Details: _____

Miscellaneous

Carotid Bruit	Yes	No
---------------	-----	----

Details: _____

Renal Bruit	Yes	No
Details: _____		
Peripheral Pulses	Yes	No
Details: _____		
Thyroid Normal	Yes	No
If no, details: _____		

Summary

INVESTIGATIONS

ECG Done?	Yes	No
Rhythm Strip	Yes	No
P Wave analysis	Yes	No

Electrocardiogram / Rhythm Strip

Atrial Fibrillation	Yes	No	
Details _____			
Minnesota Coding System (for ischaemia)	Definite	Equivocal	Other
Details (code) _____			
AF Predictors	Yes	No	
P Wave Terminal Force (mcV/s) _____			
Maximum P Wave Duration (ms) _____			
Mean P Wave Duration (ms) _____			
P Wave Dispersion (Pmax-Pmin) (ms) _____			
P Wave Duration in Lead II (ms) _____			
Maximum P Wave Area (mcV/ms) _____			
Mean P Wave Area (mcV/ms) _____			
PR Duration (ms) _____			
Other Abnormalities _____			

Echocardiogram

Left Ventricle

LV Function Normal	Yes	No		
Estimated EF	<35% (severe)	36-44% (mod)	45-54% (mild)	>55%
Details: _____				
RWMAs	Yes	No		
Details: _____				
LV Wall Thickness Normal	Yes	No		
Details: _____				
IV Septal Thickness Normal	Yes	No		
If No, degree hypertrophy	Mild	Moderate	Severe	
Details: _____				
Posterior Wall Thickness Normal	Yes	No		
If No, degree Hypertrophy	Mild	Moderate	Severe	
Details: _____				
LV Diameter Normal	Yes	No		
LVIDd Normal	Yes	No		
If No, How Dilated	Mild	Moderate	Severe	
Details: _____				
LVIDs Normal	Yes	No		
If No, how Dilated	Mild	Moderate	Severe	
Details: _____				
Any Other Abnormality _____				

Right Ventricle

RV Function Normal	Yes	No		
If No, Degree Impairment	Mild	Moderate	Severe	
Details: _____				
RV Size Normal	Yes	No		
If No, Degree Dilated	Mild	Moderate	Severe	
Details: _____				

Atria

LA size Normal	Yes	No		
If No, Degree Dilated	Mild	Moderate	Severe	
Details: _____				
RA Size Normal	Yes	No		
If No, Degree Dilated	Mild	Moderate	Severe	
Details: _____				

Aortic Valve

AoV Normal	Yes	No		
Appearance of Valve: _____				

AoStenosis	Yes	No		
Peak Velocity (m/s)_____		Mild	Moderate	Severe
Peak Pressure Drop (mmHg)_____		Mild	Moderate	Severe
Valve Area (cm2)_____		Mild	Moderate	Severe
Overall Impression Severity AS		Mild	Moderate	Severe
AoRegurgitation	Yes	No		
P1/2T_____		Mild	Moderate	Severe
Overall Impression Severity AR		Mild	Moderate	Severe

Mitral Valve

MiV Normal	Yes	No		
Appearance of Valve:_____				
MiStenosis	Yes	No		
MiV Area (cm2)_____		Mild	Moderate	Severe
MiV P1/2T(msec)_____		Mild	Moderate	Severe
Mean Pressure Drop (mmHg)_____		Mild	Moderate	Severe
Overall Impression Severity MS:		Mild	Moderate	Severe
MiRegurgitation	Yes	No		
Jet Area(cm2):_____		Mild	Moderate	Severe
Jet Area / LA (%)_____		Mild	Moderate	Severe
Overall Impression Severity MR:		Mild	Moderate	Severe

Tricuspid Valve

TV Normal	Yes	No		
TR	Yes	No		
Severity TR	Mild	Moderate	Severe	
Details:_____				
PASP (RAP+RVSP mmHg)_____				
TS	Yes	No		
Severity TS	Mild	Moderate	Severe	

Pulmonary Valve

PV Normal	Yes	No		
Details:_____				

Miscellaneous

Aorta Normal	Yes	No		
Details:_____				
Diameter of Sinus of Valsalva_____				
Dilatation		Mild	Moderate	Severe
Pericardial Effusion	Yes	No		
Details (+ other pericardial problems):_____				
IVC Normal	Yes	No		

Details: _____

Summary Echo Findings

Bloods

Blood taken? **Yes** **No** Location of samples: _____

Haematology Serum

Date Blood Taken: _____

RESULTS

Record 000 if the blood tests are not carried out

Haematology

2	Haemoglobin (g/dl)	_ _ _ _ _ _ _
3	Haematocrit (fl)	_ _ _ _ _ _ _
4	MCV	_ _ _ _ _ _ _
5	Blood glucose (mmol/L)	_ _ _
6	Platelets	_ _ _
7	White Cell Count	_ _ _
8	Neutrophils	_ _ _

Biochemistry

1	Sodium (134-147 mmol/L)	_ _ _ _ _ _ _
2.	Potassium (3.5-5.0mmol/l)	_ _ _ _ _ _ _
3	Urea (3.1-7.9 mmol/L)	_ _ _ _ _
4	Creatinine (75-155 umol/L)	_ _ _ _ _
5	Calcium (2.12-2.60 mmol/L)	_ _ _ _ _
6	Corrected calcium – calcium +0.1(40-albumin value)	_ _ _ _ _
(If albumin value >40 corrected calcium = calcium +0.1(albumin value-40)		
7.	Magnesium	_ _ _ _ _
8.	Total protein (60 – 80 g/L)	_ _ _ _ _
9.	Albumin (34-50 g/L)	_ _ _ _ _
10.	Bilirubin	_ _ _ _ _
11.	Alkaline phosphatase (35-120 IU/L)	_ _ _ _ _
12.	Alanine transaminase (<45 IU/L)	_ _ _ _ _
13.	TSH (0.35-4.90 mU/L)	_ _ _ _ _
14.	Lipid Profile	
	Triglycerides	_ _ _ _ _
	HDL Cholesterol	_ _ _ _ _
	Non-HDL Cholesterol	_ _ _ _ _

24 Hour Tape / R - Test **Yes** **No**

Paroxysmal AF	Yes	No
Details: _____		

Other Arrhythmias	Yes	No
Details: _____		

Appendix III: Follow-up Data Collection Proforma

FOLLOW UP PROFORMA

Name _____ Balozzi _____ Age _____

Diagnosis:

Details:

DETAILS OF FOLLOW UP

History: 1.From patient / 2.Patient with collateral _____ /3.From collateral _____

Medication for AF/Hypertension. Drug/Dose/Frequency:
Effective: ?reduction of symptoms
Side effects:
Treatment ongoing? If not why stopped: Side effects/Can't Afford/Didn't renew prescription
Blood Pressure
Plan (?further treatment needed)

Appendix IV: Prescription / Referral Form

Northumbria Healthcare Foundation Trust, Newcastle, England Neurological Dis

I AM A DOCTOR FROM ENGLAND, I HAVE REVIEWED THE BELOW NAMED PATIENT TODAY AS PART OF A STUDY LOOKING INTO NEUROLOGICAL DISORDERS AND THEIR RISK FACTORS, I HAVE DIAGNOSED THE FOLLOWING CONDITION AND WOULD SUGGEST THE FOLLOWING TREATMENT. I WOULD BE GRATEFUL IF YOU COULD SUPPLY THIS. THANK YOU.

NAME OF PATIENT:

DATE OF BIRTH OF

PATIENT:

BALOZI:

VILLAGE:

DIAGNOSIS MADE:

TREATMENT SUGGESTED

SIGNATURE OF DOCTOR:

DATE:

NAME OF DOCTOR:

GMC NUMBER:

What is atrial fibrillation?

Atrial fibrillation is an irregular heart rhythm. It is the commonest heart rhythm disorder, and becomes more common with age. It happens as a result of interruption of the heart's normal electrical activity, causing chaotic electrical messages in the top two chambers of the heart (the atria) leading to a change in the way these chambers pump blood into the bottom two chambers of the heart (the ventricles) and a faster than normal heart rate.

What causes atrial fibrillation?

Anyone can develop atrial fibrillation; it occurs in all races, social classes, and is more common with advancing age. There are many possible causes, including high blood pressure, structural heart disease and abnormal levels of different salts in the blood.

How is atrial fibrillation diagnosed?

Normally people with atrial fibrillation are diagnosed when they are felt to have an irregular pulse. This irregular rhythm is then confirmed as atrial fibrillation by undergoing a trace of the heart's electrical rhythm, an electrocardiogram (ECG).

Can atrial fibrillation be treated?

There are some very good, cheap treatments for atrial fibrillation. These include aspirin to help thin the blood and prevent clots forming in the top chambers of the heart, and drugs such as beta-blockers which help to control the chaotic and often fast heart rates that make people feel ill.

How might atrial fibrillation affect my life?

Having atrial fibrillation increases your risk of suffering from blood clots on the brain (stroke). It can also decrease the heart's efficiency and over time cause the heart muscle to 'fail'. This can lead to symptoms of breathlessness, palpitations and swollen ankles. Simple treatments as mentioned previously can help lower this risk.

Researching atrial fibrillation in the Hai district

We would like to find out how many people in the Hai district have atrial fibrillation. This will help to provide better treatment for those people who do have this condition. For this reason we are doing a survey of all the households in the Hai district to look for people aged over 70 who might have atrial fibrillation.

If we think you might have atrial fibrillation, and you give your permission, you will be visited in your home by a doctor, who will ask more questions and examine you. If the doctor thinks you do have atrial fibrillation, your permission will be asked to give a blood sample, to have a recording of your heart beat taken (Electrocardiogram), and undergo an ultrasound scan of the heart (Echocardiogram).

The electrocardiogram takes about 5 minutes to perform. It is completely painless and involves putting some sticky labels on the chest which are then attached up to a machine to give an electrical printout of the hearts activity. The echocardiogram takes about 30 mins and again is completely painless. It involves putting some jelly on the chest and looking at the heart through an ultrasound probe placed on the chest.

Only the medical research team will be able to see any personal details about people who have atrial fibrillation,

and only people who give permission will be visited and examined by the doctor. Any food or transport costs will be paid for by the research team.

Many people who have atrial fibrillation do not know that they have this condition. If we find anybody who we think has atrial fibrillation, we can offer information and advice to both them and their families. We can also help with arranging for people to get the right kind of treatment.

CONSENT FORM – Person with Atrial Fibrillation

Atrial Fibrillation Study for the Hai District

Name:
Ballozi:
Village:

Have you read the information sheet? Yes No

Have you had the opportunity to ask questions and discuss the study?
Yes No

Have you had all your questions answered correctly? Yes No

Who have you spoken to? _____

Do you understand that you can withdraw from the study:

- at any time,
 - without having to give a reason,
 - without affecting my future care.
- Yes No

Do you agree to take part in the Atrial Fibrillation study for the Hai District?
Yes No

Signature of person consenting

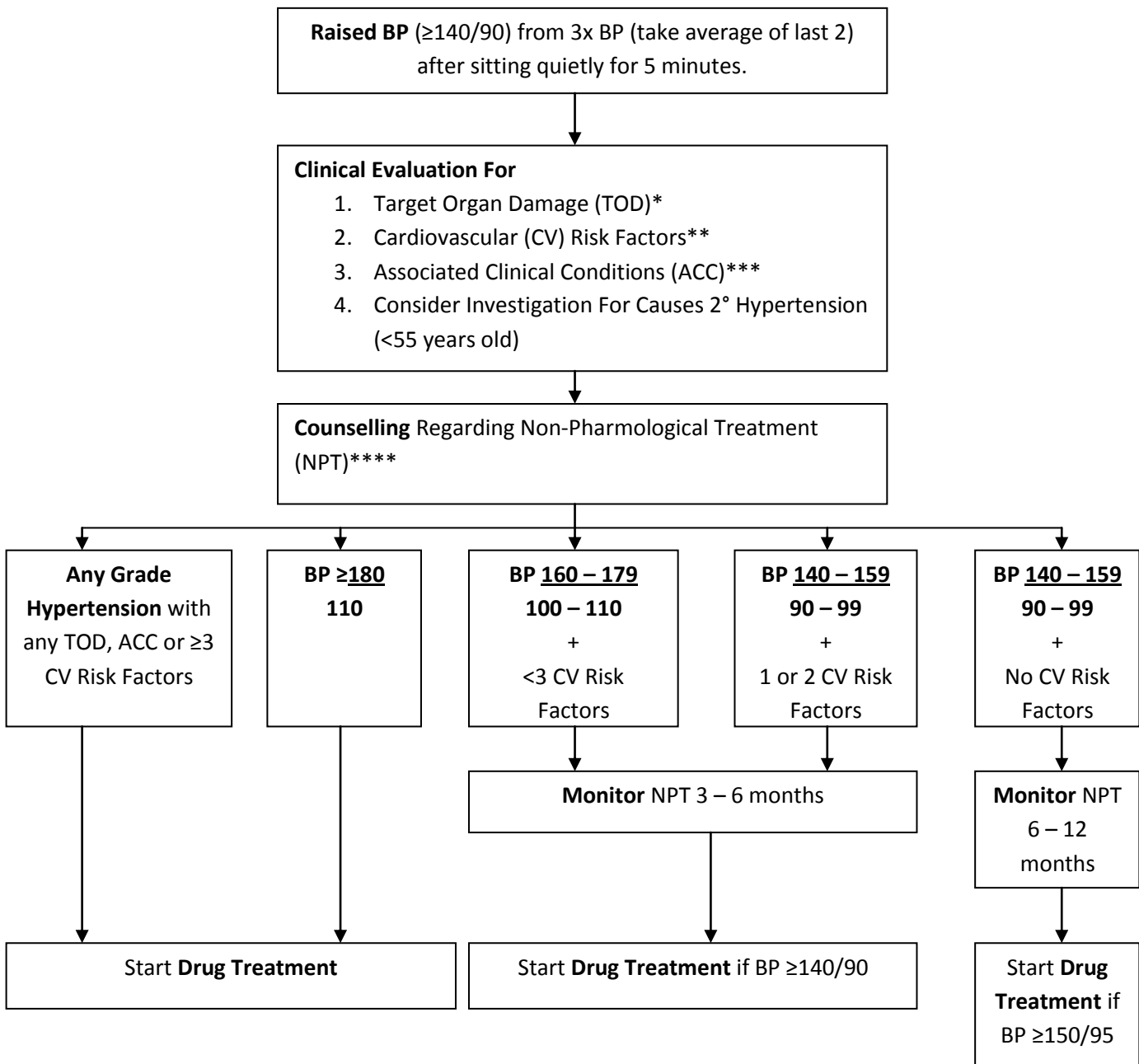
Print name _____ Date/...../.....

Signature of doctor/medical assistant/nurse _____

Print name _____ Date/...../.....

drwalker/patient.consent.form

Appendix VI: Hypertension Guidelines for Diagnosis and Treatment in the Hai District
Blood Pressure Assessment and When to Initiate Treatment



Target Organ Damage*	CV Risk Factors**	Associated Clinical Conditions***	Non-Pharmacological Therapy****
1.Left Ventricular Hypertrophy 2.Renal Impairment (proteinuria / raised Creatinine) 3.Grade 2 Hypertensive Retinopathy	1.Men>55, Women>65 2.Diabetes Mellitus 3.Smoker 4.Family History Premature CV Disease (stroke / Myocardial Infarction)	1.Stroke / TIA 2.Angina / Myocardial Infarction 3.Congestive Cardiac Failure Chronic Renal Failure 4.Grade 3/4 Hypertensive Retinopathy	1.Stop Smoking 2.Decrease Salt Intake 3.Decrease Alcohol Intake 4.Weight Loss 5.Increase Physical Activity 6.Increase Fruit/Vegetables

Drug Treatment For Hypertension



Guidance Notes	3rd Line Agents
<p>*treatment includes Isolated Systolic Hypertension (i.e. Raised Systolic BP with Normal Diastolic BP, and vice-versa)</p> <p>**Good Practice to monitor Renal Function initially and with every dose titration</p> <p>***Care in Elderly (>70 years), frail or those with Postural BP drop (>20/10mmHg or Symptomatic)</p>	<ol style="list-style-type: none"> 1.Methyldopa initially 250mg three times daily increased to maximum 1g tds (elderly 125mg twice daily initially, max 1g bd) 2.Propranolol initially 80mg twice daily, max 160mg twice daily 3.Captopril** initially 12.5mg twice daily, max 50mg twice daily (elderly initially 6.25mg bd)

Appendix VII: Fieldwork Photographs



Traditional homestead in Hai district (Mount Kilimanjaro in background)



The Hai district research team



Examining a patient with AF



Running Repairs to the Project Car (a common sight!)

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