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International Journal of Cardiology 108 (2006) 101 – 108

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Mapping the emergence of heart disease in a black, urban population in Africa: The Heart of Soweto Study

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Received 22 November 2005; accepted 8 January 2006
Available online 7 February 2006

Abstract

Background: There is increasing evidence that many populations in the developing world are in "epidemiologic transition" with the subsequent emergence of more "affluent" disease states. The "Heart of Soweto Study" will systematically investigate the emergence of heart disease (HD) in a large urban population in South Africa.
Methods: Part of the conurbation of Johannesburg, South Africa, Soweto is a predominantly Black African community of 1 million individuals. During an initial two year period, all individuals presenting to the local Baragwanath Hospital (3500 beds) with any form of HD will be studied. Demographic and diagnostic coding data in those with pre-established HD will form an abbreviated clinical registry of >12,000 "prevalent" cases. Similarly, socio-demographic, clinical and diagnostic data (e.g. echocardiography and ECG) in newly diagnosed patients will form a more detailed clinical registry of >5000 "incident" cases. Sub-studies of the relationship between HIV status and HD and the optimal management of chronic heart failure will also be performed.
Results: These data will provide a unique insight into the causes and consequences of a broad spectrum of HD-related conditions in a "developing world" community in epidemiologic transition. Initially documented population rates, in addition to detailed examinations of the underlying risk factors and causes of HD-related morbidity/mortality will provide an important platform for future stages of the study: a community-based, population screening program and culturally specific primary and secondary programs of care.
Conclusion: There is an urgent need to systematically track the emergence of HD in the developing world. Initially involving more than 15,000 individuals, the unique *Heart of Soweto Study* has the potential to provide a wealth of information in this regard.

1. Introduction

Although cardiovascular disease, and its major component heart disease, exists in epidemic proportions in Western developed countries, it is also an increasing problem in the developing world; contributing to significant morbidity and premature mortality in vulnerable populations [1]. The overall burden of cardiovascular disease is predicted to rise by approximately 150% in the developing world within the next 20 years. In Africa alone, it is predicted that it will affect 1.3 million people per annum during this period [2]. Even in low to middle income countries such as South Africa it is already responsible for close to 10% of healthy life years lost; being second only to HIV/AIDS in this regard [3]. Such data support the hypothesis that the overall health status of human societies is linked to economic development. With industrialization the major causes of death have shifted from infectious diseases and nutritional deficiencies to more chronic disorders: a phenomenon with distinct stages known as "epidemiologic transition" [1,4]. For example, there are strong indications that in South Africa this phenomenon is occurring even within a specific

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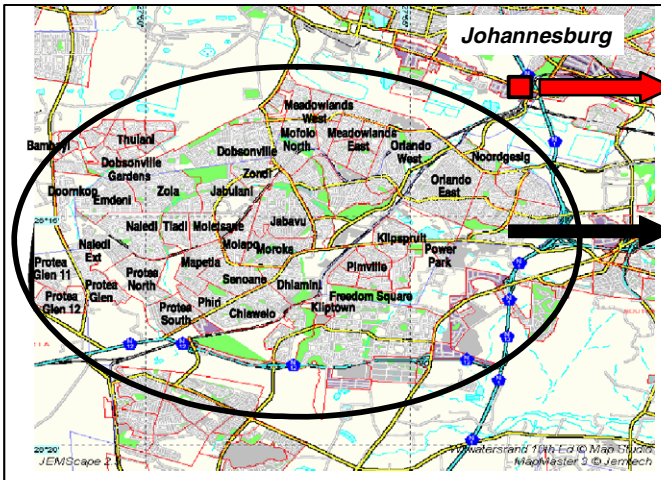
doi:10.1016/j.ijcard.2006.01.001



Baragwanath Hospital, comprising 3,500 beds, is the largest hospital in the Southern Hemisphere. It sits on the main road between Soweto and Johannesburg and provides the only point of specialist care for the population of Soweto. It therefore "captures" nearly every individual seeking medical care for a heart disease-related condition via its specialist cardiologic services

SOWETO represents a geographically distinct area south-west of Johannesburg and comprises a number of townships. It is one of the largest urban concentration of Black Africans on the continent: in 2001 an official census, reported the population of Soweto as just under 1 million people and rising. A population truly in transition, it continues to grow via a steady influx of migrants (one third have lived locally for < 5 years) and the socio-economic status of the community, while still poor, is also improving.

Fig. 1. Key features of Soweto and the Baragwanath Hospital, South Africa.

disease category: rheumatic heart disease of the young. Although it is still prevalent, there is some evidence that it is giving way to hypertension [5,6], coronary artery disease (CAD) [7,8] and acute coronary syndromes (ACS) including acute myocardial infarction (MI) [9,10] — all common precursors of chronic heart failure (CHF). Similar to other countries in transition, therefore, South Africa is suffering a double or even triple burden from: a) the historical and lingering burden of infectious disease, b) an emerging epidemic of chronic disease (particularly heart disease) and c) the re-emergence of infections such as HIV/AIDS and tuberculosis.

Despite obvious trends in health care utilisation rates and some research reports from the African continent [5–10] there is a paucity of data collected on a systematic basis to describe this "epidemiologic transition" in the developing world; particularly in a large vulnerable population subject to generally improved economic conditions.

2. The Heart of Soweto Study

It is within the broad context described above, that the "Heart of Soweto Study" was established. The primary purpose of the "Heart of Soweto Study" is to systematically examine the epidemiologic transition in risk behaviours and clinical presentations of heart disease in the predominantly Black African population of approximately one million people living in the townships that comprise the internationally renowned and celebrated area of Soweto. The study will also focus on designing and applying culturally sensitive models of health care to reduce the current and future burden of heart disease in the local population.

Established close to the city of Johannesburg, South Africa 100 years ago, Soweto now represents one of the largest urban concentrations on the African continent [11]. Fig. 1 outlines the key features of Soweto and the initial focus of the study — individuals attending the cardiac clinical services (inpatient and outpatient) at the Baragwanath Hospital. The clear advantages of an initial focus on individuals presenting with cardiac-related problems to this hospital can be summarised as follows:

- Soweto is a large and geographically distinct urban community in Africa in the process of significant socio-economic change [11].
- It has historically low levels of heart disease and underlying risk factors for the same [12].
- A preponderance of Black Africans with the presence of significant racial minorities (including Caucasians and Asians) providing comparative data [11].
- The availability of only one point of care for cardiology services for the local population: the majority of individuals seeking care for cardiac-relating problems have no other contact with health care services (and therefore treatment) prior to their assessment and treatment at the Baragwanath Hospital.
- The large number of individuals seeking health care (the cardiac clinic at Baragwanath Hospital currently manages 10–15,000 patient contacts per annum) and the availability of advanced diagnostic equipment.

The *Heart of Soweto Study* is designed, therefore to exploit a unique opportunity to systematically investigate the spectrum and characteristics of heart disease in a large urban population in the developing world setting using health care facilities close to "first world" standards. Preliminary studies provide supportive evidence of the potential importance of data derived from cardiac patients being managed via the Baragwanath Hospital.

3. Preliminary evidence of an emerging epidemic of heart disease in Soweto

As part of the African component of the INTERHEART Study [13], we recently recruited a total of 120 Black

African patients presenting to the Baragwanath Hospital with an AMI over a 12 month period. While this would be deemed unremarkable in the developing world, we have formally compared the population rate of acute coronary events requiring admission to the Coronary Care Unit in the year 2004 ($n=154$) with equivalent data reported for the period 1975–1980 ($n=59$) [7]. Consistent with a population in epidemiological transition [5,6], there was a >10-fold increase in the rate of such events. Significantly, compared to Caucasian and Asian patients, Black African patients were significantly younger, had a markedly lower rate of positive family history for heart disease (approximately 10% versus >25%) and a higher rate of underlying single coronary vessel disease (>50% versus <30%) determined via coronary angiography ($P<0.05$ for all comparisons). Alternatively, they demonstrated similarly high rates of major modifiable risk factors [14].

The potential for clinically significant differences in the pattern of CAD based on race, coupled with some evidence from Western countries demonstrating an increase in coronary events in HIV/AIDS infected patients via localised lesions in affected coronary arteries [15] and a potential exacerbating role for highly active antiretroviral therapy (HAART) [16], has led to immediate plans for a sub-study examining the potential interaction between CAD and the highly prevalent HIV/AIDS in this population.

This apparent increase in rates of CAD does not appear to be confined to those presenting with acute manifestations of heart disease. Preliminary estimates suggest that one third of cardiac patients being treated at Baragwanath Hospital suffer from some form of heart failure (confirmed by echocardiography); many of whom suffer chronic symptoms indicative of CHF. Consistent with outcome data derived from patient cohorts in Western developed countries [17], 20% of hospitalised patients with CHF at Baragwanath Hospital die within one year and 60% of survivors are readmitted to hospital within 18 months. Given the compelling data in favour of CHF management programs overall [18,19], there are also immediate plans to undertake a second major sub-study to determine if a culturally specific program of care extending to the community for patients with CHF will confer similar benefits to those seen in a range of developed countries.

4. Study hypotheses

The *Heart of Soweto Study* will initially examine the following primary hypothesis:

> The profound political and socio-economic changes in South Africa overall will exert a negative impact on the risk behaviour profile and subsequent incidence and prevalence of heart disease in those living in the geographically distinct community of Soweto.

Given preliminary data suggestive of a significant interaction between CAD and HIV status, the following hypothesis will also be examined:

> An increasing incidence of HIV, compounded by the recent introduction of anti-retroviral therapy will be associated with a parallel increase in acute myocardial infarction due to thromboembolic events.

Finally, in relation to the immediate need to optimise the management and subsequent health outcomes in a large group of patients being actively managed for CHF via the Baragwanath Hospital, the following hypothesis will be examined:

> A culturally specific program focussed on specialist management of CHF, initially based at Baragwanath Hospital and extending to nurse-led community centres in Soweto, will significantly improve morbidity and mortality rates during a mean of 12 months follow-up in patients being treated for the syndrome attributable to underlying left ventricular systolic dysfunction.

5. Study design

As shown in Fig. 2, in order to examine the above hypotheses, the “Heart of Soweto Study” will involve parallel streams of research based on a simple prospective clinical registry of all prevalent/pre-established cases of heart disease (estimated total of 6000 to 9000 individual patients per annum) and a more detailed clinical registry of all newly diagnosed cases of heart disease (estimated total of 2500 to 4000 patients per annum) being routinely managed via the cardiac clinic at Baragwanath Hospital. From this pool of patients, more detailed sub-studies focussing on the interaction between HIV and CAD and the management of CHF in a developing world setting will be undertaken.

5.1. Abbreviated clinical registry of pre-existing cases of heart disease

All patients attending the cardiac clinic and Coronary Care Unit at the Baragwanath Hospital are routinely assessed by Cardiologists (and trainee Cardiologists under the supervision of a senior Cardiologist) and subject to a full range of diagnostic testing (including echocardiography, coronary angiography and nuclear imaging). The hospital performs all forms of advanced coronary interventions (e.g. coronary bypass and cardiac valve replacement).

Using these routine diagnostic and treatment procedures, the spectrum of pre-existing cases of heart disease being managed via the clinical cardiac services at the hospital over a two year period will be documented (estimated total of 12,000 to 18,000 cases). Specifically, based on a verbal confirmation from the treating Cardiologist, brief patient

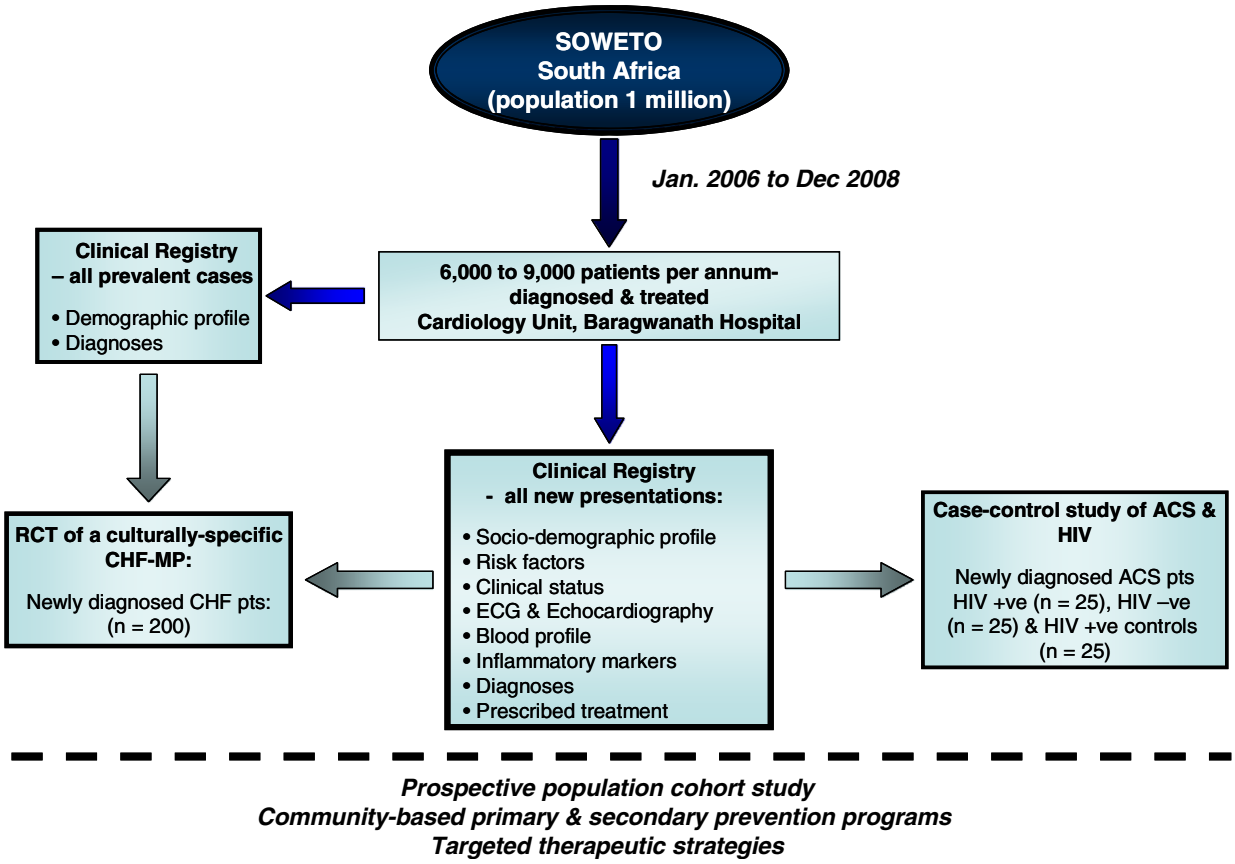


Fig. 2. Study schema.

interview and clinical records detailing current diagnoses, the dedicated study research team (comprising a physician/PhD candidate and a team of experienced cardiac nurses and other dedicated personnel) will maintain an abbreviated clinical registry of all pre-existing patients being actively managed by the cardiology team as they return to the clinic for either pre-planned follow-up or for a new cardiac problem. Each record in the registry will document the following:

- Date of clinic contact
- Socio-demographic profile (including number of years living in Soweto)
- All major cardiovascular diagnoses (up to six diagnoses recorded): ICD 10 coding [20]
- Case-record number for further follow-up if required
- A unique study identifier.

During the study period, each patient's hospital record will be labelled with the date of study contact followed by subsequent data analysis of hospital record numbers to prevent patient duplication in the registry.

5.2. Detailed clinical registry of newly diagnosed cases of heart disease

In order to more fully investigate the spectrum of incident heart disease in this population, a more detailed clinical registry of all newly diagnoses cases of heart disease will also be established and maintained for a minimum of two years (estimated total 5000 to 8000 patients). Specifically, all new patients being routinely assessed and managed via the Cardiology Unit during the study period will be identified by dedicated clerical staff at initial point of contact with the cardiac clinic or CCU. In all patients being managed through the cardiac clinic (the majority of patients), the dedicated research team described above will document the following prior to any cardiologic assessment via a structured patient interview and physical assessment:

- Demographic profile: age, sex and race
- Socio-economic profile (educational level, dwelling location in Soweto and duration of residency in Soweto)
- Self-reported cardiac risk factors (e.g. smoking and family history) and pre-existing cardiovascular conditions (e.g. hypertension)
- Functional status according to Canadian Heart Classification (anginal symptoms) and New York Heart Association Class (dyspnoea)
- Physical status: height, weight, waste circumference and calculated body mass index [kg/m^2]
- Clinical status: Following 5 minutes rest, non-invasive blood pressure measurements will be performed by use of a Dynamap (Critkon) monitor. The mean of

three successive readings separated by 2 min rest will be used to estimate seated systolic and diastolic blood pressure (mm/Hg) and the heart rate (beats per minute).

A venous blood sample will be obtained via the antecubital vein to assess the following parameters (where clinically indicated):

- Non-fasting glucose and HbA1c ratio
- Fasting lipid profile
- Blood counts (e.g. platelet and white cell counts and haemoglobin)
- Renal function: with calculation of creatinine clearance
- Inflammatory markers (e.g. C-reactive protein)
- HIV status
- Brain natriuretic peptides
- Cardiac enzymes (e.g. troponin levels).

As part of routine clinical practice all patients undergo the following cardiac investigations:

- *12-lead ECG*: performed by the same dedicated ECG technician. As part of this study, a copy of every ECG will be subject to blinded coding according to published Minnesota criteria [21] to determine any pathological abnormalities including underlying left bundle branch block, S–T segment changes indicative of underlying myocardial ischemia and left ventricular hypertrophy in addition to arrhythmias such as atrial fibrillation.
- *Two-dimensional targeted M-mode echocardiography*: with Doppler colour flow mapping is performed using a Hewlett Packard Sonos 5500 echocardiograph attached to a 2.5 or 3.5 MHz transducer by trained operators. Left ventricular dimensions is routinely measured according to the American Society of Echocardiography guidelines [22] and for left ventricular measurements, an average of >3 beats is obtained. Diastolic mitral flow is assessed by pulsed-wave Doppler echocardiography from the apical four-chamber view. The E wave deceleration time is also measured as the interval between the peak early diastolic velocity and the point at which the steepest deceleration slope is extrapolated to the zero line. As part of this study, if no abnormalities are detected during the initial echocardiographic assessment, no further specific measurements will be recorded. Alternatively, any abnormality routinely prompts a detailed echocardiographic assessment with detailed assessment of ventricular function, valvular integrity and function and regional wall abnormalities. These data will be recorded and entered into the clinical registry.

All patients routinely undergo a detailed cardiologic assessment by a Cardiologist or trainee Cardiologist and the following data arising from such assessment will be entered into the clinical registry:

- Heart sounds (e.g. presence of 3rd Heart Sound)
- Pulmonary sounds (e.g. basal crepitations)
- Presence/absence of raised jugular venous pressure
- Peripheral oedema
- Ascites
- Other abnormalities indicative of underlying cardiovascular disease.

The results of any further clinical investigations, depending on the initial cardiologic assessment and provisional diagnoses, will be recorded for each patient. These will typically include:

- ECG Stress test: using modified Naughton [23] or standard protocol.
- Pulmonary function tests
- Radio nucleotide perfusion scans
- Chest radiography
- Coronary angiography.

Once definitive cardiologic assessment and treatment has been applied as a result of their initial contact with the cardiology unit (all data forms will be finalised within one month of initial contact), in addition to the above, the following specific data will be documented for each individual:

- All major cardiovascular diagnoses: according ICD 10 coding [20]
- Up to six non-cardiovascular diagnoses: according ICD 10 coding [20]
- Prescribed pharmacological therapy
- All surgical interventions.

5.2.1. CCU cohort

Parallel data will be collected from the detailed assessment and investigations typically associated with the management of those with an acute form of heart disease in a specialised CCU.

6. Data collection, verification and security

All procedures for identifying patients and collecting and processing study data (including all forms and the study database) have been subject to extensive pilot testing for a period of six months prior to formal commencement of the study. The accuracy of data collection and transfer to the study database has been subject to external scrutiny to ensure data accuracy of >95%. During the study period, 5% of data

records will be subject to extensive audit relative to the patient's medical records and an intensive review of data collection procedures and accuracy rates undertaken every six months. Consistent with the ethical requirements for maintaining an anonymous clinical registry (the study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the regional Ethics of Human Research Committee), all data forms will be stored in a dedicated and secure study office and a password secure computer. All records will also be de-identified with the unique study code in order to protect the identity of all participants.

7. Data analysis

All study data will be initially entered into a specifically designed dataset using Microsoft © Access 2002 and then transferred for detailed analysis to SPSS version 12.0.

Consistent with the primary purpose of the *Heart of the Soweto Study*, the clinical registry of pre-existing cases will provide an important insight into the entire spectrum of symptomatic heart disease that currently exists in the predominantly Black African population living in Soweto. Using official census data [24], estimates of the underlying prevalence of the different forms of heart disease (e.g. rheumatic heart disease and CAD) will be calculated as the number of "known" cases per 1000 population on an age- and sex-specific basis and according to race. These estimates will be used to compare with similar registries from developed countries [25,26]. Moreover, a comparison between the number of "prevalent" cases recorded in the first and second 12 months of the study period will provide preliminary evidence of potential differences in the number and spectrum of cases over time.

More importantly, detailed analysis of the extensive data (>100 variables) collected from all newly diagnosed cases of heart disease will provide a wealth of information in respect to the overall "heart health" of Soweto, including estimates of the:

- Incidence of clinical manifestations of heart disease (age- and sex-specific number of cases/100,000 population per annum). A time-series analysis (i.e. four quarterly comparisons over the 12-month study period) will identify potentially important trends in relation to the "direction" of HD in Soweto.
- Prevalence and overall spectrum of underlying traditional risk factors for cardiovascular disease in those with diagnosed heart disease.
- Spectrum of structural and functional abnormalities, co-morbidities, ECG-related abnormalities and other markers of cardiovascular dysfunction in those with diagnosed heart disease.
- Potential seasonal variations in the rate of presentations as observed in a range of developed countries.
- Potentially important race-based differences in clinical presentation, spectrum and extent of heart disease and other forms of cardiovascular disease.

Consistent with the longer-term purpose of the *Heart of Soweto Study*, these baseline data, largely derived from a convenience sample, will be used to plan the next phase of the study: a prospective, longitudinal, population cohort study of cardiovascular disease in Soweto. They will also provide comparative data for continued monitoring of heart disease-related morbidity being managed via the institution and designing other important secondary studies.

8. Key sub-studies

As discussed earlier two of the most urgent clinical issues arising from our preliminary investigations of heart disease in Soweto relate to the potential association between HIV/AIDS and ACS and the need to optimise the management and subsequent health outcomes of an increasing number of patients with CHF.

8.1. Does HIV/AIDS increase the risk of an acute cardiac event?

In order to investigate the potential association between HIV/AIDS status and the development of CAD all individuals presenting to the CCU at Baragwanath Hospital with a first-ever presentation of ACS during the study period will be identified. As the HIV/AIDS status of all patients attending the CCU are routinely assessed via a rapid HIV/AIDS and confirmation ELISA test, the proportion of individuals who are HIV positive on admission will be initially determined. An overall comparison of risk factor profile, presenting clinical characteristics, type/extent of CAD (via cardiac catheterisation) and concurrent disease states according to HIV/AIDS status will be initially undertaken to investigate the following research questions:

- Are the clinical features of CAD different in the presence or absence of positive HIV status? Furthermore, are there detectable differences within the HIV positive cohort on the basis of prior treatment with HAART?

The pattern of HIV positive individuals requiring CCU admission for an ACS will also be monitored over the two year study period to investigate the following research question:

- Is the incidence of ACS with concurrent HIV positive status increasing over time and/or associated with a different pattern of clinical presentation and extent/nature of CAD?

To further examine the potential relationship between HIV/AIDS status and CAD, a prospective 1:1 case–control study, involving three distinct patient cohorts, will be undertaken. These groups will comprise the following:

Group A: 25 consecutive HIV positive CCU patients with an ACS (*Index cases*).

Group B: 25 consecutive HIV negative CCU patients to with an ACS (*ACS control group*)

Group C: 25 asymptomatic HIV positive patients without a history suggestive of underlying heart disease managed via the Baragwanath Hospital Medical Unit, who are matched for age, sex and viral load with those patients in Group A (*HIV status control group*).

Case–control comparisons will then be performed to examine the following research questions:

- Are inflammatory markers significantly increased in HIV positive patients with an ACS (Group A versus Group B)? If they are elevated, does this correlate with differences in clinical presentation/nature of underlying CAD?
- Are inflammatory markers in HIV positive patients with an ACS significantly different from HIV positive patients without symptomatic CAD? (Group A versus Group C)?

8.2. Specialised CHF management: does it work in the developing world?

In order to test the efficacy of specialist CHF management based on those programs demonstrated by recent meta-analyses to significantly reduce morbidity and mortality in the developing world [18,19], an appropriately powered, randomised controlled trial will be undertaken. Using similar criteria used to enrol patients with CHF related to left ventricular systolic dysfunction in contemporary trials of CHF management programs in developed countries [18], participating patients will be randomised (on a 1:1 basis), to usual care ($n=100$) or the study intervention ($n=100$). The latter will incorporate key components of successful programs of care in developed countries in respect to accurate risk assessment for future morbidity/mortality, optimal pharmacologic and non-pharmacologic intervention, promoting self-care and increased vigilance for impending crises [18]. Importantly, the delivery of health care will be culturally specific and relevant to those living in Soweto.

The primary end-point of the study will be event-free survival from all-cause death or hospital admission within 12 months. Secondary end-points will be length of hospital stay, self-report adherence to treatment, functional status (NYHA Class and 6-min walk test) and health-related quality of life (as measured by the SF-36) at 12 months.

9. Study limitations

Clearly, a clinical registry (even when associated with a geographically discrete population serviced by only one major hospital) is less preferable than a prospective, population cohort study. As such, study data will not provide definite information on the full spectrum of risk factors and manifestations of heart disease in Soweto. In particular, the study will not "capture" asymptomatic individuals, those tolerating milder symptoms of heart disease or, indeed, those who suffer a sudden fatal cardiac event. Moreover, many Black Africans continue to rely on traditional healers and treatments rather than seek medical care via Baragwanath Hospital. All population estimates and inferences from data describing the spectrum of heart disease, therefore, are likely to be conservative and require further corroboration. However, study data will provide invaluable information to monitor longitudinal trends relating to the epidemiological transition of heart disease and provide a strong platform for future, more comprehensive phases of the "Heart of Soweto Study".

Deriving population estimates is always problematic: particularly when the estimated size of Soweto has varied. Current estimates (i.e. beyond the official census performed in 2001 [24]) suggest that in the past five years its population has increased from just fewer than 1 million to between 1 and 1.5 million: these data will be monitored closely to derive realistic population rates of disease.

10. Strategic directions

It is also important to recognise the inherent barriers in undertaking such an ambitious research program in a developing world setting; even one as advanced as South Africa. A key long-term strategy associated with the initial phases of the study is to develop local research capacity in the form of advanced cardiology trainees undertaking PhD's (with potential support from the newly formed World Heart Failure Society), continued development and involvement of the local research team in piloting and undertaking the research and investing in the infrastructure (e.g. information technology) to computerise data collection and build an interactive web-site. The study is also more likely to succeed if the community of Soweto recognises its overall importance in achieving positive long-term health outcomes and supports its activities through active community participation and engagement.

11. Summary

Heart disease represents an increasing problem in developing world populations in epidemiologic transition. The true extent of the problem is unknown given the

inherent difficulty in tracking the emergence of new patterns of disease and related morbidity/mortality in countries where both health care resources and research capabilities are sub-optimal. It is within this context that this study, in taking advantage of the discrete geographic location of Soweto and the almost exclusive reliance of the community on the well resourced Baragwanath Hospital for cardiac services, will initially document and monitor potentially important changes in the risk profile and clinical manifestations of heart disease in a large populace of predominantly Black Africans exposed to profound socio-economic changes. As such, data from the initial and subsequent phases of the *Heart of Soweto Study* are likely to play a vital role in understanding and then limiting the emergence and impact of heart disease in populations in epidemiologic transition.

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