CHAPTER 1. INTRODUCTION

1.0 Introduction

Epidemiology of Cardiovascular Disease

Eighty percent of the worldwide cardiovascular disease (CVD) mortality occurs in low and middle-income countries (LMIC) and non-communicable diseases account for US $250 billion in lost productivity in these countries, nearly 4% of the GDP of these countries (1–3). While the rates of death attributable to CVD has been declining in almost all high-income countries for the last 3 decades (4), an epidemic of CVD is occurring in LMIC. Between 1998-2008 in the US, for example, the rate of death attributable to CVD declined by 30% (5), and even greater declines have been observed in some European countries such as Finland where CVD mortality has been reduced by 85% in the last 35 years (3,4). This decline has provided hope that the tide of CVD can be stemmed with appropriate public health measures including better prevention, diagnosis and treatment. For these reasons, global attention to the problem of CVDs in LMIC has been growing, and has rapidly gained momentum since the 2011 United Nations Political Declaration on the prevention and control of non-communicable diseases (6).

Epidemiology of Hypertension - Global

Hypertension is the major driver of this epidemic of CVDs in LMIC and worldwide (7,8). Hypertension is responsible for 9.4 million deaths per year worldwide, nearly half of all
deaths due to cardiovascular disease, and most of these deaths are preventable (9).

One-quarter of the world’s adult population has hypertension and this proportion will likely increase to 29% by 2025 (2). By age 70, 70% of US citizens have hypertension (10). According to one recent report, worldwide, “hypertension is singlehandedly responsible for 13% of all global deaths, 51% of stroke deaths, and 45% of coronary heart disease deaths” (11). Based on the most recent data from the Global Burden of Diseases Study, hypertension is the single most important risk factor for disease burden worldwide and causes 7% of all worldwide Disability Adjusted Life Years (DALYs) (12).

**Epidemiology of Hypertension - Africa**

Historically, hypertension was rare in sub-Saharan Africa. In 1929, the first publication of hypertension surveillance in Africa reported that, “Over two years at a native hospital in the South of Kavirondo in Kenya, during which period approximately 1800 patients were admitted, no case of raised blood pressure was encountered” (13). Another study in Ethiopia in the 1940’s described a prevalence of hypertension of 1.8% (14), and a third study in rural Egypt in the 1950’s revealed a prevalence of 3.8% (15).

The prevalence of hypertension began to increase rapidly in Africa in the 1960-1980’s as urbanization and industrialization commenced. Due to economic and infrastructure limitations, the data that document this rise in the prevalence of hypertension are scarce. In the only survey and resurvey in the same areas using the same methodology, among adults 47-57 years old, the overall prevalence of hypertension increased from 25.4% in men to 41.1% and from 27.2% to 38.7% in women (16).
In sub-Saharan Africa, the prevalence of hypertension in the general population is the highest of any region in the world (Figure 1)(3). In 2008, the age-adjusted prevalence of hypertension was 23.3%, similar to that seen in the US and Europe, and the prevalence of hypertension was continuing to rise rapidly (17). According to the WHO’s latest report, Africa now has the highest age-standardized prevalence of raised blood pressure in the world in adults over the age of 25 (3). In 2025, the prevalence of hypertension is projected to further increase so that the number of people with hypertension in sub-Saharan Africa would increase 68% from 74.7 million to 125.5 million (17). In a striking prospective multicenter cohort study from South Africa, hypertension was the single most common reason for outpatient consultation in that country and accounted for 12% of all visits (18).

**Risk Factors for Hypertension**

The risk factors for this epidemic of hypertension in sub-Saharan Africa have not been well defined (2,16,19). In developed countries, adiposity is the most common risk factor for hypertension (20), and the population attributable fraction has been estimated to be approximately 70% in men and 60% in women (21,22). Although the rates of obesity are increasing in sub-Saharan Africa, they still remain much lower than those observed in
the US and Europe. In one survey of adult females between the age of 47-57 years in urban Tanzania, the mean BMI increased significantly between 1987 and 1998 but the overall rate of obesity remained <5% with higher obesity rates in urban (8%) than rural areas (2%) (16). In a more recent community survey of chronic diseases in East Africa, rates of obesity ranged 9.5% in rural Kenya to 17.4% in urban Tanzania (23). The fact that obesity alone cannot fully explain the epidemic hypertension occurring in sub-Saharan Africa makes the exploration of other, region-specific determinants of hypertension critical to fully understanding both the pathophysiology and best approach for combating this epidemic (24).

There is good reason to believe that the pathophysiology of hypertension in Africans may be different from that of other ethnic groups given what is known about African-Americans. African-Americans have some of the highest rates of hypertension in the world (41%), and, unlike in other race/ethnic groups in the US, these rates are continuing to rise (36 – 41% between 1988 – 2002) (5). Compared with whites in the US, African-Americans develop hypertension earlier in life, and their average blood pressures are much higher. Also, African-Americans have a 320% greater rate of end-stage kidney disease, an 80% greater rate of fatal stroke and a 50% greater rate of death attributable to heart disease (5,25). African-Americans with hypertension have also been shown to have more salt-sensitivity and lower renin levels, with blood pressure that responds better to thiazide diuretics and calcium channels and less to ACE-inhibitors and beta-blockers (26,27). Understanding the unique mechanisms of
epidemic hypertension in sub-Saharan Africa could provide unique insights into the overall mechanisms of hypertension, particularly among people of African descent.

### 1.2 Primary Care for Hypertension

Primary healthcare is the cornerstone for diagnosing and treating hypertension and preventing cardiovascular disease (3,25,28,29). In large part, the reductions in cardiovascular mortality in high-income countries are due to better primary healthcare for hypertension (4). Primary healthcare is critical for hypertension because primary healthcare facilities provide the ideal context for health education, prevention, diagnosis and treatment (3). Lifestyle modifications have been proven to be effective in delaying the onset of hypertension, but only with the regular reinforcement of health messages in a primary healthcare facility (25). Even with a healthy lifestyle, though, more than 50% of adults will develop hypertension by 70 years of age (25).

Primary healthcare facilities are critical for early diagnosis of hypertension. Most adults with hypertension are asymptomatic until they develop complications such as heart failure, stroke, heart attack or renal disease. Once these complications develop, they are usually irreversible. Therefore, international guidelines consistently recommend that blood pressure screening should be performed every 1-2 years in adults (3,25,28,29).

Primary healthcare facilities are critical for early initiation of treatment of hypertension. In clinical trials, antihypertensive therapy has been shown to reduce stroke incidence by 35-40%; myocardial infarction by 20-25%; and heart failure by 50% (25). The successful management of hypertension requires frequent clinic visits, regular lifestyle advice and
medications that must be taken on a daily basis (3,25,28,29). Hypertension treatment is most successful when provided as a collaboration between care providers and pharmacists (28). Provision of medication must be integrated with culturally-appropriate healthy lifestyle advice that addresses barriers to medication adherence (3).

Until recently, primary care health facilities in sub-Saharan Africa have focused almost entirely on the acute management of infectious diseases such as malaria, diarrhea and respiratory infections (30). In the face of the rising prevalence of hypertension and other NCDs, there has been increasing recognition that primary care health services will need to change (1,31). This reorientation of healthcare systems in sub-Saharan Africa has been described by experts as a “Grand Challenge” of modern science (31).

Mathematical modeling research has shown that providing antihypertensive treatment for adults with high cardiovascular risk could be an inexpensive and cost-effective way to reduce early mortality in Africa (24). Many questions remain, though, as to the best strategy for providing these primary care services.

The provision of primary healthcare for hypertension will be a critical first step to improving primary care for chronic, non-communicable diseases in Africa. Hypertension is a logical place to start in improving primary care services since hypertension is common in Africa and hypertension is a leading risk factor for other NCDs such as heart failure, stroke and kidney disease (32). Both primary and secondary prevention of hypertension have been proven to be cost-effective public health strategies (33).
Hypertension is also relatively easy to diagnosis and treat. Inexpensive, easy-to-use and reliable digital blood pressure machines are available and recommended by the WHO (3). The annual cost of anti-hypertensive drugs is $1-10 (30). Furthermore, if primary healthcare systems in Africa can be strengthened to provide basic services for hypertension, these systems will be better equipped to provide services for more complex non-communicable diseases.

1.3 Hospital Care of Hypertension-Related Diseases

Hospital care for hypertension represents the tip of the iceberg of the problem of hypertension in any region. Most cases of hypertension are not obvious to the community until a hospitalization occurs. Hypertension is generally hidden and often asymptomatic until some complications occur. Most hospitalizations are not due to hypertension itself but rather due to complications of hypertension such as stroke, heart failure and kidney disease (34). In addition, most cost incurred during the course of a lifetime with hypertension is incurred during hospital admissions for complications of hypertension (24).

Most hospitalizations related to hypertension are preventable. Hospitalizations related to hypertension illustrate the failure of primary and secondary prevention in primary care settings (33). Hospitalizations related to hypertension usually occur only after decades of uncontrolled hypertension. Published studies have demonstrated that hypertension is a “primary care sensitive condition” for which effective primary care can prevent hospitalizations (34).
Hospital outcomes for patients with hypertension can and should be improved. Between 1980 and 2000 in the US, for example, hospital mortality rates for adults with heart failure decreased from 10% to 5% (25). Hospital outcomes are also important because most medical doctors and nurses are trained in hospitals. The knowledge, attitude and practice of these medical trainees to hypertension are largely formed through their experiences in the hospital context and training healthcare workers who are comfortable and experienced with hypertension prevention and management will be critical to improving primary healthcare services (31). Hospitals also serve as a catalyst for innovation. For example, a hospital in Cambodia created one of the first integrated clinics for HIV, hypertension and diabetes (30).

1.4 Links between Hypertension and HIV

Experts have described hypertension and HIV as being on a “collision course” in sub-Saharan Africa (35). HIV remains common in sub-Saharan Africa; 70% of HIV-infected adults reside on this continent and 1 out of 20 adults are infected (36). With the roll out of antiretroviral therapy (ART) in Africa, the infection-related mortality rate has declined and life expectancy has increased (37). This rapid increase in life-expectancy will almost certainly result in a rapid increase in the number of HIV-infected adults with hypertension (38).

HIV-infected adults have significantly increased rates of cardiovascular disease including myocardial infarction, stroke, and sudden cardiac death. The relationship
between HIV and cardiovascular disease is particularly important for sub-Saharan Africa since most HIV-infected adults live in this region. This relationship is likely due to a complex interaction between traditional cardiovascular risk factors, side effects of antiretroviral therapy (ART), and HIV-induced chronic inflammation (39). Although hypertension is the single most important cardiovascular risk factor worldwide (12), little attention has been given to the relationship between HIV and hypertension.

Some experts have suggested that hypertension is more common in HIV-infected vs. uninfected adults but data are conflicting (40). ART could lead to hypertension due to weight gain, ART drug toxicities or through an immune-related phenomenon. In the US and Europe, some studies have confirmed higher rates of hypertension among HIV-infected adults on ART compared to uninfected adults (41), but most studies have shown no difference (40,42–45).

The association between hypertension and HIV might illuminate important pathophysiologic aspects of hypertension. HIV infection is associated with chronic vascular inflammation as measured by markers such as highly sensitive C-reactive protein (hsCRP) and interleukin-6 (IL-6) (46). These same markers of vascular inflammation predict hypertension onset (47). In addition, HIV depletes CD4+ T cells. These CD4+ T cells play a critical role in the pathophysiology of hypertension (48). Therefore, the rapid rise of CD4+ T-cell counts after ART initiation could be associated with an increased risk of hypertension.
From a health systems perspective, the relationship between HIV and hypertension is important because primary care HIV services in Africa represent the first successful, multinational program for primary care of a chronic disease in this region. The organization of HIV primary care services should serve as a model for the initiation and organization of primary care services for chronic, non-communicable conditions such as hypertension (30). In addition, hypertension services will need to be integrated into HIV services as more HIV-infected adults develop hypertension (49).

The relationship between HIV and hypertension might provide a model for the relationship between other infectious and non-communicable diseases in other LMICs. Many LMICs are characterized by persistently high rates of infectious diseases together with rising rates of chronic, non-communicable diseases. Many of the infectious diseases that occur in these LMICs – such as HIV, tuberculosis, malaria and neglected tropical diseases – are relatively rare in high-income countries. Data suggests that there are important links between these infectious diseases which are common in LMIC and chronic, non-communicable diseases. HIV and tuberculosis are both associated with diabetes mellitus (40,50). Schistosomiasis is associated with renal disease (51). Malaria may cause hypertension (52). Influenza infection increases the risk of acute myocardial infarction (53). Despite the evidence for these associations, very little research has been conducted as to how these associations might be important for disease prevention and health systems. The example of HIV and hypertension might provide a starting point for this line of research.
1.5 Rationale for these 4 Studies

In 2010, very little published data existed regarding the clinical epidemiology of hypertension in East Africa. Clinicians across Africa were recognizing the growing importance of hypertension as a cause of morbidity and mortality in their patients. The medical literature, though, provided very few clues as to why the tide of hypertension was rising, who was most affected and how it might be turned. In particular, there were 4 major gaps in the medical literature regarding hypertension in Africa at that time.

First, prospective data regarding the contribution of hypertension to in-hospital mortality and morbidity in sub-Saharan Africa were lacking. Although hypertension had been considered rare in Africa as late as the 1990’s (54,55), recent reports suggested that the prevalence of hypertension was rising throughout sub-Saharan Africa (16,23,56). A few studies from South Africa and Nigeria reported that hypertension-related diseases such as stroke, heart failure and kidney disease were an increasingly common cause of death in adults hospitalized in those countries (57,58). No published data existed from East Africa.

Second, data to quantify the preparedness of primary care health facilities in sub-Saharan Africa to cope with the rising tide of hypertension were lacking (31,59,60). This lack of data made it difficult to plan appropriate programs for hypertension and to assess the quality and effectiveness of services for hypertension (61). The result was a vicious cycle in which the absence of necessary data, the absence of evidence-based policies and an inadequate response at a primary care level reinforced each other, thus
perpetuating a problem that was becoming worse with time. Many experts had recognized this dire situation and had reported the urgent need for high-quality research to guide policies and to improve primary care for patients with hypertension in Africa (31,61,62).

Third, although hypertension control rates were reportedly low in Africa (63), factors associated with better or worse control had not been described in the published literature. Tanzania, in fact, had one of the lowest rates of hypertension control of any country in Africa (23,63,64). Only 5-10% of patients with hypertension in Tanzania achieved blood pressure control (23,63,64), compared to 35% in the US (25). In order to increase rates of blood pressure control, it was critical to gain a better understanding of the factors associated with blood pressure control in adults in East Africa.

Fourth, although HIV and hypertension were both common in East Africa, the exact relationship between HIV and hypertension in East Africa had not yet been determined. In the US and Europe, some studies had shown higher rates of hypertension among HIV-infected adults on ART compared to uninfected adults (41), but most studies have shown no difference (40,42–45). In Africa as well, data were conflicting. Some uncontrolled studies of HIV-infected African adults showed that hypertension was common in this population (49,65), but a large meta-analysis of data from HIV-infected adults in Africa reported that HIV-infected adults generally had lower blood pressure than uninfected adults (40). This meta-analysis, though, was limited by the fact that almost all study subjects were severely immunosuppressed and very few had been on
ART for more than a year. Data comparing rates of hypertension in comparable groups of HIV-uninfected adults, HIV-infected adults not yet on ART and HIV-infected adults on ART for >2 years were needed to guide public health efforts for prevention and early diagnosis of hypertension and cardiovascular disease in HIV-infected adults in Africa.

1.6 Study Objectives

Based on these critical gaps in published data, the objectives of my studies were:

1) To determine the admission rates and outcomes for patients with hypertension-related complications in Tanzania (Study I).

2) To determine the current level of preparedness of primary health clinics in Tanzania for diagnosing and treating hypertension (Study II).

3) To determine the rates of hypertension control and factors associated with hypertension control in adults attending a hypertension clinic in Tanzania (Study III).

4) To determine the relationship between hypertension and HIV in Tanzanian adults (Study IV).