THE CLINICAL AND ANGIOGRAPHIC PROFILE OF VERY YOUNG PATIENTS WITH CORONARY ARTERY DISEASE

By

DR AK PILLAY

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As the candidate's supervisor I have/have not approved this thesis for submission.

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Overview

Coronary artery disease (CAD) is a a major contributor to mortality and morbidity worldwide. Premature coronary artery disease (PCAD), in particular, has been observed to be an emerging problem, with a higher incidence of myocardial infarction (MI) in young patients being reported in recent years. Most studies have focused on patients under the age of 45 years as 'young'; however less is known about the clinical and angiographic profile of very young patients with CAD, under the age of 35 years. Given the potentially devastating psychosocial and economic effects of this diagnosis at an early age, it is necessary to identify the risk factors and clinical characteristics of patients and groups at increased risk in order to inform the processes of screening and primary prevention.

The purpose of this descriptive study was to identify and describe the demographic data, cardiovascular risk factors, clinical and biochemical profile, as well as coronary angiographic findings in very young patients (under 35 years of age) referred with a diagnosis of coronary artery disease to the Cardiology unit at Inkosi Albert Luthuli Central Hospital over a ten year period, between 2003 and 2012.

This was accomplished by conducting a retrospective chart review and collecting data on patient demographics, modes of presentation, risk factors, clinical examination findings, laboratory tests, electrocardiogram and radiological imaging and coronary angiogram reports. Data was gathered using a computerized database and subjected to statistical analysis in order to identify the prevalence of major and non-conventional risk factors, and the key determinants of disease severity.

It is hoped that the information gained on the profile of these very young subjects will answer, to some extent, the paucity of local data on PCAD and pave the way for further multi-center studies to substantiate the findings. Furthermore, this study may assist health care providers, at primary, district and tertiary care levels, with the identification of young patients at increased risk of CAD and initiate cost-effective and targeted preventative strategies, such as the modification of lifestyle and environmental risk factors.

Table of Contents

Chapter 1: Literature review

Introduction

Coronary artery disease (CAD), manifested by myocardial infarction, angina pectoris, heart failure and coronary death, remains a leading cause of morbidity and mortality globally. It commonly arises from the development of atherosclerotic plaque in the coronary arteries that may eventually lead to myocardial ischaemia and infarction. In most cases, CAD is a chronic condition that begins as a fatty streak at the adolescent stage and slowly progresses throughout an individual's life. However, it may present acutely due to rupture of the atherosclerotic plaque and subsequent thrombosis with occlusion of the coronary vessel [7]. Major risk factors such as smoking, hypertension, diabetes mellitus, obesity and a sedentary lifestyle contribute to its pathogenesis[23]. It has been observed that a family history of premature cardiac disease is a major risk factor, particularly among younger individuals [1,2]. Other risk factors have also been increasingly recognized such as psychosocial stress[62,63], elevated levels of serum inflammatory markers (including C-reactive protein[3], IL-6[4], myeloperoxidase), microalbuminuria, chronic kidney disease, human immunodeficiency virus (HIV) infection[5,6] and mediastinal radiation. However, strong causal evidence of these risk factors is yet to be established.

Premature CAD (PCAD) is commonly defined as age of onset before 55 years in men and 65 years in women[8]. However, most studies concerned with PCAD consider ages below 40 to 45 years as young, and those below the age of 35 as very young[9]. Among the age range of 30 to 56 years, the prevalence of CAD is on the rise[10] and this appears to be the result of various environmental as well as genetic factors. PCAD can have devastating consequences, as it affects the most active and economically productive age group and may lead to long term disability[11]. Although, a small percentage of patients with CAD belong to the PCAD group, it has been assumed that the figure is not representative of the actual scenario and can be just the "tip of the iceberg", as asymptomatic young adults rarely consider seeking medical attention[9]. Those that are diagnosed with CAD are patients that present for medical intervention due to symptomatic disease. This assumption is supported by a study by Tuzcu et al, which investigated the intravascular health of patients with recent heart transplants, with an age range of 33.4 ± 13.2 years, and found that at least one in six teenagers showed evidence of coronary lesions[12].

Therefore, the extent of the problem of PCAD and undiagnosed CAD in very young individuals may be significantly underestimated.

Critical Literature review

Much of the epidemiological data on CAD is gathered from national survey data and observational cohorts. The American Heart Association's Heart Disease and Stroke Statistics (2010) reported 17.6 million individuals with CAD (8.5 million with MI and 10.2 million with angina) in the United States, with increasing prevalence by age for both men and women[17]. It has been estimated that the lifetime risk of CAD for individuals in the U.S. aged 40 years is 49 percent in men and 24 percent in women[109].

CAD remains a major cause of death and disability throughout the world. While the CAD mortality rate has declined in the developed world over the past several decades, it is on the rise in developing countries. The Global Burden of Disease Study (2013) attributed 17.3 million deaths to cardiovascular disease, an increase of 41% since 1990[13]. This rise in prevalence of the disease in the developing world is attributed to lifestyle changes, socioeconomic conditions, increased use of tobacco, decreased physical activity and dietary changes[14,15]. Even though there has been a decline in mortality rates due to cardiovascular disease, CAD remains the cause of one-third of total deaths of people above the age of 35[16,17].

Prevalence

It is challenging to accurately establish the prevalence of CAD in young subjects as it is frequently a silent process and may not manifest until later in life. Autopsy studies, in some cases, have identified advanced coronary atheromata in a significant number of very young subjects. For example, a study by McGill et al (2000) found advanced coronary lesions in 20% of men and 8% of women between 30 to 34 years of age [18]. The Framingham Heart Study documented the incidence of myocardial infarction (MI) over a 10 year follow-up period as 12.9/1000 for men 30 to 34 years of age, and 5.2/1000 for women 35 to 44 years of age [19]. A number of studies have found between 4 and 10 percent of patients with MI under 40 or 45 years of age [9,20,21].

The prevalence of PCAD may be dependent on the population and ethnic group under investigation, as considerable variation has been observed among different ethnic groups. For example, Crystel et al (2015) reported inter-ethnic differences in the prevalence of CAD , with South Asians having increased CV risk compared to Caucasians, and other non-Caucasian populations having a more favorable risk profile and a lower prevalence of CAD[22]. The differences observed in the prevalence of PCAD may be influenced by various risk factors, the extent of which may vary with individual lifestyles, as well as genetic predisposition.

Risk Factors

It has been estimated that over 90 percent of patients with CAD have at least one cardiovascular risk factor[23-25]. Major modifiable risk factors identified by the INTERHEART study include smoking, dyslipidaemia, hypertension, diabetes and glucose intolerance, abdominal obesity, low HDL and high LDL cholesterol levels [23]. These factors may account for more than half of cardiovascular mortality. Even 'borderline' risk factors have been found to confer increased risk of CAD [24]. In contrast, the absence of major risk factors predicts a much lower risk of CAD [25]. Traditional risk factors, such as serum cholesterol and systolic blood pressure, appear to increase in their relative importance for the development of CAD with increasing age [26]. Young patients with CAD are often found to have multiple risk factors present for atherosclerosis. Some studies have found over 90 percent of young subjects had at least one major risk factor for CAD [27,28] with a corresponding increase in mortality rate with the number of associated risk factors [29].

Gender

A predisposition for PCAD among men has been observed in various studies, however the potential mechanisms for this increased risk are not fully understood. Inherited variations in sex chromosomes may play a role[33]. Some series of young patients (<40 years) with CAD have found women comprised between 5.6 to 11.4 percent of patients[19]. Furthermore, cardiovascular risk factors may differ in their impact between genders. For example, smoking, diabetes and low HDL-cholesterol may confer greater CV risk in women [34-36].

Serious manifestations of coronary disease including MI are rare in premenopausal women. However, the cardiovascular risk for women increases dramatically after menopause, possibly

because of the loss of cardioprotective effect of oestrogen[35]. The difference among males and females is much more significant in younger age groups when compared to older groups[32].

Family History

A family history of premature CAD is considered an independent risk factor, particularly among young patients. This is generally agreed to refer to atherosclerotic CAD or CAD-related death in a first degree relative under age 55 (males) or 65 (females)[8]. However a wider definition may include other manifestations of atherosclerosis including stroke or peripheral vascular disease. Several large cohorts have demonstrated a 40 to 60 percent increase in CV risk in the presence of a positive family history [37-39]. A higher incidence of a positive family history in young patients compared to middle aged and elderly individuals has been noted[40]. Coronary risk factors such as obesity, dysipidaemia and dysglycaemia are more likely to be present in the offspring of patients with PCAD[41]. Therefore, a combination of genetic and environmental factors may account for this strong association.

Genetic factors that have been proposed as increasing familial risk of PCAD, include variations in vascular biology genes such as thrombospondins [42], abnormal lipoprotein levels, C-reactive protein or apo-isoforms[43] and impaired endothelium-dependent coronary blood flow regulation[44].

Smoking

Smoking is perhaps the most common modifiable risk factor among young patients with CAD. A recent study by Christus et al found that 71% of patients with CAD below the age of 35 had a history of smoking[45]. In smokers between 35–44 years old, the risk of CAD is three times higher compared to non-smokers[46-48]. Frequent exposure to cigarette smoke and the resulting increase in catecholamines may induce endothelial and the vascular intimal injury. The strong association between CAD and smoking is also reported in the INTERHEART[23] and Framingham Heart Study[1].

Hypertension

Hypertension is a well-recognized risk factor for CAD and is associated with adverse cardiovascular outcomes, including an increase in mortality[49]. In a meta-analysis of 61 studies that encompassed over a million subjects, high blood pressure was linked to fatal CAD regardless of age[110]. An estimated rise in 20 mmHg is associated with doubling the risk of fatal

outcomes due to coronary events[50]. While less common among young patients with CAD[40], lifestyle factors may increase the risk of hypertension in this population.

Diabetes mellitus and dysglycaemia

Type 2 diabetes mellitus, while designated a CAD risk equivalent and associated with increased disease severity and mortality [51-53], is also less commonly seen among young patients with CAD. However, other forms of dysglycaemia including insulin resistance, hyperinsulinaemia and impaired glucose tolerance may contribute to an elevated risk profile in this population. A study of non-diabetic patients under age 45 presenting with myocardial infarction found 65 percent of subjects had impaired glucose tolerance [54]. Among patients with type 1 diabetes mellitus, often diagnosed at an early age, the relative risk of CAD compared to non-diabetics of similar age may be even higher [55].

Dyslipidaemia

Dyslipidaemia is noted to be far more prevalent among young patients with CAD, as high as 85%, compared to aged-matched controls without CAD. Furthermore, abnormalities of lipoprotein metabolism are often familial, with up to 70% of patients with dyslipidaemia in some series reporting a familial disorder [56].

The association of a low concentration of high-density lipoproteins (HDL) and the risk of cardiovascular disease is well-established[56-58]. Sharett et al (2001), after a 10-year follow-up study involving 12,339 middle-aged patients with coronary heart disease (CHD), observed that a lower incidence of CV events was associated with reduced levels low density lipoprotein (LDL)-cholesterol, with the converse also being observed[59].

Young patients are more likely to have a lower mean HDL level and higher serum triglycerides than their older counterparts[56]. In some studies, hypertriglyceridaemia, often associated with glucose intolerance and an increase in small atherogenic LDL particles, is the most common lipid abnormality observed in young patients with MI [54].

Obesity

Obesity has emerged as a widely prevalent condition among adolescents and young adults, contributed to by changes in diet and a sedentary lifestyle, and is considered an independent risk factor for CAD, particularly among young men. An autopsy study of approximately 3000 young

individuals between the ages of 15 and 34, who died of non-cardiac causes, found that increasing body mass was associated with the presence of both fatty streaks and raised atherosclerotic plaques in the right and left anterior descending coronary arteries in young men [60]. The relationship between obesity and CAD appears to be largely independent of its effects on other CV risk factors such as dyslipidaemia, glucose intolerance and hypertension, although how this occurs has not been fully determined [61].

Psychosocial factors

Psychosocial factors including stress, depression and anger may contribute to the development of CAD. The incidence of coronary atherosclerosis is also noted to increase in association with stressful conditions[62]. A systematic review and meta-analysis of 14 cohort studies encompassing 83,104 subjects revealed a 50% higher risk of cardiovascular diseases among employees working under stress[63]. A study by Chang et al (2002) also found that psychosocial factors such as anger may predispose to the development of PCAD[64]. The link between psychosocial factors and CAD may be direct, via changes in the inflammatory response, endothelial dysfunction as well as increased levels of platelet aggregation, or indirect, via the aggravating effects on CV risk factors such smoking, drug use and hypertension.

Other Risk Factors

A number of additional factors apart from psychosocial stress, such as raised inflammatory markers (including C-reactive protein[3], interleukin 6[4], myeloperoxidase), microalbuminuria, chronic kidney disease, HIV-infection and mediastinal radiation have also been associated with an increased risk of CAD, although their causal relationships have not been established.

Illicit drug use, seen more commonly among younger individuals, is often found to be associated with a higher incidence of CV events and increased mortality due to CAD. A 20-year prospective study found that one of the major causes of mortality in opioid addicts was CAD-related and further estimated a higher mortality rate with cardiac events compared to the general population[65]. Similarly, cocaine use has been linked to myocardial infarction, particularly among younger patients from 18 to 45 years of age[66]. In the Third National Health and Nutrition Examination Survey, which included 10085 adults between the ages of 18 and 45, frequent cocaine use accounted for 25 percent of non-fatal MIs[67]. However, a study by Chang et al.

(2011), of 912 patients including 157 cocaine addicts found no significant relationship between cocaine abuse and incidence of atherosclerotic CAD or calcification of the coronary artery[68]. The mechanism in these subjects may therefore include the induction of coronary vasospasm as well as platelet activation, leading to coronary arterial thrombosis. Marijuana, a commonly used recreational drug in South Africa, may also be a potential trigger for MI [69].

Cardiovascular disease has emerged as an important cause of death in the HIV-infected population, as patients live longer due to more effective and widespread treatment. While low overall, the incidence of CAD in HIV-infected individuals has been found in a number of age- and sex-matched studies to be approximately 1.5 times higher than in HIV-uninfected patients[70,71]. A study by Currier et al (2003) found a significantly higher incidence of CAD among young men (up to 34 years) and women (up to 44 years) with HIV-infection compared to uninfected individuals, with an increased risk (RR 2.06) among individuals aged 18-33 years on antiretroviral therapy compared to those not on treatment ($p<0.001$)[70].

The Heart of Soweto study, based on an urban African population, found only 14 of 581 cases (2.4%) of CAD to have concurrent HIV infection[72]. It is thought that HIV infection itself, antiretroviral therapy and traditional cardiovascular risk factors may contribute to the increased incidence. Studies have suggested a protective effect of HIV suppression on the risk of cardiovascular events, despite the metabolic complications of the drugs themselves[70]. Adverse changes to the lipid profile have been observed in HIV infected patients, including lower HDL-cholesterol and elevated triglycerides, and may be exacerbated by antiretroviral drugs. An increased propensity for the development of thrombosis has been observed in HIV-infected individuals[73,74], due to multiple factors including acquired deficiencies in protein C and protein S[75], the presence of antiphospholipid antibodies[76] and an increased incidence of thrombotic microangiopathy[77]. Furthermore, HIV infection has also been linked to vascular disease, with an independent increase in the risk of peripheral artery disease[78].

Coronary artery disease has a number of other recognized 'non-conventional' risk factors. Connective tissue disorders such as systemic lupus erythematosis (SLE) may confer an increased risk of CAD compared to the normal population. It has been observed that myocardial infarction occurs at a younger average age among these patients[79]. A study by Manzi et al (1997) found that

the incidence of MI in young female patients with SLE aged between 35−44 years was 50 times higher compared to the general population[80].

Other factors that may contribute to a prothombotic state in young individuals and result in myocardial infarction include the use of the oral contraceptive pill in women[81] (particularly among smokers), and the presence of factor V Leiden[82]. Paradoxical coronary artery embolism through an anatomical defect such as a patent foramen ovale has also been observed as a rare cause of MI in young patients[83].

Cardiovascular risk factors may emerge in childhood and confer an increased of CAD later in life. These include childhood obesity with associated metabolic abnormalities, smoke exposure, renal disease and inflammatory disorders such as Kawasaki disease[84,85].

CAD in different ethnic groups

Growing evidence from population-based studies suggests a considerable difference in the prevalence of CAD across various countries and ethnic communities around the world. This may be due to differences in lifestyle or possibly due to a genetic predisposition towards the disease. A study by Lanza (2004), among residents of Singapore, for a time period of almost 10 years, saw a higher incidence of acute myocardial infarction in Indians and Malays compared to East Asians, although the latter group constituted about 62% of the total population of the city[86]. The data suggests either a genetic predisposition to cardiovascular events among the former groups or protective factors among the latter. Environmental factors probably account for within group differences that have been observed among Thai Buddhists and Thai Muslims, with Muslims having a higher prevalence of CAD compared to Buddhists[87]. In a multi-centre study, Crystel et al (2015) reported ethnic differences in the severity of CAD across four population groups (whites, blacks, Indians and Malays), which was attributable to differences in the strength of association between risk factors among these communities[22]. The study found that triple vessel disease was found most frequently in Malays, followed by blacks and Indians, and the least among whites, although overall prevalence of CAD was higher in South Asians compared to both blacks and whites.

Similarly, the higher risk of CAD amongst African Americans compared to whites in the United States has been associated with greater clustering of risk factors and inflammatory markers such as C-reactive protein in this group[88]. In contrast, the prevalence of PCAD in young adults is lower among Hispanics and African Americans as compared to US Indians and Caucasians[89]. These studies document the differences in association of various risk factors among different communities.

Coronary Artery Disease among the Indian Diaspora

It is estimated that 80% of deaths due to cardiovascular disease are in low and middle income countries[13] such as India. In the Indian population, it has been estimated that a nine-fold increase in the incidence of CAD is expected by 2015, with a doubling of mortality[90]. The Asian–Indian population presents a combination of CV risk factors and visceral adiposity as described by the INTERHEART study[23] as well as a higher expression of inflammatory markers such as C-reactive protein[91]. To what extent a genetic predisposition may explain the high prevalence of CAD among Indians in the global diaspora is not clear.

Among Indians in the United States, a 10% prevalence was demonstrated in the Coronary Artery Disease among Asian Indians (CADI) study in the 30-69 year age group as compared to the reported standard sample of 2.5% in the Framingham study[92]. An increased prevalence of CAD has also been observed among the migrant Indian population in UK compared to the Indian population on the subcontinent[93], which indicates that lifestyle adaptation may be a major contributor to the disease.

Local data

An increase in prevalence of CAD in sub-Saharan Africa has been attributed to multiple factors, including rapid urbanization with the adoption of western lifestyle and dietary patterns, as well as an increase in risk factors such as smoking[94,95]. While the overall prevalence remains low relative to economically developed countries, CAD appears to be on the rise throughout the region[94]. The THUSA study evaluated the effects of lifestyle changes on CAD risk in a cross-sectional population-based study of black South Africans, and suggested that socio-economic

factors which influence diet and nutrition has a potentially major role in the emergence of CAD in this population[96].

The Heart of Soweto study by Sliwa and colleagues (2008) sought to identify the characteristics and burden of heart disease in an urban African population undergoing epidemiological transition[97]. The majority of patients were black Africans (85%), with a higher number of women in the study population, and 25% of patients were under the age of 40. While heart failure was the most commonly identified cardiac disease, it was most commonly due to hypertensive heart disease or dilated cardiomyopathy. Among black African patients, CAD was significantly less common than among non-black patients (6% vs 38%, $p<0.0001$), despite a high prevalence of cardiovascular risk factors such as hypertension and obesity.

The relatively low burden of CAD in the presence of multiple risk factors was also noted in a study by Stewart et al (2012), also in the township of Soweto, which evaluated 1311 patients presenting to primary care facilities with cardiovascular disease[98]. Of the 99 patients referred for further cardiologic assessment, only three patients were found to have coronary artery disease. Cardiovascular risk factors identified among the subjects included hypertension (predominantly among women), obesity and smoking (predominantly men). This study sought to highlight the role of primary prevention against the background of these emerging risk factors.

South Africa, being a heterogenous and multi-ethnic society, with marked socio-economic disparity, provides an opportunity to assess the effects of environmental risk factors across various ethnic groups and social classes. A study by Seftel et al (1993) found that among young individuals (aged 15-20 years), coronary risk factors, such as dyslipidaemia, were much more prevalent and severe among white, Indian and coloured subjects than their black counterparts [99]. Urbanization and higher socio-economic class were associated with an increase in cardiovascular risk among black subjects.

However, the relative weight of various risk factors may differ among ethnic groups, as suggested by a study by Nethononda et al (2004) comparing coronary risk factors in different South African groups in patients with angiographically documented CAD[100]. It was found that the majority of black patients with significant CAD on coronary angiography had cholesterol levels within the target range of the adult treatment panel III (ATP III) guidelines of the National Cholesterol Education Program (NCEP). This suggests other factors may also play a role in the

development of CAD in these patients. For example, some local studies have found metabolic syndrome, insulin resistance and postprandial lipaemia to be highly prevalent in urbanised South African blacks with CAD[101,102]. Furthermore, the chronic inflammatory state associated with metabolic syndrome, marked by a rise in high-sensitivity C-reactive protein, may play a role in coronary atherogenesis in these patients[103].

A high prevalence of CAD, and PCAD in particular, among South Africans of Indian descent has been noted in a number of studies. It is thought that a combination of genetic and lifestyle factors contributes to the disproportionately high prevalence in this minority group. Ranjith et al (2002), analyzed 245 Indian patients below the age of 45, who were admitted to the coronary care unit with acute myocardial infarction. Smoking (74%) and hypertriglyceridaemia (54%) were the most common risk factors noted in these patients[57]. Other risk factors included hypertension and low HDL-cholesterol levels. In another study by Ranjith et al (2004), the risk factors for CAD among young South African Indians below the age of 45 years were found to be differ significantly between genders and age groups[104]. Male patients had a higher relative risk due to smoking compared to female subjects, whereas the incidence of diabetes mellitus and abnormal HDL-c was higher in females than in males. A strong association of genetic factors was also observed among young patients of Indian origin[105].

Coronary angiography in young patients

Young patients with CAD are often referred for coronary angiography following an acute coronary syndrome. Differences in angiographic findings between older and younger subjects have been noted in a number of studies. For example, the results of the CASS study, involving 504 young men (<35 years) and women (<45 years) with a history of MI, found a higher frequency of normal coronary arteries, non-occlusive disease as well as single vessel disease, in younger patients compared to older patients[106]. Another large series of 823 young patients found single vessel disease in up to sixty percent of cases[40]. A predilection for involvement of the left anterior descending artery in young subjects has also been noted in some studies[107]. Gender differences have also been observed, with women being investigated for angina having a lower

prevalence of significant coronary disease on angiography, and more likely to have normal coronary arteries[108].

The high incidence of CAD in South Africa, particularly among the Indian community, and the concerning rise in incidence among younger patients (<45 years), with a risk factor profile that potentially differs from older patients, warrants further investigation as well an estimation of the magnitude of the problem. Moreover, assessment of risk factors associated with very young patients diagnosed with CAD may be of value in screening individuals or groups at risk and identifying targets for primary prevention. The limited local data available on very young patients also highlights the need for further study in this area.

Research question:

What are the most prevalent risk factors, clinical characteristics and angiographic findings among very young subjects with CAD?

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Chapter 2: Manuscript

The clinical and angiographic profile of very young adults with coronary artery disease.

AK Pillay*, DP Naidoo**

***Department of Internal Medicine, University of Kwazulu-Natal, Durban, South Africa**

****Department of Cardiology, University of Kwazulu-Natal, Durban, South Africa**

Correspondence to:

Dr AK Pillay

Department of Internal Medicine

Nelson R Mandela Medical School

Private Bag 7

Congella

South Africa

4013

Tel: +27 (0)31 2604216

Email: asheganp@yahoo.com

Abstract

Background: There is a paucity of local data on the profile of young adults with coronary artery disease (CAD).

Objectives: This study evaluated the clinical characteristics and angiographic profile of young adults with CAD.

Methods: A retrospective chart review was performed on patients 35 years and younger with CAD referred to Inkosi Albert Luthuli Central Hospital from 2003–2012.

Results: Of 100 patients meeting the study criteria, the majority were male (90%) and of Indian ethnicity (79%). Smoking (82%), dyslipidaemia (79%) and dysglycaemia (75%) were the most prevalent risk factors. Almost half the subjects (48%) met criteria for the metabolic syndrome. Most patients presented with ST-elevation myocardial infarction (66%) and multiple-vessel disease was the most common angiographic finding (42%). Disease severity was influenced by dyslipidaemia ($p = 0.001$), family history ($p = 0.04$) and central obesity ($p=0.04$).

Conclusions: Clustering of major cardiovascular risk factors is common in young subjects with CAD, the majority of whom present with ST elevation MI and almost half of these have multivessel coronary disease.

Keywords: coronary artery disease, young adults, risk factors, metabolic syndrome

List of abbreviations:

HPT = Hypertension

DM = Diabetes mellitus

FH = Family history

DL = Dyslipidaemia

RVD = Retroviral disease (HIV infection)

RVHD = Rheumatic valvular heart disease

SLE = Systemic lupus erythematosus

PIH = Pregnancy-induced hypertension

OCP = Oral contraceptive pill

CSA = Chronic stable angina

U/A = Unstable angina

EST = Exercise stress test

STEMI = ST elevation myocardial infarction (L = received thrombolytic therapy, NL = did not receive thrombolytic therapy)

NSTEMI = Non-ST elevation myocardial infarction

VT = Ventricular tachycardia

VF = Ventricular fibrillation

SVT = Supraventricular tachycardia

AVB = Atrioventricular block

CHB = Complete heart block (third degree AVB)

CHD = Coronary heart disease

CP = Chest pain

BMI = Body mass index (kg/m^2)

HR = Resting heart rate

BP = Resting, seated blood pressure

HF = Heart failure

TC = Total cholesterol

TG = Triglycerides

HDL = High density lipoprotein

LDL = Low density lipoprotein

GM = Fasting plasma glucose

HbA1c = Glycated haemoglobin (A1c)

Hb = Haemoglobin

MIBI – Sestamibi perfusion scan (stress and resting)

LMS = Left mainstem artery

LAD = Left anterior descending artery

RCA = Right coronary artery

Cx = Circumflex artery

Medical Mx = Medical management

PCI = Primary cutaneous intervention

CABG = Coronary artery bypass graft

TPM = Temporary pacemaker

IABP = Intra-aortic balloon pump

Introduction

Premature coronary artery disease (PCAD) is an emerging problem, and an increasing incidence of myocardial infarction in young patients has been noted in recent years.[10, 104] Most studies consider patients under the age of 40 to 45 years as young.[9] However, little is known about the clinical and angiographic profile of very young patients, under the age of 35 years.

Coronary atherosclerosis, beginning as a fatty streak and raised atheromatous plaque, has been noted to begin as early as adolescence[12]; however the majority of young patients with CAD may be asymptomatic until later in life.[9] Therefore, the magnitude of the problem may be significantly underestimated, with only a minority of individuals presenting at an early age. The silent process involved in the development of PCAD makes the estimation of disease prevalence a particular challenge. Autopsy studies have found advanced coronary atheromata in up to 20 percent of men and 8 percent of women between 30 and 34 years of age[18], and international studies have found a prevalence of between 4 and 10 percent of individuals with myocardial infarction under age 40 or 45 years.[20,21] Twelve years ago, Ranjith et al (2004) reported that 20 percent (n=491) of 2290 patients admitted to the coronary care unit between 1996 and 2002 were under the age of 45 years.[104] The increased cardiovascular risk among the Indian community has also been observed in a number of local studies.[57,104,105]

In contrast to older subjects, hypertension and diabetes mellitus are less commonly observed among very young patients.[40] However, subtle forms of dysglycaemia such as insulin resistance and impaired glucose tolerance may be more common in this age group and add to the risk of CAD.[54] Risk factor clustering in the form of the metabolic syndrome has also been reported to be common among young patients.[40] Additional, 'non-conventional' risk factors may also be more commonly found among younger subjects. These include psychosocial factors such stress[62,63] and

anger[64], the use of recreational drugs such as cocaine[66] and marijuana[69], and inflammatory conditions such as connective tissue disease[79,80] and HIV infection.[70,71]

Major cardiovascular (CV) risk factors as described in the INTERHEART study[23] were identified in the majority of young patients with CAD, with some studies finding at least one risk factor in over 90 percent of subjects.[27,28] A corresponding increase in mortality rate has also been associated with an increasing number of risk factors.[29]

With an increasing prevalence of PCAD being reported in local centers and the presence of multiple CV risk factors in the South African (particularly Indian) population, we elected to analyze the available data on the clinical and angiographic profile of very young patients presenting to the Cardiology Unit at Inkosi Albert Luthuli Central Hospital over a ten year period.

Methods

A retrospective chart review was conducted on patients 35 years or younger referred to the Cardiology Department at Inkosi Albert Luthuli Central Hospital (IALCH) for coronary angiography over a ten year period between 2003 and 2012. Patients referred for coronary angiography for reasons other than assessment of CAD (such as chest trauma or prior to elective valve replacement) were not included. Patients were identified using the Speedminer software program, which is a Data Warehouse Management software package, used by the hospital to manage, process and categorize the data collected on its database. All patient charts were accessed via the software program and data extracted on demographics, clinical and biochemical parameters as well as investigations including SestaMIBI and coronary angiography. PCAD in young subjects was defined as CAD occurring in subjects below 35 years of age.

Various clinical and biochemical parameters were assessed to determine the risk of CAD as well as factors that could influence the clinical outcome of patients. Clinical parameters (cut-offs in parentheses) included body mass index [overweight >25 kg/m^2 (>23 in Indians[148]); obese >30 kg/m^2], waist circumference [>94 cm (males, 90 cm Indians[109]; >80 cm (females)], resting blood pressure (>130/85 mmHg) and resting heart rate (>65 bpm). Laboratory parameters assessed included total cholesterol (>4.5 mmol/l), triglycerides (>1.7 mmol/l), HDL-cholesterol [<1.03 mmol/l (males), <1.29 mmol/l (females)], LDL-cholesterol (>1.8 mmol/l), fasting glucose (>5.6 mmol/l), glycated haemoglobin (HbA1c >6.5%), haemoglobin [<13 g/dl (males), <12 g/dl (females)], microalbuminuria (30-300 mg/l) and proteinuria (>300 mg/l).

In addition, the International Diabetes Federation consensus criteria (harmonized definition) (2006) were used to identify subjects with the metabolic syndrome (MetS)[109]. This included at least three of the following factors:

- Central obesity, defined by a waist circumference of 94 cm in males (90 cm in Indians)[109] and 80 cm in females
- Triglycerides >1.7 mmol/l
- HDL-cholesterol <1.03 mmol/l (males) / 1.29 mmol/l (females)
- Blood pressure >130/85 mmHg (or previously diagnosed hypertension)
- Fasting plasma glucose > 5.6 mmol/l (or previously diagnosed type 2 diabetes mellitus)

Patients with a combination of three or more of these five factors were considered to have metabolic syndrome (MetS) and the remainder were classified as not having metabolic syndrome (non-MetS).

Coronary stenosis of ≥50% in any of the major coronary arteries was designated occlusive CAD, and stenosis of <50% non-occlusive coronary disease (NOD). For scoring severity of CAD (CAS), stenosis of 50% was given a score of 1, 50–74% of 2, 75–99% was scored as 3 and total occlusion scored as 4. Additional stenosis scores, in case of multiple vessels, were added to give a final CAS score.[82]

Statistical Analysis

Statistical Package for the Social Sciences (SPSS version 23.0) was used for data analysis and a 95% level of confidence interval (CI) was estimated, and a global significance level of ά = 5% was chosen. Simple descriptive analysis was used to identify clinical characteristics and present results as frequencies, means and percentages. The chi-squared test and Mann-Whitney U test were used for categorical variables to determine the relationship between discontinuous variables or continuous variables in assessing the significance of risk factors between subjects with and without angiographic CAD. Binary logistic regression analysis was used to analyze confounding factors when assessing the independent relationships between risk factors and the outcome variable (CAD). A 2-Way ANOVA analysis was used to assess the effect of clinical criteria and other risk factors on the presence or absence of metabolic syndrome and the likelihood of CAD.

Ethical approval

The Ethics Committee of the Faculty of Health Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal granted approval for the study (BE324/13).

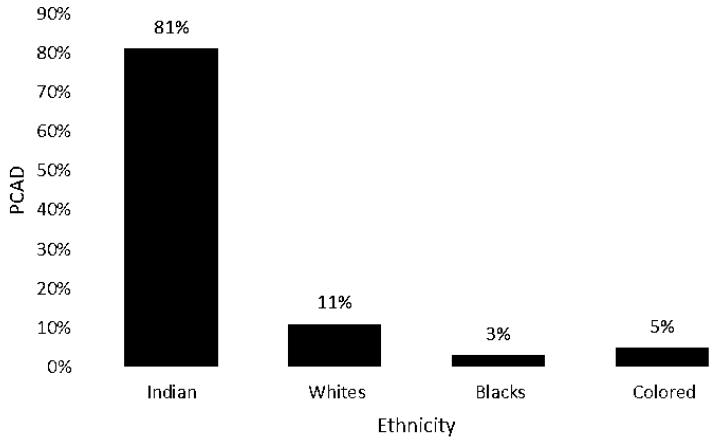
Results

Of the 7575 patients referred to cardiac catheterization laboratory with CAD over the study period, we identified 100 subjects (1.3%) under the age of 35 (90 males, 10 females). The mean age of the patients in the study was 31.9 years, with a median age of 27.5 years. Five patients (5%) were in the age range of 25 years and younger; 18 patients (18%) were between the ages of 25 and 30 years, with the remainder (77) being between 30 and 35 years of age. The ethnic distribution of the patients were as follows: 79% identified as Indian, 11% white, 7% black and 3% coloured [Table 1]. Occlusive CAD on angiography (CAS>50%) was diagnosed in 53 Indian subjects (81%), 7 whites (11%), 2 blacks (3%) and 3 coloured patients (5%) [Figure 1].

Table 1: Patient Demographic Profile

Characteristics	No. (SD) or No. (%)
Mean Age (yrs.)	31.9 (3.2)
Median Age (yrs.)	33
Age Range (yrs.):	
20-25 years	5 (5%)
26–30 years	18 (18%)
31–35 years	77 (77%)
Ethnicity:	
Indian	79 (79%)
Whites	11 (11%)
Blacks	7 (7%)
Coloured	3 (3%)

Figure 1: Prevalence of PCAD among Ethnic Groups



Varying combinations of cardiovascular risk factors were present in almost all but one subject, a 32 year old black male who had no CV risk factors and presented with chronic stable angina. A thrombophilic state was suspected in this patient but not proven with the available laboratory tests.

The two most common risk factors identified were smoking (82%) and dyslipidaemia (79%), with the latter being most often recognized after presentation. Seventy-four patients (74%) were reported to have a family history of CAD; of these a history of premature CAD in the immediate

family [a first degree relative under age 55 (males) or 65 (females)] was documented in 44 patients.

There were 41 patients who were classified as overweight (BMI >25 kg/m2, >23 in Indians) and 30 subjects (30%) were classified as obese. (body mass index >30 kg/m2). Increased waist circumference was found in 44 patients (42 males and 2 females).

Hypertension was present in 28% of subjects, and diabetes mellitus in 26 patients (26%), one of whom had type 1 diabetes diagnosed in childhood. Six of these patients were newly diagnosed with diabetes mellitus during their admission for the acute coronary syndrome. Dysglycaemia was present in 75 (75%) subjects. Forty-nine non-diabetic patients (49%) were found to have impaired fasting glucose (>5.6 mmol/l). Twenty-five patients had a glycated haemoglobin (HbA1c) greater than 6.5%. The average HbA1c among diabetic subjects was 10.0%, indicating a poor level of glycaemic control.

On applying the ethnic-specific harmonized criteria 48 subjects (48%) were found to have the MetS. [Table 2]

Table 2: Metabolic Syndrome Data

	MS (n=48)	No MS (n=52)	Total (n=100)
Criteria:			
WC >94(90) / 80	46	14	60
BP >130/80	14	9	23
FPG >5.6	41	12	53
TG >1.7	39	23	62
HDL <1.0 / 1.2	30	21	51
Other factors:			
BMI >25 (23)	47	34	81
Family history	38	38	76
Smoking	40	43	83
Gender:			
Male	43	47	90
Female	5	5	10
Race:			
Indian	41	38	79
Whites	3	8	11
Blacks	2	5	7
Coloured	2	1	3

Abbreviations: AC = waist circumference; BP = blood pressure, FPG = fasting plasma glucose; TG = triglycerides; HDL = high density lipoprotein

Non-conventional risk factors were found in 21 subjects. These included drug use (cocaine, heroin, cannabis, and the street drug 'sugars') in eight patients, systemic lupus erythematosus (1) and retroviral disease (2) [Table 3]. Two patients had co-existing rheumatic valvular heart disease, but did not have infective endocarditis or atrial fibrillation as predisposing factors for coronary embolism.

Table 3: Non-conventional Risk Factors

Non Coronary Risk Factors	Numbers
Drug use	8
Alcoholism	2
Valvular heart disease	2
HIV	2
SLE	1
Oral contraceptive	1
Hypothyroidism	1
Post-operative	1
Thrombophilia (suspected)	1

Abbreviations: HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus

Of the five patients in the study who were 25 years of age or younger at the time of presentation, four of whom had a positive family history of premature coronary artery disease as well as dyslipidaemia [Table 4]. The youngest subject was a 20 year old Indian male who presented with an anterior STEMI and was subsequently found to have non-occlusive disease on angiography with a kinked distal LAD. There was no evidence of hypertrophic obstructive cardiomyopathy

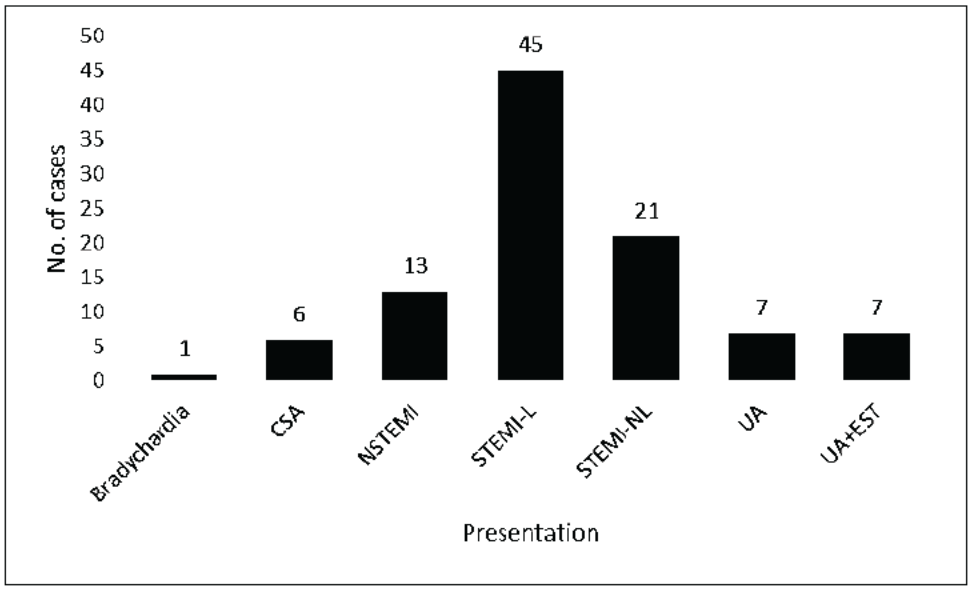
(HOCM) in this case. One patient, aged 25 years, also had a long history of uncontrolled type 1 diabetes mellitus and hypertension. Another 25 year old black male patient had a history of smoking and illicit drug use, but no other risk factors, and was found to have normal epicardial coronary arteries. It was suspected that the aetiology in this patient was coronary spasm related to illicit drug use.

Table 4: Risk factors in different age groups

Age (years)	**20-25**	**26-30**	**31-35**	**Total:**
Smoking	1	12	69	82
Hypertension	1	7	20	28
Diabetes	1	3	22	26
Dyslipidaemia	4	16	60	80
Obesity	0	8	22	30
Family history	4	12	58	74
Drugs	1	2	7	10

The majority of patients (n= 92), were referred from their base hospital following a diagnosis of acute coronary syndrome. Sixty-six patients (66%) were referred with a diagnosis of ST-elevation myocardial infarction (STEMI), of which 45 patients received thrombolytic therapy (STEMI-L) at the referring hospital. The reason most often cited for failure to administer thrombolysis in the remaining 21 patients (STEMI-NL) was late presentation (>24 hours since onset of chest pain). A further 13 patients were referred with non-ST-elevation myocardial infarction (NSTEMI), and 14 patients presented with unstable angina. Six subjects presented with chronic stable angina and were referred following positive exercise stress tests. One patient presented with symptomatic bradycardia (complete heart block) [Figure 2, Table 5].

Figure 2: Representative Data of Number of Patients with Mode of Presentation



Abbreviations: CSA=chronic stable angina, NSTEMI = non-ST-elevation myocardial infarction, STEMI-L = ST-elevation myocardial infarction – thrombolysed, STEMI-NL = ST-elevation myocardial infarction – not thrombolysed, UA = unstable angina, UA+EST = unstable angina with positive exercise stress test.

Table 5: Presentation at Referral Hospital

Presentation		
STEMI	Lysed	45
	Not Lysed	21
NSTEMI		13
Chronic stable angina	-	6
Unstable angina	-	14
Symptomatic bradycardia	-	1
Arrhythmia	-	8
	Tachyarrhythmia	4 (1 SVT, 2 VF, 1 VT)
	Bradyarrhythmia	4 (1 AVB1, 2 AVB2, 1 CHB)

Abbreviations: STEMI=ST elevation myocardial infarction; NSTEMI=Non-ST elevation myocardial infarction; SVT=supraventricular tachycardia; VF=ventricular tachycardia; AVB=atrioventricular block; CHB=complete heart block.

The majority of patients (82%) presented with 'typical' acute ischaemic chest pain – crushing substernal pain with radiation to the neck, shoulder and arms, and associated autonomic symptoms (nausea, vomiting, sweating, dizziness). Atypical chest pain was reported in eighteen cases (18%); the description included sharp, stabbing pain, symptoms suggestive of dyspepsia or heartburn, and pain localized outside the chest.

Eight patients were identified as having an arrhythmia at the time of presentation. In one patient, symptomatic bradycardia was the only presenting manifestation of CAD**.** Of the eight, four patients presented with tachyarrhythmias (1 supraventricular tachycardia, 1 ventricular tachycardia, and 2 ventricular fibrillation). Bradyarrhythmias identified on presentation included first-degree heart block (1), second-degree heart block (2) and complete heart block (1).

On clinical examination, 65 patients presented with a resting heart rate greater than 65 beats per minute, and 19 patients had a resting blood pressure greater than 130/85 mmHg. Clinical signs of heart failure (elevated jugulovenous pressure, lower limb oedema, pulmonary crepitations) were identified in 5% of patients on presentation.

Dyslipidaemia was identified in 79 subjects (79%). Of the available data, hypercholesterolaemia was found in 62/92 (67.4%) subjects, hypertriglyceridaemia in 58/91 (63.7%), and low HDL-cholesterol in 52/92 (56.5%). In the 87 patients in whom low-density lipoprotein (LDL) could be calculated by the Friedewald formula, 78 (90%) were found to have levels greater than 1.8 mmol/l. The combination of raised TG and low HDL was found in 30 subjects [Table 6].

Table 6: Biochemical Profile of Patients

Lipids		
TC >4.5mmol/l	62/92	67%
TG >1.7 mmol/l	58/91	63%
HDL <1mmol/l (M) 1.2mmol/l (F)	52/92 78/87	56% 90%
LDL >1.8 mmol/l		
Additional laboratory investigations:		
Fasting Glucose >5.6mmol/l	49/99	49.5%
HbA1c > 6.5%	25/97	26%
Hb <13 g/dl (M) 12 g/dl (F)	10/100	10%
Microalbuminuria	24/32	75%

Abbreviations: TC = total cholesterol; TG = triglycerides; HDL = high density lipoprotein; LDL = low density lipoprotein.

Anaemia was identified in 10% of patients (Hb <13 g/dl in n males, <12 g/dl in n females); however, the individual causes of anaemia were not documented in the available records. Whether this was a precipitating factor in any of the coronary events was not clear in these cases. Thirty-two patients had urinalysis results recorded, with 24 (67%) showing either microalbuminuria or overt proteinuria [Table 6].

The admission electrocardiogram (ECG) revealed that the majority of patients (65%) had evidence of anterior ischaemia or infarction; further classified as anterior (n=9), anterolateral

(32) and anteroseptal (24). Thirty percent presented with inferior (15), inferolateral (13) or inferoposterior (2) involvement. Fully evolved Q-waves were identified in 63% of patients, indicating late presentation or previous infarction in these subjects.

Impaired left ventricular function (ejection fraction (EF) <50%) was documented on echocardiography in 42/99 subjects (42%) with evidence of regional wall motion abnormalities in 83%. Left ventricular thrombus was identified in nine patients. Twenty-nine subjects also underwent technetium (99mTC) SestaMIBI scanning to assess myocardial perfusion. Of these, 19/29 (65%) were found to have reversible ischaemia. The data was collected before percutaneous coronary intervention or coronary artery bypass graft.

Coronary angiography revealed single-vessel disease in 36 subjects, with the left anterior descending (LAD) artery being the most commonly involved vessel (n=33, 92%). Multi-vessel disease was found in 42 patients; of which 27 patients had two-vessel disease [19 (70%) with LAD involvement] and 15 patients had triple-vessel disease [14 (93%) with LAD involvement]. Non-occlusive coronary artery disease was found in 20 patients (20%). Among subjects with diabetes mellitus, the majority was found to have multiple-vessel disease (n=11) [two-vessel disease in 9 subjects; three-vessel disease in 3 subjects], followed by single-vessel (n=7) and non-occlusive disease (n=6).

Of the eight subjects with a history of illicit drug use, four were found to have single vessel disease on coronary angiogram, three had normal or non-occlusive disease and one subject had three-vessel disease. Two patients had a normal coronary angiography. One was a 25 year old black male with no cardiovascular risk factors but did have a history of drug use. He presented with typical chest pain and was diagnosed with an anterolateral STEMI, receiving thrombolytic therapy at his base hospital within three hours of symptom onset. The mechanism of MI in this patient was suspected to be acute coronary spasm. The other patient was a 34 year old black male who was HIV-positive and a smoker (pack-year history of 5), but had no other cardiovascular

risk factors. He presented with an anterior STEMI and received thrombolysis. A prothrombotic state or possibly a vasculopathy related to HIV infection was suspected in this case.

Two subjects in the study group had concurrent HIV infection, and were found to have single vessel disease and normal coronaries respectively. One patient with SLE was found to have single vessel disease with involvement of the LAD.

The prevalence of major CV risk factors was also assessed among the various ethnic groups. Indians were most likely to have a positive family history of PCAD (78%), a smoking history (83%) and dyslipidaemia (81%). White subjects had the lowest rates of hypertension (29%) but were more likely to be obese (36%). Black patients were less likely than other groups to have a family history of CAD, dyslipidaemia or obesity [Figure 3; Table 7].

Figure 3: Prevalence of Dyslipidaemia in Different Ethnic Groups

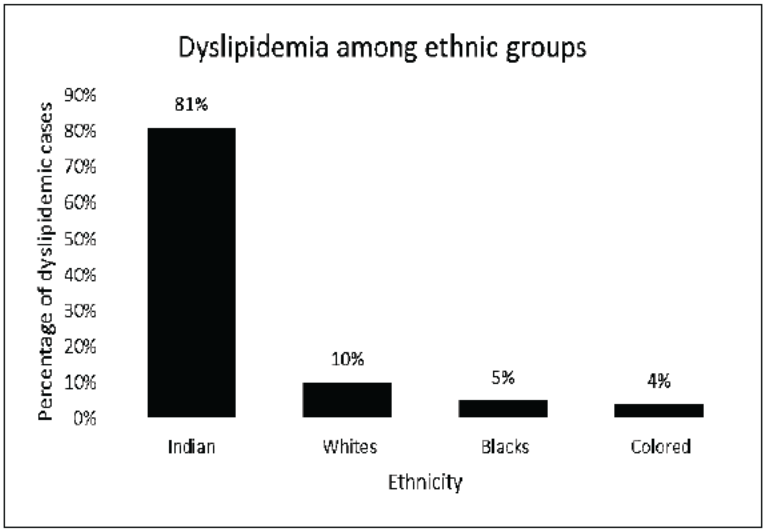
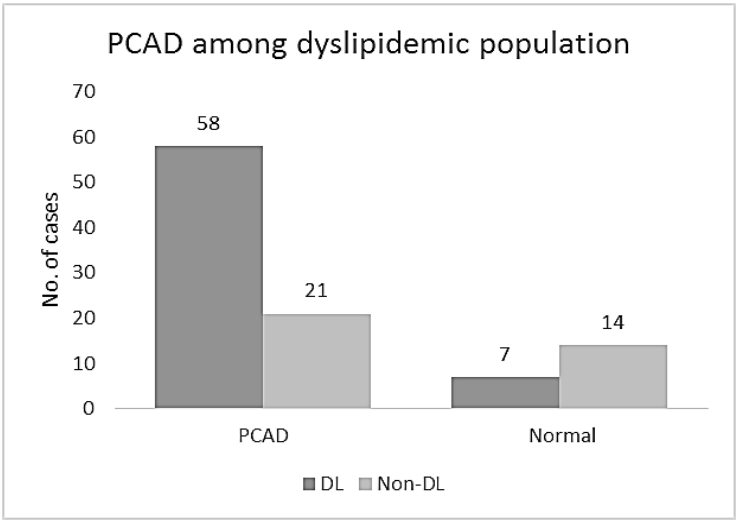


Table 7: Prevalence of Risk Factors among Ethnic Groups

	Hypertension	Dyslipidemia	Smoking	Obesity	Family History	Diabetes
Colored	1/3 (33%)	3/3 (100%)	2/3 (67%)	1/3 (33%)	2/3 (66%)	1/3 (33%)
Indian	22/79 (28%)	64/79 (81%)	66/79 (83%)	24/79 (30%)	62/79 (78%)	24/79 (30%)
Whites	3/11 (27%)	8/11 (72%)	9/11 (82%)	4/11 (36%)	8/11 (73%)	0/9 (0%)
Blacks	2/7 (29%)	4/7 (57%)	5/7 (71%)	1/7 (14%)	2/72 (26%)	1/5 (20%)

To determine the relationship between risk factors and CAD, a chi-square test was conducted with either dyslipidaemia, obesity, smoking, familial history, hypertension, diabetes or MetS as independent factors and CAD as the dependent factor. On bivariate analysis, a strong association between dyslipidaemia and CAD was observed $\chi 2 = 13.35$, $p = 0.001$, OR = 7.53 [Figure 4]. However, other factors such as hypertension ($p = 0.46$), diabetes ($p = 0.60$) smoking ($p = 0.23$) and familial history ($p = 0.11$) were not associated with CAD. The presence of MetS was not significantly predictive of CAD ($p = 0.6$). Obese persons had twice the odds of having occlusive CAD but this was not statistically significant ($p = 0.13$), OR = 2.4.

Figure 4: Comparison of PCAD in patients with and without dyslipidaemia



DL=dyslipidaemia, Non-DL = no dyslipidaemia

To determine the association of various risk factors on the severity of stenosis or number of vessels affected, we conducted a Mann-Whitney U test with CAS or number of vessels as the dependent variable and major risk factors as the independent variable.

Dyslipidaemia was strongly associated with with severity of stenosis (p = 0.002) and number of vessels involved (p = 0.041), particularly low HDL cholesterol (p = 0.008). A positive family history was also found to be associated with severity (p = 0.045) and number of vessels (p = 0.002). However, hypertension (p = 0.372), diabetes (p=0.63), metabolic syndrome (p = 0.8) smoking (p = 0.41) were not predictive of severity of CAD. Although not statistically significant, a higher percentage of coronary artery stenosis was noted among patients with increased waist circumference (p = 0.06) as well as obesity (p = 0.08).

To determine the effect of various risk factors on the severity of CAD in combination with MetS, a 2-way ANOVA analysis was conducted with CAS as the dependent variable and MetS as the grouping variable, along with various risk factors. Obesity along with MetS seemed to influence CAD severity (p = 0.004). However, a strong association was not demonstrated when combined with smoking (p = 0.85) or family history of CAD (p = 0.591).

To further assess the association of various risk factors with CAD, a binomial regression analysis was conducted with CAD as the dependent variable and gender, ethnicity, CV risk factors and the presence or absence of MetS as covariates. For ethnicity, three dummy variables were created and compared with Indians as the baseline, similarly with respect to age, age range of 20−24 was taken as baseline for comparison, and 25−30 years and 31−35 years were assigned dummy variables. None of the factors showed statistically significant associations with CAD except dyslipidaemia (p = 0.002 at 5% CI). Family history and obesity, which earlier showed a p value of 0.131 and 0.161, improved to 0.073 and 0.068 showing significance at 10% CI. The result suggests a strong association between dyslipidaemia and CAD and also points toward the additional influence of family history and obesity.

In terms of management outcomes, 39 patients (35 male and 4 female) underwent percutaneous coronary intervention (PCI) and 22 (all male) had coronary artery bypass grafts (CABG) [Table 8]. The remaining 39 patients received medical management only without coronary intervention being required. Some of the acute complications encountered included cardiogenic shock (n=3), post-infarct angina (n=1), acute pulmonary oedema (n=1) and ventricular arrhythmia (n=2). Long term complications included complete heart block (n=1) requiring permanent pacemaker insertion, and dilated ‘ischaemic’ cardiomyopathy (n=1). The in-hospital mortality among the subjects studied was 4%; one of these occurred following failed PCI and the onset of severe cardiogenic shock requiring an intra-aortic balloon pump.

Table 8: In-hospital Complications and Management

Shock	**3**
Post-infarct angina	**5**
Acute pulmonary oedema	**1**
LV thrombus	**9**
Arrhythmia	**2**
Dilated cardiomyopathy	**1**
Management:	
Medical Management	**39**
PCI	**39**
CABG	**22**
Mortality	**4**

Abbreviations: PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Discussion

This study shows a high prevalence of atherosclerotic disease in young subjects presenting with acute coronary syndrome. While often regarded as a disease of advancing age, CAD has been noted with increasing frequency among younger individuals[104] and atherosclerotic changes in the coronary vessels have been found as early as adolescence[12]. With changes in lifestyle and dietary habits, particularly in the developing world[94-96], the incidence of PCAD is likely to rise without adequately addressing the environmental risk factors that contribute to its pathogenesis.

As age is an independent risk factor for CAD[30], we proposed that the pathophysiology and clinical profile of young patients may differ from the older population. Instead we found that the majority had atherosclerotic CAD. The demographic profile of our study group appears to be in agreement with international studies on the age, gender and ethnic disparities in the prevalence of PCAD. Only five subjects in the study were at or below the age of 25 years at presentation, with 18 subjects in the range of 26-30 years and the majority (n = 77) being 31-35 years of age. This supports the contention that age itself is an independent risk factor for PCAD, even after adjusting for risk factors among the younger population[19,93].

We also found a male preponderance in young patients with CAD with a male:female ratio of 9:1. This finding is also in keeping with previous studies which have found similar ratios between young men and women[19]. We take into account that women with CAD are found on average to present about 10 years later than men and often carry a higher burden of risk factors at the time of presentation[113]. The lower incidence among young women has been attributed both to non-modifiable factors such as the protective effect of oestrogen, and a lower prevalence of smoking among women[29].

Although Indians represent a minority group in South Africa, the community bears a comparatively high burden of PCAD. The majority of subjects in our study were identified as Indian (79%), of which 53 (81%) were diagnosed with occlusive CAD [Figure 1]. The observation that CAD prevalence differs significantly among ethnic groups is in agreement with numerous earlier studies,[104,105] both internationally and locally. Studies in the United States, for example, have shown a 50% higher risk of CAD among expatriate Indians compared to other ethnic groups such as Hispanics and blacks[89] even after adjusting for lifestyle factors [114]. The data is also in agreement with the CADI study, which estimated a higher risk of CAD among Indians[92].

The higher prevalence among Indians has been attributed to genetic factors, such as a high frequency of the apo-E3/E4 genotype[117] and elevated C-reactive protein[91], as well as higher rates of visceral obesity, higher triglyceride levels and a tendency to glucose intolerance[115]. Hypercholesterolaemia is a significant contributor to PCAD in the Indian population, accounting for 59% of the CAD burden in subjects over age 30 in one study[105]. In addition, the coronary anatomy of Indian subjects may also predispose to the higher prevalence of CAD, with narrower coronary blood vessels, often presenting a technical difficulty during invasive techniques [116].

As documented in previous studies, we have found that multiple CV risk factors are present in young patients with CAD[116,117]. The risk factors identified most frequently in our study population included smoking (82%), dyslipidaemia (80%) and a positive family history (74%). Hypertension and diabetes mellitus, while comparatively less prevalent among these young subjects (28% and 26% respectively), were still relatively frequent as compared to the general population. Almost a third of subjects (30%) were classified as obese, with 41% being overweight. We noted a significant number of subjects were drug users (10%), including cannabis, heroin, cocaine and a local street drug ('sugars').

The majority of our subjects (80%) were found to have associated dyslipidaemia, in keeping with other studies[119]. However, in contrast to previous studies which have demonstrated a predominance of hypertriglyceridaemia and low HDL-cholesterol in young patients[56], we noted elevated LDL-cholesterol to be the most common lipid abnormality identified (78/87, 90%). However, close to two thirds of the study group were found to have hypertriglyceridaemia (63%) and low HDL-cholesterol (56%), the combination of factors being noted in 30 subjects. Familial dyslipidaemia was documented in only 15 subjects, however the genetic predisposition to lipid abnormalities may have been underestimated. Our data presents a strong association between dyslipidaemia, particularly low HDL-c, and the presence of occlusive CAD and increased severity of disease. Low HDL-c has been linked to premature atherosclerosis, endothelial dysfunction and a reduction in vasodilatory nitric oxide[130], and should be considered a target for dietary and pharmacological intervention for patients at risk of PCAD.

The very high rates of smoking among young patients with CAD have been documented in numerous studies[45-48]. A registry study by Larsen et al (2013) of patients with STEMI being treated with PCI found that smoking rates were highest among the age range of 18-34 years (78%) compared both to older age groups and the general population of similar age (23%)[118]. Smoking conferred a greater risk (OR 2.9) among Indian and white subjects. Therefore, it is likely that smoking may act in concert with other CV risk factors to result in PCAD, and remains an important target for lifestyle modification among patients at risk.

The third most prevalent risk factor among the subjects was a positive family history of CAD (74%), which influenced both the extent and severity of CAD ($p=0.045$ and $p=0.002$ respectively). Our findings concur with previous studies, which have found young patients more often have a positive family history than middle-aged or elderly patients[37-41], with contributions to this increased risk from both genetic and environmental factors. In the INTERHEART study parental CAD was a strong predictor of MI in their offspring, with this association extending across ethnic, geographical and socio-economic groups[38]. A study by Ranjith et al (2011) among South African Indians with MI found a family history of PCAD in 54% of subjects, and adds that other heritable traits such as type 2 diabetes mellitus, hypertension and obesity may add to this increased risk[118].

Obesity has been described as an independent risk factor for CAD[61], and we noted a high number of obese (30%) and overweight (51%) subjects in our study. Of the obese subjects, 19 (63%) were found to have occlusive CAD on coronary angiography. Obesity appeared to influence the severity of stenosis ($p=0.08$) but did not have an association with the number of vessels involved. With a high prevalence of obesity in the South African population, estimated at 42% among women and 13.5% among men[141], and rising in the adolescent and young adult population, the burden of PCAD may be expected to increase in the coming decades without appropriate public health-based intervention.

Type 2 diabetes mellitus has also been demonstrated to be a strong predictor of CAD, particularly among groups usually considered 'low risk' such as young patients, women and non-smokers[25]. We found a relatively high prevalence of diabetes among our study group (26%), although it did not statistically influence the extent or severity of disease ($p = 0.63$). Impaired fasting glucose was also a common finding (53%), with 75 subjects in total showing signs of dysglycaemia. The high prevalence of subtle abnormalities of glucose metabolism, including insulin resistance and impaired glucose tolerance, among young subjects with CAD has been documented in previous studies[54], although the extent this contributes to the development of vascular disease in non-diabetic patients has been questioned[131].

Risk factor clustering in the form of metabolic syndrome (MetS) has been well recognized as a significant predictor of CAD[37] and has been noted to differ significantly among ethnic groups[142] and between age groups, rising from less than 10% in the 20-29 year age group to between 38 and 67% in the 60-69 year age group[143]. Almost half the subjects in our study (48%) met the modified IDF criteria[120] for MetS. In a previous study, Ranjith et al (2007) assessed the prevalence of MetS among young South African Indian subjects with MI using the NCEP ATP III and IDF, and found between 57 and 60% of subjects met the respective criteria[140]. This study suggested that the use of the modified IDF ethnic-specific waist circumference cut-offs as the determinant of abdominal obesity was more useful to accurately identify patients in this population group. A predominance of visceral adipose tissue among Indian subjects with increasing waist circumference, as compared to white and African subjects, is a major contributor to the increased risk of hyperinsulinaemia, insulin resistance, diabetes and dyslipidaemia in this population[143].

Previous studies have shown MetS to be associated with extensive (three-vessel) disease[140]. However, our findings did not demonstrate a strong association between the presence of MetS and occlusive CAD (n=34 without MetS; n=31 with MetS), with fairly equal numbers of subjects with non-occlusive disease in both groups (n=18 without MetS; n=17 with MetS). Among the

factors that may have contributed to this indeterminate result include the age range studied and the sample size, which was not sex-matched. We note the low number of female subjects in the study, among whom MetS has been more often found in association with PCAD than males[122]. A larger study sample across different age groups may have further validated the previous findings of MetS being predictive of occlusive CAD.

We also assessed the individual risk factors associated with MetS for their relative contribution and predictive value for occlusive CAD and disease severity. A significant relationship was demonstrated only for dyslipidaemia (p=0.002). Of the other CV risk factors assessed in association with MetS, only obesity (p=0.068) and family history (p=0.073) was found to influence the risk of occlusive CAD.

Coronary artery severity (CAS) scores were calculated according to extent of stenosis in the coronary vessels and were analysed to determine the key predictors of disease severity in young subjects. Previous studies have demonstrated that the severity of CAD may be dependent on risk factors such as family history, smoking or dyslipidaemia[126]. Our finding of higher CAS scores in association with a positive family history of PCAD and dyslipidaemia, low HDL-c in particular, is in agreement with earlier observations[59]. However, despite having a high prevalence in the study group, smoking did not appear to contribute significantly to the severity of CAD (p=0.41).

In keeping with these previous observations, we found a majority of young subjects (n=94) presented with an acute coronary syndrome. Young patients are less likely to present with symptoms of angina[144], and the first manifestation of CAD is most often an ACS, which untreated or unrecognized, progresses rapidly to MI, STEMI in particular[19,56]. A study of 200 subjects with angiographic CAD by Chen et al (1995) also found a lower incidence of stable angina (24%) and a higher incidence of ACS (76%) in subjects younger than 45 years compared to subjects over age 60, with a higher likelihood of complex lesions on angiogram[56]. Young patients are therefore less likely to present with a preceding history of exertional chest pain.

Indeed, previous reports have found up to two-thirds of young subjects deny a history of chest pain before the infarct[145], and when present, angina tends to occur most often in the week preceding the event[19].

STEMI is often associated with risk factors such as smoking and dyslipidaemia, and presents more commonly in males than in females[60]. Though our study could not determine gender bias in the presence of STEMI as a small number of the study group (10%) were female subjects, we could find a considerable number of male patients with this particular presentation were smokers and a high proportion also had dyslipidaemia, as observed in earlier studies[135]. Young patients below the age of 30 with acute coronary syndrome who present with STEMI may still have a more favorable long-term prognosis, as compared to older patients[136, 146].

In contrast to the findings of the CASS study which found a higher frequency of non-occlusive and single vessel disease in young subjects[19], we found a significantly higher incidence of multiple vessel stenosis among young subjects — 42 with multi-vessel disease (27 double vessel and 15 triple vessel stenosis) as compared to 36 with single vessel disease. The left anterior descending (LAD) was the most frequently involved coronary vessel in both groups, as noted in previous studies[107].

Limitations

Our study was limited to a specific geographical area and more specifically to a single study centre. We found a much higher prevalence of PCAD among Indians, and although this ethnic group does not represent a majority in the province concerned, the community is largely concentrated in the Durban area. Our study, did not represent an equivalent population of ethnic groups and genders, which limited analysis on gender and ethnic differences in risk factors.

Few ‘conventional’ cardiovascular risk factors, common in the older population, were found to have a statistically significant relationship with PCAD in very young patients, as documented in previous studies.

Conclusion

We have noted a significantly higher prevalence of PCAD in young adults among Indians compared to other ethnic groups, which may be due to genetic predisposition as well as lifestyle factors. Young adults with CAD were more likely to present with ACS, especially STEMI, and had multivessel disease. The most prevalent risk factors among very young subjects were smoking, dyslipidaemia and a positive family history. Risk factor clustering in the form of metabolic syndrome was noted in almost half the subjects. The factors most predictive of disease severity were dyslipidaemia, low HDL-cholesterol in particular, and a positive family history.

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Appendices

Appendix 1: Study Protocol

Candidate: Ashegan Kandasamy Pillay

Department of Cardiology, Nelson R Mandela School of Medicine, University of Kwazulu-Natal, Durban, South Africa

Title of study:

The clinical and angiographic profile of very young patients (35 years and younger) with coronary artery disease: A retrospective review.

Aim of study:

To identify and describe the clinical profile of very young patients (35 years and younger) with coronary artery disease, including cardiovascular risk factors and modes of presentation.

To describe the coronary angiographic findings in these patients.

To document the therapeutic outcomes in this subset of patients.

Specific objectives:

Assessment of clinical profile including:

- Demographic data (age, gender, ethnicity, linguistic group)

- Cardiovascular risk factors (family history, smoking, hypertension, dyslipidemia, diabetes mellitus, body mass index, waist circumference, microalbuminuria, others: collagen vascular disease, drugs)
- Biochemistry (glucose, lipids, uric acid, haemoglobin, microalbumin)
- Clinical presentation (angina, acute coronary syndrome, arrhythmia)
- Physical examination (obesity, blood pressure, heart rate, heart failure, complications)
- Results of preliminary investigations (ECG, echocardiogram, MIBI)

Assessment of coronary angiographic findings (single vs multi-vessel disease, lesion complexity)

Description of clinical outcomes (medical management, percutaneous coronary intervention, coronary bypass graft)

Introduction:

Young patients represent a minority of cases of coronary artery disease (CAD), but the social, psychological and economic impact of this diagnosis is significant. A number of studies have sought to identify the common clinical characteristics and angiographic findings found in this particular population. For example, these patients are most often male and smokers, and may have a family history of premature ischaemic heart disease. However, local data is limited. We undertake to document the experience at a quarternary referral center in Durban, and identify the clinical and angiographic profile of very young patients with coronary artery disease. This is with a view to identifying patients at greater risk of CAD in the local setting, and predicting the pattern of disease and therapeutic outcome.

Background and Literature:

While CAD has traditionally been thought of as a condition associated with the older patient, it is increasingly being recognized among young adults. Interest in the prevalence and clinical

characteristics of young patients with coronary artery disease (CAD) has been expressed in the academic literature as early as the 1930's [1]. The clinical and angiographic profile of this particular group may demonstrate certain distinctive features that may help in the early detection and appropriate management of these subjects. Although local data is limited, international reviews have identified particular risk factors and angiographic findings associated with premature CAD and myocardial infarction.

While young patients represent a minority of cases of CAD, the social and economic consequences of coronary events among the young may be devastating. It has been suggested that despite the relatively low incidence of clinically manifest CAD in this group, they are perhaps the 'tip of the iceberg', having come to medical attention when symptoms arise, with a larger asymptomatic or subclinical population that goes undetected until a later stage[2]. A study by Tuzcu et al (2001) utilizing intravascular ultrasound in heart transplant recipients found coronary lesions in one out of six teenagers, indicating an early age of disease onset[3].

It has been well-recognised that young patients with CAD are most often male and smokers[2, 10, 14]. Indeed, the Framingham Heart Study found a relative risk for CAD three times higher among smokers aged 35-44 than among non-smokers[4]. Conventional risk factors seen in older patients such as dyslipidaemia and diabetes, also contribute to CAD risk in young patients[2, 10]. Elevated triglycerides and lipoprotein (a) levels as well as low high-density lipoprotein (HDL) levels have been associated with early onset of CAD[6]. In addition, high homocysteine levels confer additional risk in young patients[7].

Increased body mass index (BMI) and truncal obesity have been implicated as independent risk factors for CAD in young patients, substantially increasing predictive power in one study cohort assessing for coronary artery calcification[8]. With obesity rates dramatically rising in South Africa, particularly among the youth[9], this poses a special concern. Family history is commonly cited as a significant risk factor for premature CAD, probably representing a number of

genetically determined predisposing factors such as hyperlipidemia and diabetes. Ranjith et al (2002) propose this underlies the high prevalence of CAD among the South African Indian population[17]. Some studies have indicated the presence of lipid abnormalities in the children of patients with CAD[11].

Other factors which may be under-recognized are the impact of psychological factors such as emotional distress[12], and the role played by chronic systemic inflammation. Recreational drug use, such as cocaine, and even acute ethanol intoxication have been implicated in acute myocardial infarction among young patients, likely by inducing coronary vasospasm, plaque rupture or thrombosis[5]. Hypercoagulable states and collagen vascular disease also confer increased risk for CAD among young patients with these conditions[2]

In terms of the angiographic profile of young patients with CAD, some authors have proposed distinct patient subpopulations with characteristic patterns of disease. Klein et al (1987)[13] and Chen et al (1995)[12] suggest the more common subtype presents with single vessel disease, with generally good outcomes following revascularization. Recent studies in China[16] and Turkey[15] corroborate this finding. The less common subtype, it is proposed, presents with extensive and more rapidly progressive multiple vessel disease, with poorer outcomes despite interventional measures[13]. Other data, however, has suggested a high incidence of non-occlusive or angiographically normal coronary arteries in young patients presenting with acute myocardial infarction, with relatively good short- and long-term prognosis[17, 21].

A recent report has documented CAD in young subjects in the Durban functional region[17]. There is little data on even younger subjects (<35 years) presenting with myocardial infarction with regard to the pattern of presentation, the clinical profile and the approaches to management in these subjects. This study describes the clinical, biochemical and angiographic profile of such patients in the hope of identifying at-risk groups and possibly, predicting the pattern of coronary atherosclerosis in these patients.

Study design:

Study sample:

All patients 35 years or younger presenting to the Cardiology unit with coronary artery disease between 2002 and 2012

Sample size

100 patients

Inclusion / exclusion criteria

Inclusion criteria:

Patients with documented coronary artery disease (acute coronary syndrome, chronic stable angina) diagnosed at age 35 years or younger

Exclusion criteria:

Patients older than 35 years

Non-cardiac chest pain (ie. no documented coronary artery disease)

Data collection methods and tools

Retrospective chart review using Speedminer search program to identify cases

All charts accessed via the Soarian network (including migrated documents from older Medicom system)

Data analysis techniques

Descriptive study

Statistical analysis

Simple descriptive analysis will be used to identify clinical characteristics and results will be presented as frequencies, means and percentages.

Categorical variables will be analyzed using Chi square test and non-parametric testing for continuous variables.

Student's T test will be used to compare the clinical and angiographic features and the significance level will be taken at 5%.

Study location:

Inkosi Albert Luthuli Central Hospital

Study period:

2002 – 2012

Limitations to the study:

This is a single center study and the study sample includes only those patients referred for coronary angiography from their base hospital.

Certain clinical data and biochemical tests may be inaccessible from very old migrated charts on the Soarian computer system, although every attempt will be made to collect available data.

Ethical considerations:

Patient confidentiality will be respected throughout the data collection process and subjects will be identified by hospital number only.

No direct patient contact is required for this study.

Patient information will be used only for the purposes of the study.

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Appendix 2: The Guidelines for Authorship: Cardiovascular Journal of Africa

All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by fax or mail (fax number +27 21 976 8129 or PO Box 1013, Durbanville, 7551) or e-mail to **info@clinicscardive.com**

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed

within the context of current knowledge, leading to specific conclusions where possible.
Acknowledgements. References, figures and tables as above.

Appendix 3: Ethical approval

Included hospital and provincial approvals as well as the BREC approval (or waiver if appropriate).

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

21 November 2013

Dr AK Pillay
P.O Box 23976
Isipingo
4110
asheganp@yahoo.com

PROTOCOL: The Clinical and Angiographic Profile of very Young Patients with Coronary Artery Disease. REF: BE324/13.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 20 August 2013.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 19 November 2013 to queries raised on 16 October 2013 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 21 November 2013.

This approval is valid for one year from **21 November 2013.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **10 December 2013.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]
Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 298/13
Enquiries : Mr X Xaba
Tel : 033 – 395 2805

Dear Dr AK Pillay

Subject: Approval of a Research Proposal

1. The research proposal titled **'The clinical and angiographic profile of very young patients (35 years and younger) with coronary artery disease: A retrospective review'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 06/11/2013

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

1 October 2013

Dr AK Pillay
Department of Cardiology
IALCH

Dear Dr Pillay

Re: Research Approval: Ref No: BE324/13: The Clinical and Angiographic Profile of very Young Patients with Coronary Artery Disease.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg , 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr P D Ramdas
Acting Medical Manager

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: BE324/13
Enquiries: Medical Management

1 October 2013

Dr AK Pillay
Department of Cardiology
IALCH

Dear Dr Pillay

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **The Clinical and Angiographic Profile of very Young patients with Coronary Artery Disease.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr P D Ramdas
Acting Medical Manager

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

03 September 2013

Dr AK Pillay
P.O Box 23976
Isipingo
4110
asheganp@yahoo.com

Dear Dr Pillay

PROTOCOL: The Clinical and Angiographic Profile of very Young Patients with Coronary Artery Disease. REF: BE324/13.

PROVISIONAL APPROVAL

A sub-committee of the Biomedical Research Ethics Committee has considered application received on 20 August 2013.

The study is given **PROVISIONAL APPROVAL** pending receipt of responses to the following queries from reviewers:

1. Gatekeeper's Permission
2. Remove hospital number from data sheet.

Please refer to attached document "Permission to Conduct a Research Study/Trial". This must be completed and submitted to the Hospital Manager for signature. For King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH) studies please submit the document **together with items 1 to 5 as outlined on the form.**

Once the document has been signed it should be returned to this office.

Only when full ethical approval is given, may the study begin. **Full ethics approval has not been given at this stage.**

PLEASE NOTE: Provisional approval is valid for 6 months only - should we not hear from you during this time - the study will be closed and reapplication will need to be made.

Your acceptance of this provisional approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

Yours sincerely

[redacted]

Professor D Wassenaar
Chair: Biomedical Research Ethics Committee

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH)** and **Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Declaration of all funding applications / grants, please supply substantiating documentation.
5. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to Biomedical Research Ethics Administrator, Room N3, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:
Inkosi Albert Luthuli Central Hospital
300 Bellair Road
Cato Manor

Investigator/s:
Principal: Dr AK Pillay
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager:
[redacted]
Date: 3/10/2013

Site 2 address:
_____
_____
_____

Investigator/s
Principal: _____
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:
_____
Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

Appendix 4: Data collection tools

Patient Data Capture Sheet (MMed – Medicine)

Title: The clinical and angiographic profile of very young patients with coronary artery disease: A retrospective chart review

Principal Investigator: Dr AK Pillay

Supervisor: Prof DP Naidoo

Age	
Gender	
Ethnicity	
Risk factors:	
- Smoking	
- Hypertension	
- Diabetes mellitus	
- Family history	
- Dyslipidemia	
- Obesity	
- Other (specify)	
Clinical presentation:	
- Acute coronary syndrome - Unstable angina - STEMI - NSTEMI	
- Chronic stable angina	
- Arrhythmia	
- Typical/Atypical chest pain	
Clinical exam:	
- Body mass index	
- Waist circumference	
- Heart rate	
- Blood pressure	
- Heart failure	
- Complications (eg. CVA)	
Laboratory:	
- Lipids - Cholesterol - Triglycerides - HDL - LDL	
- Plasma glucose	
- HbA1c	
- Haemoglobin	
- Uric acid	
- Microalbumin	
ECG - Infarct territory - Old infarct (Q waves) - Arrhythmia	
Echocardiogram - Ejection fraction - RWMA - Thrombus	
MIBI - Reversible/irreversible ischaemia	
Angiogram - Number of vessels - Site - % Stenosis	
Outcomes - Medical management - PCI - CABG - Mortality	