

Risk Factors Associated with Acute Coronary Syndromes in South African Asian Indian Patients [The AIR Study]

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Abstract

Aims: To examine the association between traditional risk factors and acute coronary syndrome [ACS] in the South Asian Indian population in KwaZulu Natal, South Africa.

Methods and Results: The study population comprised 4418 patients with a mean age of 54.6 ± 10.9 years, of whom 67% were males. The majority presented with STEMI [75%], 16% had NSTEMI, and 9% unstable angina. Visceral obesity [82%, mean waist circumference 101.43 ± 10.34 cm] was the most commonly observed risk factor, while 78% had hypercholesterolaemia [mean 5.97 ± 1.11 mmol/L] and 74% a family history of vascular disease. More males compared to females were smokers [$p < 0.0001$], while females were more likely to have visceral obesity, diabetes, hypertension, increased BMI, and low HDL cholesterol levels [$p < 0.0001$]. Young patients [≤ 45 years, $n = 968$] had a higher incidence of family history of vascular disease [83%, $p = 0.019$], smoking [79%, $p < 0.0001$], and hypertriglyceridaemia [62%, $p = 0.014$] compared to middle [46 – 65 years, $n = 2708$] or old age [> 65 years, $n = 742$] groups, whilst older patients were more likely to have diabetes [59%, $p = 0.001$], and hypertension [68%, $p < 0.0001$].

Conclusion: Asian Indians in South African have multiple risk factors for ACS, possibly contributing to the increased incidence of coronary heart disease at a young age. This study further confirms that a family history of vascular disease is strongly associated with the presence of ACS, and should be incorporated in future risk factor analyses.

Keywords: Acute coronary syndromes, Asian Indians, Vascular disease, Visceral obesity

Introduction

Coronary heart disease [CHD] is a global health problem that affects all ethnic groups and contributes substantially to premature death, disability and the escalating costs of health care [1]. Variations in risk factor profiles for CHD, the age of onset of the disease, and mortality ratios have, however, been observed between different populations. This is particularly noticeable in migrant South Asian Indians who are reported to have a consistently higher incidence of CHD, when compared with host country populations [2]. In addition, CHD in this population tends to present earlier in life, and mortality rates in young Asian Indians are markedly higher in comparison with other ethnic groups [3].

Several international studies to date have reported that lifestyle modification alone, can significantly reduce the risk of CHD [4-6]. One such report is that on the INTERHEART study, which showed that [9] common and easily measured risk factors have an association rate of more than 90% with the risk of acute myocardial infarction [AMI]. The African contribution to this study was explored in greater detail in the INTERHEART Africa Study [7], to which South Africa contributed approximately 80% of the participants. Whilst the relationship between various risk factors and AMI was investigated in three ethnic groups comprising Black Africans, Coloreds [mixed ancestry], and European/other African subjects, individuals of Indian ancestry living in South Africa were not examined in depth.

Although it is well recognized that the earlier age of onset of AMI in sub-continental Asian Indians is most likely related to the early development of risk factors in this group, there is a paucity of comparative data on migrant Asian Indians living elsewhere in the world. The AIR [Acute coronary syndromes in Indian patients admitted to R. K. Khan hospital] study was, therefore, initiated to examine the association between traditional risk factors and acute

coronary syndromes [ACS] in the South Asian Indian population resident in South Africa.

Methods

A total of 4700 patients with ACS, admitted to the coronary care unit at the R. K. Khan Hospital, Durban, South Africa over a 15 year period [May 1995 to June 2010] was studied. Of these, 282 patients were excluded either because of insufficient data or failure to satisfy the inclusion criteria, leaving a total of 4418 patients for analysis. All individuals were of Asian Indian origin. Acute coronary syndrome was defined according to the definitions outlined by the Joint International Society and Federation of Cardiology/ World Health Organization Task Force on Standardization of Clinical Nomenclature [8] and The Joint European Society of Cardiology/American College of Cardiology Committee [9]. This included patients with ST-elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], and unstable angina [UA], based on a characteristic history of chest pain / discomfort plus electrocardiographic changes consistent with ischaemia or infarction and diagnostic cardiac biomarkers [Troponin T or creatinine kinase muscle brain isoenzyme] in the case of myocardial infarction.

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Demographic data stored in an electronic database were obtained from all patients: these included age, gender, weight, height, waist circumference, and the presence of risk factors such as diabetes, hypertension, smoking status, and a family history of vascular disease. Height, weight and waist circumference were measured using standardized protocols by trained staff and all results were validated by the investigator. Current smokers were defined as those individuals who smoked any tobacco in the previous 12 months and former smokers as those who had not smoked for a period of at least a year. A family history of premature atherosclerosis was defined by a history of myocardial infarction in either parents, or in siblings or first degree relatives at the age of 55 years or younger for males and 65 years or younger for females, whilst a family history of diabetes, hypertension, and cerebrovascular disease was defined as these conditions occurring at any age.

Anthropometric measurements

Anthropometric measurements including body mass index [BMI] and waist circumference were used to define obesity. The BMI was calculated as weight [kilograms] divided by height² [meters] according to World Health Organisation guidelines [10]. A BMI ≥ 30 kg/m² was used as a cut-off to indicate obesity. Waist circumference, which is considered the most practical way to assess central obesity, was measured midway between the lowest rib and the iliac crest on standing subjects, using a soft tape. The central obesity threshold limits proposed by the International Diabetes Federation [IDF] [males ≥ 90 cm, females ≥ 80 cm] were used to define visceral obesity [11].

Biochemical analyses

Blood samples for routine biochemistry were collected from all subjects on hospital admission. Analyses were carried out using conventional methods. In addition, blood samples were also collected within 48 hours of admission after an overnight fast for lipid analyses. Total cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride levels were determined using standard enzymatic methods on a Beckman Synchron CX7 auto analyzer. Low-density lipoprotein [LDL] cholesterol levels were calculated utilizing the formula of Friedewald [12]. The cut-points used to stratify patients were based on the updated South African Guidelines [13] levels were considered abnormal if total cholesterol was > 4.5 mmol/L, LDL cholesterol > 2.5 mmol/L, triglycerides ≥ 1.7 mmol/L, and HDL cholesterol < 1.03 mmol/L in males and < 1.29 mmol/L in females].

Statistics

Statistical analyses were performed by using Microsoft Excel and R 2.10.0 software packages. Frequencies were obtained by using descriptive statistics and odds ratios with 95% confidence intervals determined by standard methodology. Statistically significant differences between different groups were determined by using Yates' corrected chi-square (χ^2) analysis. Differences were considered statistically significant when $p < 0.05$.

Ethical approval

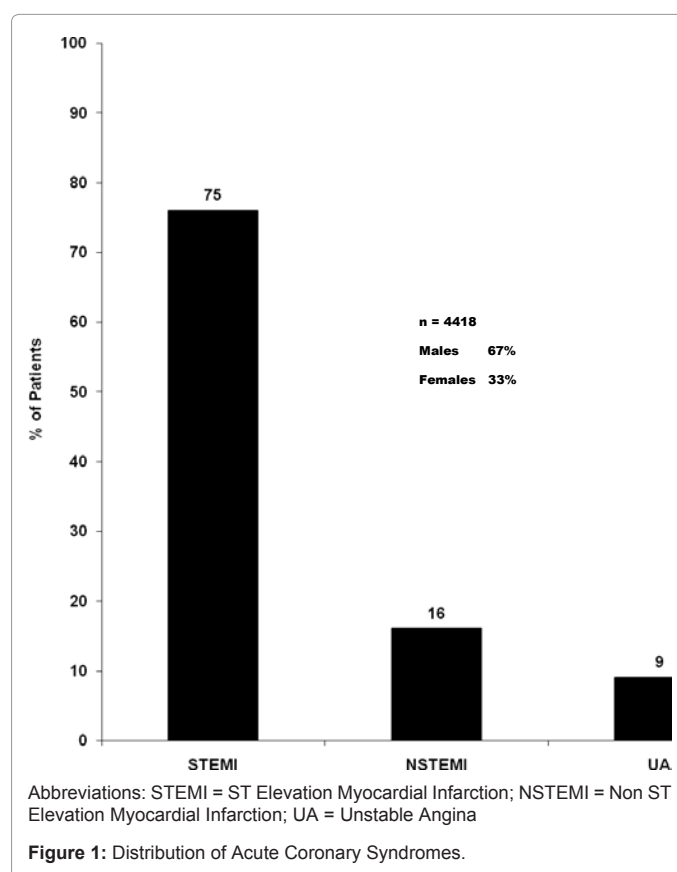
The investigations conform to the principles outlined in the Declaration of Helsinki. Informed consent for study related procedures and laboratory analyses were obtained from all individuals in the study and approval was granted by the Ethics Committee of the Faculty of Health Sciences, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal.

Results

The study population comprised 4418 patients with a mean age of 54.6 ± 10.9 years, of whom 67% were males. All patients were of Asian Indian origin. With respect to the categorization of ACS, the majority of patients presented with STEMI [75%], 16% had NSTEMI, while only 9% were diagnosed with unstable angina (Figure 1). The group with unstable angina should be interpreted with caution. It may not accurately reflect the overall prevalence of this condition as most patients with unstable angina are admitted to the general medical wards and were therefore not included in the analysis. Data were missing on BMI for 8.3% [n = 365] of the participants; total cholesterol, 1.9% [n = 85]; triglycerides, 2.9% [n = 130]; HDL cholesterol, 13.3% [n = 589]; and LDL cholesterol, 15.9% [n = 706].

Cardiovascular risk factor profiles and lipid data are shown in (Table 1). Visceral obesity [82%, mean waist circumference 101.43 ± 10.34 cm] was the most commonly observed risk factor in the study population. In contrast, only 16% of patients had obesity based on BMI measurements. Seventy eight percent of the patients presenting with ACS had hypercholesterolaemia [mean 5.97 ± 1.11 mmol/L], while 82% had elevated LDL cholesterol levels [mean 3.87 ± 0.96 mmol/L]. Significant gender differences in risk factors were found in individuals presenting with ACS, with a greater number of men having a history of smoking [current / former] compared to their female counterparts [$p < 0.0001$]. In contrast, women were significantly more likely to have visceral obesity [95%, mean 101.03 ± 11.65 cm versus 75%, mean 101.73 ± 9.28 cm for men], diabetes mellitus, hypertension, increased BMI, and low HDL cholesterol levels [$p < 0.0001$].

Fifty four percent of patients had a family history of premature myocardial infarction with equal gender prevalence (Table 2). A



significantly greater number of females had a family history of diabetes and hypertension when compared to males [$p < 0.001$].

The association between risk factors for ACS and age was also examined (Table 3). Patients were divided into 3 categories: < 45 years [young age], 46 - 65 years [middle-age], and > 65 years [old age]. The majority of patients with ACS were middle-aged [61.3%], while 16.8% were older than 65 years of age. A total of 21.9% of the study population fell into the young age group with a mean age of 39.9 ± 4.5 years. These younger patients had a higher incidence of family history of vascular disease [83%, $p = 0.019$], smoking [79%, $p = <0.0001$], and hypertriglyceridaemia [62%, mean 3.35 ± 2.01 mmol/L; $p = 0.014$] compared to the middle or old age groups, whilst older patients were more likely to have diabetes [59%, $p = 0.001$], and hypertension [68%, $p = <0.0001$]. No significant difference was observed for visceral obesity between the three age groups [≤ 45 years, mean waist circumference 101.24 ± 10.33 cm; 46 - 65 years, 102.09 ± 10.50 cm; and > 65 years, 99.97 ± 9.80 cm]. In addition, no significant difference was found for the risk factors studied and the different types of ACS [data not shown].

Figure 2 shows the proportions of patients who had varying combinations of 2 or more of common risk factors, namely visceral obesity, family history of vascular disease, hypertension, diabetes and smoking. Since visceral obesity and a family history of vascular disease were the 2 most predictive variables for ACS, most combinations included these risk factors. Sixty-five percent of patients had both visceral obesity and a family history of vascular disease, 49% presented with visceral obesity and diabetes, while 45% presented as smokers with either visceral obesity or a family history of vascular disease. Only 9% of patients with ACS had all 5 risk factors.

Discussion

In this study on South African Asian Indians with ACS, the majority of patients presented at a younger age [mean age of 54.6 ± 10.9 years], a finding which is consistent with previously published reports on South Asian Indians [14,15]. There was a clear preponderance of male subjects. In addition, most patients presented with STEMI [75%]. These findings are in agreement with the CREATE registry, which analyzed

RISK FACTOR	All Patients [n = 4418] % Total	Males [n = 2963] % Total	Females [n = 1455] % Total	OR [95% CI] [Males vs. Females]	p value
Visceral Obesity	82	75	95	0.15 [0.10 – 0.22]	<0.0001
FH of Vascular Disease	74	74	75	0.97 [0.84 – 1.12]	0.64
Current / Former Smoker	60	80	20	16.05 [13.72 – 18.78]	<0.0001
Diabetes	46	37	65	0.31 [0.27 – 0.35]	<0.0001
Hypertension	45	33	68	0.24 [0.21 – 0.27]	<0.0001
BMI ≥ 30 kg/m ² *	16	11	24	0.40 [0.34 – 0.47]	<0.0001
ABNORMAL LIPID LEVELS	% Total [mean \pm SD]	% Total [mean \pm SD]	% Total [mean \pm SD]		
Total Cholesterol ≥ 4.5 mmol/L*	78 [5.97 \pm 1.11]	78 [5.91 \pm 1.09]	79 [6.09 \pm 1.15]	0.92 [0.80 – 1.10]	0.44
Triglycerides ≥ 1.7 mmol/L*	51 [3.07 \pm 1.81]	50 [3.08 \pm 1.74]	51 [3.04 \pm 1.94]	0.97 [0.85 – 1.10]	0.65
HDL Cholesterol Males <1.03 Females <1.29 mmol/L*	68 [0.86 \pm 0.17]	63 [0.81 \pm 0.14]	79 [0.94 \pm 0.19]	0.47 [0.40 – 0.55]	<0.0001
LDL Cholesterol >2.5 mmol/L*	82 [3.87 \pm 0.96]	81 [3.86 \pm 0.96]	82 [3.89 \pm 0.96]	1.03 [0.86 – 1.23]	0.81

Abbreviations: FH = Family History; BMI = Body Mass Index; HDL = High-Density Lipoprotein; LDL = Low Density Lipoprotein; * = Data missing for some patients

Table 1: Risk Factor Profiles in Patients with ACS.

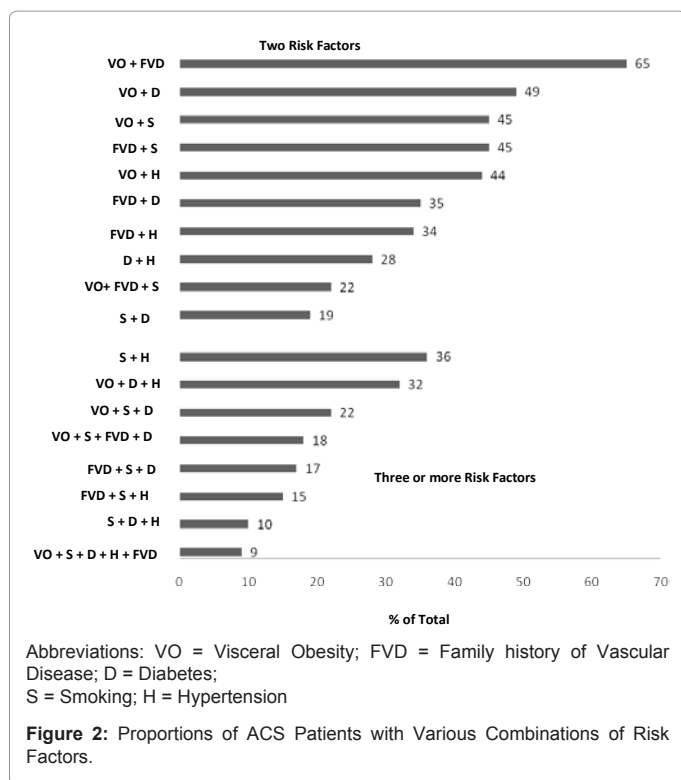
Family History	All Patients [n = 4418] % Total	Males [n = 2963] % Total	Females [n = 1455] % Total	OR [95% CI] Males vs. Females Coronary heart	p value
disease	54	54	0.99	0.96 [0.88 – 1.13]	54
Diabetes	42	39	48	0.68 [0.60 – 0.77]	<0.001
Hypertension	38	36	42	0.77 [0.68 – 0.88]	<0.001
Cerebrovascular Disease	18	18	17	1.09 [0.92 – 1.29]	0.31

Table 2: Prevalence of Family History of Vascular Disease in Patients with ACS.

RISK FACTOR	≤ 45 years n = 968 [21.9%] % Total	46 – 65 years n = 2708 [61.3%] % Total	> 65 years n = 742 [16.8%] % Total	p value
Visceral Obesity	78	82	87	0.25
FH of Vascular Disease	83	74	61	0.019
Current / Former Smoker	79	60	35	<0.0001
Diabetes	30	48	59	0.001
Hypertension	22	46	68	<0.0001
BMI ≥ 30 kg/m ² *	17	16	14	0.71
ABNORMAL LIPID LEVELS	% Total [mean \pm SD]	% Total [mean \pm SD]	% Total [mean \pm SD]	
Total Cholesterol ≥ 4.5 mmol/L*	82 [6.13 \pm 1.24]	79 [5.96 \pm 1.10]	72 [5.75 \pm 0.90]	0.28
Triglycerides ≥ 1.7 mmol/L*	62 [3.35 \pm 2.01]	50 [3.05 \pm 1.83]	38 [2.54 \pm 0.92]	0.014
HDL Cholesterol Males <1.03 Females <1.29 mmol/L*	70 [0.82 \pm 0.15]	67 [0.86 \pm 0.18]	71 [0.88 \pm 0.19]	0.60
LDL Cholesterol >2.5 mmol/L*	82 [3.99 \pm 1.15]	82 [3.85 \pm 0.91]	78 [3.74 \pm 0.85]	0.63

Abbreviations: FH = Family History; BMI = Body Mass Index; HDL = High-Density Lipoprotein; LDL = Low Density Lipoprotein; * = Data missing for some patients

Table 3: Risk factors for Acute Coronary Syndromes in Different Age Groups.



data on a large number of Indian patients with ACS and showed that about 60% of patients presented with STEMI [14]. In contrast, reports from developed countries indicate that fewer than 40% of patients with ACS had STEMI [16], suggesting that Asian Indians are more likely to have extensive myocardial infarcts and worse prognoses than other populations.

The most commonly observed risk factors in the current study population included visceral obesity, a family history of vascular disease, and smoking, while diabetes, hypertension and increased BMI occurred less frequently. The majority of patients presented with dyslipidaemia as was reflected by hypercholesterolaemia [78%], elevated LDL cholesterol [82%], low HDL cholesterol [68%], and hypertriglyceridaemia [51%]. Although the findings presented here are consistent with those of the INTERHEART study population [4], a greater proportion of patients in this study had diabetes and hypertension when compared with the INTERHEART study [46% and 45% vs. 18.5% and 39%, respectively]. In comparison to the Indian subjects in the CREATE registry, 14 Asian Indians residing in South Africa also had a higher prevalence of concurrent diabetes and hypertension [46% and 45% vs. 30.4% and 37.7%, respectively].

Another interesting finding in this study was the high incidence of a family history of vascular disease. While it is possible that the effect of a family history of vascular disease could be mediated through known risk factors, it is important, however, to consider that a significant gene-environmental interaction may exist, particularly since diabetes, obesity and dyslipidaemia have strong heritable traits. Fifty four percent of our patients had a family history of premature CHD, while 42% and 38% had a family history of diabetes and hypertension, respectively. A significantly greater proportion of females had a family history of diabetes and hypertension compared to males. These findings concur with a recent publication of the INTERHEART study, which showed that having one or both parents with AMI, is a strong predictor of

future AMI in their offspring [17]. Furthermore, it was observed that the association with parental history persists throughout different regions of the world as well as across socioeconomic, age, and gender groups. The present study confirms these findings and suggests that a family history of vascular disease should be incorporated into risk factor analyses to assist clinicians in identifying high-risk individuals for preventative action, early diagnosis and treatment.

The prevalence of several of the risk factors analysed in this study differed substantially when assessed in terms of gender. Significantly more females than males were found to have visceral obesity, diabetes, hypertension, and low HDL cholesterol levels, while males had a stronger history of smoking. The metabolic syndrome has been shown previously to be a common finding in South African Indians with AMI, with proportionately more females than males having the syndrome [18]. This may be reflected by the increased prevalence in this study of risk factors, which are common components of the metabolic syndrome.

Earlier studies on migrant Indian populations did not focus on the importance of smoking. This is an important modifiable risk factor for CHD in Western countries, accounting for about 36% of the population adjusted ratio of AMI, worldwide [19]. Our data reinforce the importance of smoking as a risk.

The association between risk factors for ACS and age was also examined. Of note, is that 21.9% of the study group had a mean age of 39.9 ± 4.5 years. These younger patients had a significantly higher incidence of a family history of vascular disease, hypertriglyceridaemia, and smoking compared to middle-age and older patients, which is in agreement with previous reports on premature AMI in South Asian Indians [20,21].

Patients in this study also presented with multiple risk factors, which possibly contributed to the higher incidence of CHD. When combinations of risk factors were assessed 65% of patients were found to have both visceral obesity and a family history of vascular disease, while 36% presented with visceral obesity, family history of vascular disease and were smokers. Nine percent of patients had a combination of 5 risk factors.

Several limitations of this study should be addressed. Firstly, not all the risk factors for AMI, which were reported in the INTERHEART study, were assessed. These factors included lack of physical activity, dietary factors, psychosocial habits, psychiatric illness such as depression, and alcohol consumption [4]. However, in a more recent analysis of the INTERHEART data, the addition of these risk factors was not shown to improve score discrimination in an external cohort [22]. The current study did, however, include all the risk factors used to calculate the INTERHEART modifiable risk score, which was subsequently proposed for the estimation of CHD risk in multiple regions of the world. Secondly this study was conducted in a single center. This shortcoming was minimized by using standardized methods for data collection, while the large study population allowed for greater statistical power. Thirdly, the lack of a matched control group and the fact that our data were drawn from hospital based patients already diagnosed with ACS could possibly have biased results. Nevertheless, our results are qualitatively similar for most risk factors in all regions of the world.

In conclusion, our results have clearly demonstrated that Asian Indians residing in South Africa have multiple risk factors for ACS. This finding may contribute to the explanation as to why this particular population presents with CHD at an earlier age. In addition to the

conventional risk factors for CHD, a family history of vascular disease was strongly associated with the presence of ACS, suggesting that it may have a role in future risk factor analyses.

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