RISK FACTORS FOR CORONARY ARTERY DISEASE IN THE ELDERLY

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DM (CARDIOLOGY) THESIS

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A THESIS SUBMITTED BY

Dr. Vrandha Garikapati

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM (CARDIOLOGY)

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DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Garikapati Vrandha, hereby certify that I had personally carried out the work in the thesis titled, "Risk Factors for Coronary Artery Disease in the Elderly"

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Dr. Garikapati Vrandha

Date: 28/08/2023

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The thesis entitled "Risk Factors for Coronary Artery Disease in the Elderly" was carried out under my direct supervision. No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

* Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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APPROVAL OF THE THESIS

The thesis entitled

"Risk Factors for Coronary Artery Disease in the Elderly"

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(Name & Signature of the Guide)

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Dr. Garikapati Vrandha

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ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACS	Acute Coronary Syndrome
ASCVD	Atherosclerotic Cardiovascular disease
AWMI	Anterior wall myocardial infarction
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CAG	Coronary Angiogram
CKD	Chronic Kidney Disease
CSA	Chronic Stable Angina
CVA	Cerebrovascular Accident
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
DLP	Dyslipidemia
DM	Diabetes Mellitus
DVD	Double Vessel Disease
ECG	Electrocardiogram
ECHO	Echocardiogram
EF	Ejection Fraction
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GDMT	Guideline Directed Medical Therapy
HDL	High density lipoprotein cholesterol
HF	Heart failure
HR	Hazard Ratio
HTN	Hypertension
IHD	Ischemic Heart Disease
IQR	Interquartile range
IWMI	Inferior wall myocardial infarction

LAD	Left anterior descending artery
LDL	Low density lipoprotein cholesterol
LM	Left Main
Lp (a)	Lipoprotein (a)
LV	Left ventricle
LVH	Left ventricular hypertrophy
MACCE	Major adverse cardiac and cerebrovascular events
NSTEACS	Non-ST Elevation Acute Coronary Syndrome
NSTEMI	Non-ST Elevation Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PVOD	Peripheral Vascular Occlusive Disease
RBS	Random Blood Sugar
SBP	Systolic Blood Pressure
SCTIMST	Sree Chitra Tirunal Institute of Medical Sciences and Technology
SD	Standard Deviation
SEC	Socioeconomic Class
SIHD	Stable Ischemic Heart Disease
STEMI	ST Elevation Myocardial Infarction
SVD	Single Vessel Disease
TVD	Triple Vessel Disease
UA or USA	Unstable Angina
WHO	World Heart Organization

RISK FACTORS FOR CORONARY ARTERY DISEASE IN THE ELDERLY

SYNOPSIS

BY

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Synopsis

Background: Coronary Artery disease (CAD) is the third leading cause of mortality worldwide and majority of deaths occur in low and middle-income countries with population aging being the most important contributing factor. Most of the trials in CAD did not include elderly and it is uncertain whether these results can be generalized to them.

Objectives: This study aimed to identify the risk factors in patients who were diagnosed with angiographically significant CAD after 65 years of age (Elderly) with a subset analysis of patients more than 75 years and to assess the Major Acute Cardiovascular and Cerebrovascular Events (MACCE) on follow up.

Methods: This was a retrospective observational study conducted at a a tertiary care hospital in South India in which patients who underwent Coronary Angiogram (CAG) for suspected CAD or diagnosed with CAD at or after 65 years of age between 2010 and 2018 were analysed for their risk factor profile and compared with those patients who had insignificant CAD. Those with angiographically significant CAD were followed up for MACCE and survival data

Significant Findings: 3670 elderly patients who underwent CAG were screened of which 1511 patients satisfying eligibility criteria were analyzed for risk factor profile and clinical characteristics. The mean age of total population was 69.38 (+/- 4.03) years with a male preponderance (69%). The prevalence of traditional risk factors was found to be high and comparable between the subgroups except chronic kidney disease (CKD) which was higher in the older subgroup of more than 75 years. Angiographically significant CAD was present in 1124 patients (74.4%) and was significantly higher in the older subgroup. Male gender, dyslipidemia and current tobacco use were found to be contributing to angiographically significant CAD in elderly by multiple logistic regression analysis but none of the studied risk factors were found to contribute to CAD in the 75 year and above age group. Female patients had higher incidence of atypical presentation, significantly less revascularizations and higher MACCE. Fourteen percent of patients with significant

CAD (912 patients) developed MACCE over a median 3.5-year hospital follow up. Survival analysis of 1027 Significant CAD showed a one, three, five-year mortality rate of 4.3%, 6.9% and 10.8% respectively. Multivariate proportional hazard model cox regression analysis showed that left ventricular dysfunction and triple vessel disease were associated with worse survival. MACCE and five -year survival were significantly better among those who underwent revascularization compared to medical management. In a sub-analysis of patients having significant left main (more than 50% lesion) or triple vessel disease, the five-year mortality rate was significantly lower among those who underwent revascularization compared to medical management while CABG and PCI were comparable.

Conclusion: Male gender, dyslipidaemia, current tobacco use were found to predict angiographically significant CAD in elderly, but none of the traditional risk factors were significantly associated in the older subgroup of more than 75 years. Mortality was significantly lower among elderly who underwent revascularization compared to medical management in this study.

Implications: Traditional risk factors for CAD don't seem to predict the presence of CAD to the same degree as in younger individuals but they continue to play a role in elderly and need to be addressed. Even though the results in this study support revascularization in elderly patients, further dedicated research is needed to decide on the optimal mode of management.

Introduction

Coronary Artery Disease (CAD) affects around 126 million individuals (1,655 per 100,000) globally, which is approximately 1.72% of the world population and is expected to exceed 1,845 per 100,000 by the year 2030.[1] In a community-based cross-sectional study by Krishnan et al showed that definite CAD in Kerala increased nearly three times since 1993 without any difference in urban and rural population.[2]

CAD is the third leading cause of mortality worldwide and accounted for more than 9 million deaths in 2016 according to the World Health Organization (WHO) estimates.[3] More than 80% of deaths from cardiovascular disease are estimated to occur in low-income and middle-income countries like India,[4] with population aging being the most important factor contributing to this trend.

Elderly of more than 65 years of age account for more than half of all cardiovascular hospitalizations and procedures in the United States, as well as 80% of all cardiovascular deaths.[5] Despite this, only a few dedicated studies have evaluated CAD in them.

In an analysis of recent late breaking clinical trials in Cardiology, 8 out of 22 trials did not include older adults of age 60 to 80 years. In trials in which the percentage of older adults were available, adults age more than 75 years constituted 9% to 55% of the enrolled subjects and in the remaining, the mean age was 54 to 66 years.[6] Generalizability of these results to all age groups can be questioned and all recommendations have uniformly emphasized the need for more research in this population as their clinical profile, management and outcomes are different compared to younger population.

The question of whether risk factors contributing to CAD different in elderly was looked into in few elderly studies or in sub analyses of these major studies which had varied settings and age range of study participants and they show conflicting results. Hence, the impact of traditional risk factors on the development of coronary

atherosclerosis in the elderly especially in developing countries like ours remains uncertain.

The current study aims to identify the risk factor profile of elderly patients diagnosed with significant CAD by coronary angiogram after 65 years of age and compare it with the population without significant CAD in a tertiary care hospital in South India. Furthermore, a subset analysis of patients more than 75 years would help contribute to the data on specific risk factors of CAD in this population so that targeted prevention and management strategies can be applied to them.

Review of Literature

Coronary Artery Disease (CAD) Epidemiology:

CAD is a major cause of morbidity and preventable death worldwide. The Global Burden of Disease (GBD) Study which included annual figures from 1990 to 2017 for CAD in all countries and regions for incidence, prevalence of CAD showed that it affects around 126 million individuals (1,655 per 100,000) globally, which is approximately 1.72% of the world population and is expected to exceed 1,845 per 100,000 by the year 2030. Men were more commonly affected than women, and incidence typically started in the fourth decade and increased with age.[1]

The recent GBD Study Update 2019, also reiterated that cases of total cardiovascular disease are likely to increase substantially as a result of population growth and aging, especially in Northern Africa and Western Asia, Central and Southern Asia, Latin America and the Caribbean, and Eastern and Southeastern Asia where the share of older persons is projected to double between 2019 and 2050.[7] In India also, studies have reported increasing CAD prevalence over the last 60 years, from 1% to 9%-10% in urban populations and less than 1% to 4-6% in rural population.[8] Similar results were reported by large population surveys done over the past two decades mainly driven by the rise in coronary risk factors as depicted in Table 1.

In Kerala, the prevalence of CAD was estimated to be 3–4 % in rural areas and 8–10 % in urban areas according to a population-based cross sectional survey in 2003.[15] In a community-based cross-sectional study of 5167 adults by Krishnan et al in Kerala in 2011, the overall age-adjusted prevalence of definite CAD was 3.5 % and prevalence of any CAD was 12.5 % which showed that definite CAD in Kerala increased nearly three times since 1993 without any difference in urban and rural population.[2]

Table 1: Prevalence of CAD and risk factors from various large Indian studies

Study	Year	N	Setting	Prevalence (%)				
				CAD	HTN	DM	High T.Ch	Smoking
Raman Kutty et al[9]	1993	1253	R	7	18.8	4	-	21.9
Chadha et al[10]	1997	14886	U/R	U 9.7/R 2.7	10.6	1.5	43.7	18.1
Singh et al[11]	1997	3575	U/R	U 9/R 3.3	23.4	7.5	22	19.7
Gupta et al[12]	2002	1123	U	8.2	36.9	12.2	39.1	23.9
Thankappan et al[13]	2010	7449	U/R	-	28.8	14.8	54.1	42
CSI Kerala CRP Study[14]	2011	5193	U/R	15.7	39	21	23	31
Krishnan et al[2]	2016	5167	U	12.5 (Any CAD)	28	15	52	33

*T.Ch – Total Cholesterol

Studies have also highlighted the changing epidemiology in recent decades. One such study done specifically done to show increasing prevalence in National Capital Region (NCR) of Delhi, between 1991-1994 (survey 1) and 2010-2012 (survey 2) among those aged 35-64, the age and sex standardized prevalence in urban Delhi increased from 10.3% to 14.1% between the two surveys and unexpectedly, the highest increase in the prevalence of CHD was reported among urban women (10.1% to 16.6%).[16] CSI Kerala CRP Study a large population survey of three geographical regions of Kerala showed that, contrary to previous Indian data there was a high prevalence of CAD among young individuals (2%) as compared to western data (1.2%), and, there was no difference between urban (15.1%) and rural (16.2%) prevalence.

Despite population aging being the most important factor contributing to this trend, most of these studies had a mean age of 50 to 60 years and didn't include elderly population except CSI Kerala CRP Study with age range of 20-79 years.

Morbidity and Mortality associated with CAD:

Cardiovascular diseases (CVD) contribute to approximately one-third of deaths worldwide.[17] Among them, CAD is the most prevalent cause (the third leading cause of mortality overall) and accounted for more than 9 million deaths in 2016 according to the WHO estimates.[3]

The GBD Study highlighted that despite the total number of global deaths due to CVD increasing 50% in 2017 compared to 1990, the age standardized death rate (ASDR) has actually decreased by 30% in that time frame. In regions with high economic income or high socio-demographic index, the decline in CVD ASDR is greater by 52.8% from 1990 to 2017 but only decreased by 13.9% in the Lower Middle Income during that timeframe.[18]

In 2019, the majority of cardiovascular disease deaths globally were ischemic heart disease and stroke, and the highest number occurred in China, followed by India, Russia, the U.S. and Indonesia. In terms of Disability adjusted life years (DALY) too, IHD is the leading cause globally, moving from the fourth position in 1990 to the first position in 2017. The large declines in the age-standardized rates of death, DALYs, Years of life lost (YLL) and Years of healthy life lost due to disability (YLD) from 1990 to 2019 together with small incremental reductions in age-standardized rates for prevalent cases, suggest that population growth and aging are big contributors to the increase in total cardiovascular disease.[7]

More than 80% of deaths from cardiovascular disease are estimated to occur in low-income and middle-income countries like India,[4] despite the mean INTERHEART Risk Score being highest in high-income countries and lowest in low-income countries but the reasons are unknown. Better control of risk factors and more frequent use of proven pharmacologic therapies and revascularization could be a factor.

In India in 2016, CVDs contributed to 28.1% of total deaths and 14.1% of total (DALYs) compared with 15.2% and 6.9%, respectively in 1990.[19] The results of GBD study state age-standardized CVD death rate of 272 per 100000 population in India which is much higher than that of global average of 235. Within India, the rates of CVD vary markedly with highest in states of Kerala, Punjab and Tamil Nadu,

particular causes of concern in being early age of onset, rapid progression and high mortality rate.[20]

Overall, these results demonstrate that global effort for controlling the CVD burden was quite successful. But CAD continues to be an important threat to sustainable development in the 21st century. The forecast of an increased disability burden due to CAD especially in developing countries like India, there is a need to promote strategies such as putting more emphasis on primary care, primary prevention and in the aging population.

Risk Factors for CAD:

It was only after the premature death of the US President Franklin D. Roosevelt in 1945 from hypertensive heart disease and stroke that research into the causes of CVD began, and new therapies were found. Major epidemiological studies like Framingham Study (FHS), and INTERHEART Study (included Indian participants) with the largest cohorts of patients have identified specific risk factors for CAD. As a result, management of these risk factors combined with advances in medical technology, led to a significant decrease in CAD mortality rates.

The concept of “risk factors” in CAD was first coined by the Framingham heart study which in 1957. This study recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts in 1948 who underwent extensive physical examination and lifestyle interviews that were analyzed for common patterns related to CVD development. They continued to review for the study every 2 years for a detailed medical history, physical examination, and laboratory tests, and in 1971, the study enrolled a second generation i.e.5,124 of the original participants' adult children, and their spouses to participate in similar examinations. The FHS is now on its third generation of participants.[22]

This study was the foundation of our current understanding of CVDs. It identified the major risk factors: high blood pressure, high blood cholesterol,

smoking, obesity, diabetes, and physical inactivity as well as other valuable information on the effects of related factors such as blood triglyceride and high-density lipoprotein (HDL) cholesterol levels, age, gender, and psychosocial issues. No single risk factor could be identified to be responsible, rather, multiple interrelated factors seem responsible. Although the Framingham cohort is Caucasian, other studies have shown that the major risk factors identified in this group apply universally to other racial and ethnic groups.

The INTERHEART study on the other hand was a large cross-sectional hospital-based study from urban areas of around 30,000 participants from 52 countries representing every inhabited continent. They were studied during the acute phase of myocardial infarction. A set of risk factors which contributed to > 90% of incident myocardial infarction in South Asian countries were identified namely, Age, Type 2 Diabetes Mellitus, Hypertension, Dyslipidemia, Smoking or tobacco use, Obesity, Physical inactivity, Psychosocial factors, Dietary patterns, Family History. The effect of the risk factors was particularly striking in young men (population attributable risk PAR about 93%) and women (about 96%) which indicated that premature myocardial infarction was preventable. It was found that more than 70% of at-risk individuals have multiple risk factors for CAD, and only 2%-7% of the general population have no risk factors.[23]

This study also highlighted the peculiarities in South Asians. Protective lifestyle factors such as leisure time physical activity and regular intake of fruits and vegetables were markedly lower while harmful risk factors such as elevated Apo-B/ApoA-1 ratio were higher. They have significantly higher population attributable risk associated with waist-hip ratio and alcohol consumption was not protective.

Since then, various cohort studies like FINRISK study, The ULSAM, PIVUS, POEM, EpiHealth, and SCAPIS studies, The PREDICT Cardiovascular Disease Cohort study have continued to study the impact of different risk factors on cardiovascular disease.[24-26] These studies classify CAD risk factors into two broad categories:

1. Non-modifiable risk factors - age, gender (Men are at increased risk compared to women), ethnicity (Blacks, Hispanics, Latinos, and Southeast Asians, are ethnic groups with an increased risk of CAD morbidity and mortality), and family

history of CAD (a father or brother diagnosed with CAD before 55 years of age, and a mother or sister diagnosed before 65 years of age are considered risk factors).

2. Modifiable risk factors - hypertension, hyperlipidemia, diabetes, obesity, smoking, poor diet, sedentary lifestyle, and stress

Among all potentially modifiable risk factors, age-standardized IHD deaths worldwide were primarily attributable to dietary risks, high systolic blood pressure, high LDL cholesterol, high fasting plasma glucose, tobacco use, and high body mass index in 2017.[1]

The strongest predictors of 10-year risk of ASCVD event are identified as age, sex, race, total cholesterol, HDL-C, blood pressure, blood-pressure treatment status, diabetes, and current smoking status and these have been included in the score recommended by AHA/ACC Guidelines. For patients 20–79 years of age who do not have existing clinical ASCVD, the guidelines recommend assessing clinical risk factors every 4–6 years.

In addition to these traditional cardiovascular risk factors, novel risk factors whose mechanism was uncertain, but thought to be due to a chronic inflammatory state have also been studied. These include:

- Non-alcoholic fatty liver disease (NAFLD):] A recent study revealed that patients with NAFLD had greater than double the risk of CVD and those with liver fibrosis had a four-fold increase.[29]
- Chronic kidney disease (CKD): CKD has been reported as an independent risk factor for CAD. Silent myocardial infarctions occur more commonly, likely due to higher incidence of diabetic and uremic neuropathy in these patients. [30]
- Systemic lupus erythematosus (SLE): There is a higher prevalence of atherosclerotic CVD in these patients. [31]
- Rheumatoid arthritis (RA): These patients have a 1.5-to-2.0-fold increased risk of CAD [32]

CKD, with a GFR of 15-59 and RA are included as risk-enhancing factors in the AHA Guideline for the Primary Prevention of Cardiovascular Disease.

- Inflammatory bowel disease (IBD): IBD is associated with a higher risk of CAD according to a 2017 meta-analysis but there was large heterogeneity of the studies included.[33]
- Human immunodeficiency virus (HIV): A 2018 expert analysis from the ACC suggested that HIV leads to a 1.5 to 2-fold increased risk of CAD.[34]
- Thyroid disease: The effect of thyroid hormone on dyslipidemia, cardiac function, atherosclerosis, vascular compliance, and cardiac arrhythmias is an area still under study.[35]
- Vitamin D: Vitamin D deficiency has been increasingly studied and debated to have increased risk of CAD. [36-38] Further studies, however, have not confirmed a beneficial effect on Vitamin D supplementation.
- Socioeconomic status is a significant risk factor for cardiovascular disease determined by financial strain, lack of affordable and nutritious food, exposure to domestic violence, and inadequate housing which has not been adequately studied as a contributor.

Women and CAD: Women were found to have non-obstructive CAD in 57% of cases, in contrast to men who more commonly had obstructive CAD. [39] Coronary microvascular dysfunction, altered endothelial tone, structural changes, and altered response to vasodilator stimuli seem to be the reasons. Estrogen is thought to have a protective role in coronary vasoreactivity and promote plaque stabilization via an anti-inflammatory effect on atherosclerosis in younger women.

Indians and CAD Risk factors:

Many of the traditional risk factors have different implications in the Indian population and the same has been shown in studies.

Dyslipidemia: Indians have a unique pattern of atherogenic dyslipidaemia with low high-density lipoproteins (HDL), high triglycerides and high small dense low-density lipoprotein (LDL) particles. An Indian Council of Medical Research (ICMR) study in 2014 brought out that more than three-fourth (79%) of the general population had abnormalities in at least one of the lipid parameters, and nearly 25% of Indians and other South Asians have raised levels of Lp (a) (50 mg/dl), with no urban rural

variation. In Kerala, the culture and practice of using coconut oil in cooking has predisposed them to the highest rates of CAD in India. Reusing oil for cooking in Indian culture is common, and it increases trans fatty acids.

It has also been shown that the benefits of reducing serum cholesterol for CHD risk are age-related: a 10% reduction in serum cholesterol produces a drop in CHD risk of 50% at the age of 40, 40% at age 50, 30% at age 60, 20% at age 70. [42]

Diabetes Mellitus: India is the diabetic capital of the world with a prevalence of 8.8% in the age group of 20 and 70 years.[43] Average Indian diets contain more amounts of carbohydrates, high fat dairy, butter, ghee and cheese in their everyday meals and Indians consume less amounts of fresh fruits and vegetables. Studies from as early as the late 1980's have documented greater insulin resistance (even during adolescence), higher insulin levels and higher prevalence of diabetes among Indians.

Malnutrition: The high prevalence of undernutrition and low birth weights on one side and rapid increase in obesity with associated morbidities on the other side is unique to India.

Every second individual is physically inactive, and less than 10% of the studied population was involved in doing regular physical activity and abdominal obesity is also more prevalent than generalized obesity.[45]

Socioeconomic status: Poor living conditions along with low education levels were also associated with higher CAD mortality. Individuals from lower socioeconomic backgrounds have more Tobacco use and low fruit and vegetable intake and frequently do not receive optimal therapy, leading to poorer outcomes.

The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB 17) study[47] is the largest survey on diabetes and other metabolic NCDs undertaken in India, and covers all 28 states, two of the union territories, and the National Capital Territory of Delhi. A total of 113 043 individuals (79 506 from rural areas and 33 537 from urban areas) participated between Oct 18, 2008 and Dec 17, 2020 and had a mean age was 43·0 years, 46·5% male. The overall weighted prevalence of diabetes was 11·4% , prediabetes 15·3% , hypertension 35·5% , generalized obesity 28·6%, abdominal obesity 39·5%, and dyslipidemia 81·2%.All metabolic NCDs except prediabetes were more frequent in urban than rural areas.

The Asian Indian phenotype, with low adiponectin concentrations, increased visceral fat, increased waist circumference, and increased insulin resistance, low HDL cholesterol and high triglycerides were uniformly prevalent across India in our study. Various other studies have also shown similar trends in the Indian population.[48-53]

The recent study published in Lancet on the CVD epidemic in India [54] shed light on various potential factors leading to CAD epidemiology among which risk factor control was highlighted. It was commented by the authors that treatment and control levels of DM and HTN in India are abysmal. Less than half of those diagnosed are being treated, and only a mere one-fifth have lab tests under control. It was found that increased inherent biological risk (lipid metabolism, glucose metabolism, inflammatory states, genetic predispositions and epigenetic) and six major transitions can be considered largely responsible for the population-level changes in India -epidemiological, demographic, nutritional, environmental, social-cultural and economic. Alternate explanations for these ecological differences have been sought and multiple hypotheses were proposed including Prenatal factors and postnatal factors.

Among the Indian studies to delineate risk factors among diagnosed CAD patients, the latest is the NORIN-STEMI (North India ST-Segment Elevation Myocardial Infarction Registry) [55]It prospectively included 3635 patients hospitalized with STEMI in 2019 to 2020, of whom 582 (16%) were female patients and the median age 55 years. Female patients were older (median age 60 years vs 53 years) and more likely to have a history of diabetes, hypertension, obesity, present with lipid profiles diagnostic of dyslipidemia and illiteracy compared with male patients, less likely to use tobacco, drink alcohol, or be physically active. A history of hypertension was present in 29%, diabetes in 24%, and obesity in 11%. A total of 53% used tobacco products.

Krishnan et al.[2] in 2016 showed high prevalence of risk factors in Kerala. In a community-based cross-sectional study, 5167 adults (mean age 51 years with 23.53% in 60-69 years, 9.75% 70-79 years age group and men 40.1 %) the age adjusted prevalence of hypertension, low HDL and family history were significantly higher in any CAD group (p value < 0.001). In addition, excluding higher cholesterol

all of these conventional risk factors was higher in definite CAD as compared to no CAD. Physical inactivity was reported by 17.5 and 18 % reported family history of CAD. Other CAD risk factors detected in the study were: overweight or obese 59 %, abdominal obesity 57 %, hypertension 28 %, diabetes 15 %, high total cholesterol 52 % and low level of high-density lipoprotein cholesterol 39 %. Current smoking was reported only be men (28 %).

Elderly:

Guidelines for Cardiovascular diseases don't define a cut off for elderly. WHO defines a chronological age of 65 and above as elderly. United Nations defined Elderly as 60 years and above. Some guidelines give specific recommendations for patients above 75 years of age.

The United Nations estimates an increase in the population aged over 65 years from one in 11 in 2019 to one in six by 2050.[56] The American Heart Association (AHA) reports that the incidence of CVD in US men and women is ~40% from 40–59 years, ~75% from 60–79 years, and ~86% in those above the age of 80.[57] The rate of increase in elderly population is especially faster in L-MIC. Data from the Global Burden of Disease showed that life expectancy at birth increased 8.1 years (12.4%) from 1990 to 2019 (65.4 years in 1990 to 73.5 years in 2019.[7] With improvements in life expectancy at birth, the life expectancy of the elderly is improving more rapidly. The global estimate is that a person 65 years old should have expected to live an additional 17 years in 2015–2020, and this number may rise to 19 years in 2045–2050. World Population Prospects estimated greater than 700 million elderly people (age ≥65 years) in 2019 worldwide, and this number should be more than 1.5 billion by 2050, which represents nearly 15% of the world's population.[57]

Europe and North America are the most aging regions worldwide, with nearly 18% of the population being elderly in 2019, followed by Australia and New

Zealand. However, the largest number of older people were in Eastern and Southeastern Asia, with 261 million old people in 2019.

Elderly population of more than 65 years of age account for more than half of all cardiovascular hospitalizations and procedures in the United States, as well as 80% of all cardiovascular deaths. Although people more than 75 years old account for only 6% of the total population, >50% of cardiovascular deaths occur in this age group.[5]According to the American Heart Association on Heart Disease and Stroke Statistics in 2019, the incidence of CVDs was typically 35–40% in people between the ages of 40 and 60, patients between the ages of 60 and 80 had an average incidence of 77–80%, and patients over the age of 80 had an incidence of over 85%.In fact, ageing problems have become prominent worldwide, and the burden of CVD is currently falling mainly on elderly individuals.[59]

The main characteristic feature of patients over 65 is multimorbidity. The ten most common diseases and their frequency among them is listed based on data from the National Council on Aging: hypertension 58%, high cholesterol 47%, arthritis 31%, ischemic/coronary heart disease 29%, diabetes 27%, chronic kidney disease 18%, heart failure 14%, depression 14%, Alzheimer's disease and dementia 11%, chronic obstructive pulmonary disease 11%. An average of 16–20% of life is now spent in late-life chronic diseases, which are dominated by CVD, cancer, and neurodegenerative diseases.

Early estimates from the United States Vital Statistics demonstrated that eliminating CVD deaths would add 5.5 years to life expectancy. Therefore, reducing CVD is very important to improve the quality of life of the elderly.[60] Of the different risk factors, the one that had the greatest impact on CVD mortality in older people was high systolic blood pressure, followed by dietary factors. The challenges in Elderly patients are:

- Polypharmacy is inevitable for patients with ACS. However, the benefits are less certain when the drugs are used in combination because few clinical trials evaluated the drug–drug interaction (DDI) of the combined use of these drugs.
- Adverse drug reactions (ADRs) are more common in older patients
- Narrow therapeutic ranges of drugs and increase in the risk of side effects

Very few studies have evaluated the long-term efficacy and safety of these frequently administered drugs especially in older adults with multimorbidity. As older patients are the fastest growing cohort dying of CAD, epidemic due to rapid aging will become an urgent public health issue and bring new challenges to global health. Further improvements in prevention, diagnosis, and treatment of CAD in this population needs attention.

Aging and CAD:

Age itself is an independent risk factor for the development of CAD. Increased prevalence of traditional risk factors with age contribute to this. In addition to this, metabolic factors associated with aging are also now found to contribute and are being studied. Biological causes of aging are not well elucidated. However, nine cellular and molecular factors have been identified:

- The accumulation of DNA damage
- Telomere shortening
- Epigenetic alterations
- Loss of proteostasis
- Deregulation of nutrient sensing
- Mitochondrial dysfunction (leading to oxidative stress)
- Cellular senescence
- Stem cell depletion
- Impaired intercellular communication

These damaging events are associated with a chronic, low-grade inflammatory state referred to as “inflamm-aging”. Healthy aging is linked to a lower frequency of inflammatory responses and more effective anti-inflammatory processes. This overall imbalance towards persistent chronic inflammation results in insufficient tissue repair and tissue degeneration and the resulting phenotypic changes are characterized by increased susceptibility to aging-related diseases (including CVD), decreased stress tolerance, a worse response to treatment, and low functional capacity. It is now widely accepted that chronic, low-grade inflammation contributes to the pathogenesis of CVD and atherosclerosis, independently of other cardiovascular risk factors.[62]

All the factors previously mentioned which seem to contribute to aging are also playing important roles in cardio-vascular aging as shown in Figure 1.[62] Specific serum markers including dehydroepiandrosterone, fibroblast growth factors (e.g., FGF-23), growth differentiation factor-15, and plasma neutrophil gelatinase-associated lipocalin have been correlated with development of cardiovascular events in older individuals. Additionally, the role of C-reactive protein, an inflammatory marker, in cardiovascular disease is emerging.

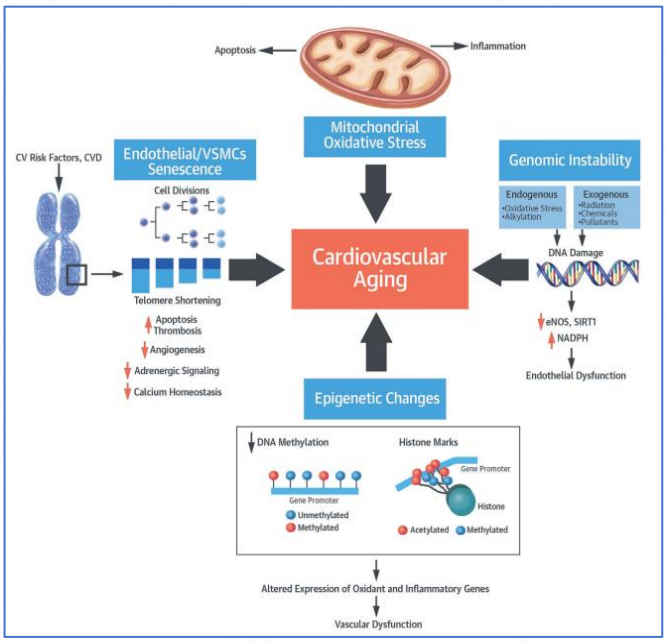

Figure 1: Molecular hallmarks of cardiovascular aging

Physiology Of Aging: **Vascular Physiology** - Normal aging is associated with a decreased compliance of the central arteries due to structural changes such as increased amounts of collagen, more permanent cross-linkages with other collagen fibers due to the nonenzymatic effects of advanced glycation end-products (AGE), age-related up-regulation of elastase resulting in lower elastin in the central arteries, with consequent reduced elastic recoil and distensibility as well as endothelial dysfunction with reduced production of nitric oxide.

As a result, decreased vascular compliance and elasticity leads to isolated systolic hypertension, increasing cardiac afterload and thus myocardial ischemia in

the elderly patient, even without severe atherosclerotic lesions, especially with increased myocardial oxygen demand.

Cardiac Physiology - The hearts of aged individuals usually have increased mass even in the absence of increased afterload due to myocyte hypertrophy which may be from the increased afterload of arteriosclerosis, as above, or may relate to chronic exposure to stress. Fibroblasts beneficially remodel the ventricle, but excess fibrosis decreases the compliance of the ventricle and leads to Stage 1 diastolic dysfunction which is a normal physiologic change of aging.

An important concept in the physiology of cardiovascular aging is "ventricular-vascular coupling". The increase in vascular and left ventricular stiffness combine to achieve stability in resting cardiac output at advanced age but also impair the ability of the cardiovascular system to accommodate to stress leading to reduced cardiac reserve.

CAD in Elderly:

The clinical profile, presentation, management and outcomes of elderly are different compared to younger population. Traditional risk factors are the same, whose harmful effects accumulate over a lifetime. Associated CKD is more common. Characteristic features of older patients with CAD are, a more extensive coronary atherosclerosis, higher prevalence of multi-vessel disease, and the obstruction of the left main coronary artery, left ventricular dysfunction than of younger adults. Symptomless manifestation or disease with atypical symptoms is relatively common (60% in those 85 years or older) leading to delayed diagnosis and intervention. Dyspnea is a very common presenting symptom, both for acute coronary syndromes and chronic CAD. ECG is not informative in most of the cases, due to other common abnormalities (left ventricular hypertrophy, pace rhythm).Frailty, limited exercise capacity, or other disease processes that diminish the ability to ambulate (e.g., pulmonary, musculoskeletal, and peripheral arterial disease) may also mask

awareness of SIHD symptoms by limiting the generation of sufficient myocardial oxygen demand.

A study using data from the LASI, Wave 1 (Longitudinal Aging Study in India),[64] a national survey of scientific investigation of the health, economics, and social determinants and consequences of population aging in India is the world's largest and India's first longitudinal aging study carried out in 2017-2018. 65562 (45 and above) individuals were interviewed and the self-reported prevalence of diagnosed CVDs was 29.4% and prevalence rate increased with age from 22% in 45–54 to 38% in age 70 and above. CVD prevalence was higher among women (32%) than men (26%), much higher among those residing in urban areas (40%) than in rural areas (25%), increased with the level of education from 26% among those with no schooling to 34% in those with secondary and above education.

Prevalence of MI in patients age > 80 years in NHANES was 17.5% for men and 11.0% for women [65] Similar results were reported from the FHS. NSTEMI is more common in older patient populations as demonstrated in the GRACE (Global Registry of Coronary Events).[66] In addition, silent or unrecognized infarctions may account for more than one-third of all MIs in older patients.

Myocardial infarction in the elderly is associated with poor prognosis. The proportion of patients aged > 70 years dying within one year following a first myocardial infarction is much higher than that of aged 40–69 years[67] Mortality rates in older patients with STEMI have ranged from 13% to 30% at 30 days and as high as 52% at 3 years, depending on the median age, study setting, and type and frequency of interventions. Among patients >80 years of age with NSTEACS, 30-day mortality rates have ranged between 12% and 16%, and 1-year mortality rates exceeding 25% have been reported.[68]

Lack of studies in elderly patients precluded specific recommendations in guidelines and individualized decision making is hence advised. Less than 10% of ACS trials have recruited patients >75 years of age.[69] Approximately 28% of STEMI patients and 38% of NSTEACS patients were >75 years of age in the NRMI (National Registry of Myocardial Infarction), CRUSADE and GRACE registries.

Medicare datasets from the early PCI era demonstrated that older patients were significantly less likely to undergo cardiac catheterization and revascularization after MI compared with their younger counterparts a discrepancy that persists in the modern era.

In the study by Bhatia et al.,[70] time from symptom onset to hospital admission was significantly longer in the case of elderly patients. The elderly were significantly less frequently revascularized, more likely to have complications of cardiac failure and arrhythmias especially atrio-ventricular blocks. Elderly were also less likely to receive betablockers and had higher in-hospital mortality.

ACC/ AHA guidelines recommend considering invasive coronary angiography for SIHD in certain clinical circumstances (history of sudden cardiac death, life-threatening arrhythmias, or heart failure) and risks of bleeding, vascular, embolic and neurological complications, and contrast-induced acute kidney injury, all of which are increased in older patients, must be considered.[71] Major vascular complications may occur in 3.6% of older patients undergoing diagnostic coronary angiography.[72]

Risk Factors for CAD in Elderly:

Elderly patients have advanced vascular pathology that leads to a coronary event rate comparable to that of the middle-aged who have already sustained a clinical event and hence the distinction between primary and secondary prevention in them is less clear. FHS showed the following with respect to age: [73]

- Prevalence of most coronary risk factors rises.
- The dominant variety of diabetes is the hyper insulinemic (type 2) variety which is associated with weight gain and abdominal obesity (probably a component of an insulin resistance syndrome)
- Isolated systolic hypertension, with widened pulse pressure is the dominant variety.
- Body mass index increases until age 65 years and then declines in both sexes.

- Prevalence of hypertension, dyslipidemia, and LVH is greater in women than men.
- The ratio of total to high-density lipoprotein (HDL) cholesterol declines steadily with advancing age in men and rises in women, so that by age 80 years this ratio is approximately equal in the two sexes.
- Fibrinogen and other hemostatic factors also tend to increase with age.
- Only cigarette smoking decreases steadily with advancing age.

The rise in prevalence of the major risk factors with advancing age is not inevitable and has been shown to be correctable, if not preventable.

Relevance Of the Risk Factors: The major coronary risk factors—except for cigarette smoking—continue to be significantly related to the rate of development of coronary disease beyond age 65 years.[73] Risk ratios diminish with advancing age, but are offset by a greater absolute risk.

Blood lipids measured after 65 years of age have not been as consistently found to be related to the rate of development of coronary disease as those measured earlier. However, when the lipoprotein-cholesterol fractions or the total to HDL cholesterol ratio are assessed, studies have shown a significant relationship between dyslipidemia and development of coronary disease in the elderly.

Obesity is not a well demonstrated hazard for development of coronary disease, but weight gain and abdominal obesity continue to adversely influence all the major coronary risk factors by promoting an insulin-resistant state.

FHS data indicate that undergoing menopause promptly escalates women's risk of coronary disease to three times that of women the same age who are still menstruating. However, the influence of an early menopause on the rate of development of coronary disease after attaining an advanced age is unclear.

Most of the patients followed up in the large epidemiologic studies were middle-aged. The question of whether the risk factor profile is different in elderly was looked into in few dedicated elderly studies or in sub analyses of these major studies which had varied settings and age range of study participants and hence the impact of traditional risk factors for the development of coronary atherosclerosis in the elderly especially in developing countries like ours remains uncertain.

One of the earliest authors to study this in India was Mukherji et al [74] in patients more than sixty years old with a mean age of 67 years who were referred for coronary angiography to evaluate chest pain. 64 consecutive patients with angiographically normal or near-normal coronary arteries (< 30% stenosis of all major coronary arteries and their branches) and 64 patients with CAD were compared for the prevalence of all traditional risk factors. The results suggested that male sex and cigarette smoking, diabetes mellitus, even under treatment continue to remain risk factors for CAD but controlled hypertension does not. Other risk factors (hypercholesterolemia, sedentary life-style, and family history) do not discriminate individuals with moderate to severe CAD from those with normal or near-normal coronary arteries in elderly.

Data from LASI wave I [64] showed that high cholesterol, diabetes and physical inactivity were key risk factors for CVDs. Singh et al [75] conducted an epidemiological study in the urban population of Moradabad in 1995 and included a random sample of 595 elderly subjects between 50 to 84 years of age which was divided into two age strata and compared. CAD was significantly higher in the elderly (65 to 84 years) group than in the middle-aged (50 to 64 years) group (168 vs. 97 per 1000), respectively. Prevalence of major risk factors and central obesity were significantly higher among patients with CAD than in the rest of the subjects. While the prevalence of hypertension was significantly higher in the elderly, central obesity was significantly higher in the middle-aged. Other risk factors including smoking were comparable in the two subgroups.

In last decade, two studies by Bhatia et al [70] and Sharma et al.[76] compared the clinical profile, risk factors and in hospital outcomes of elderly patients with acute myocardial infarction (AMI).

Sharma et al compared 97 (47.1%) elderly (≥60 years) with a mean age of 69.28 ± 5.72 years and 109 (52.9%) nonelderly (< 60 years) patients with a mean age of 50.54 ± 7.16 years in a prospective observational cross-sectional analytical study which included all consecutive patients of AMI in a single center in Himachal Pradesh between June 2011 and June 2012. Hypertension (56.7% vs 39.4%, P 0.04) was significantly higher in elderly as compared to nonelderly whereas dyslipidemia (24.7% vs 45.9%) and family history of CVD (2.1% vs 7.3%) were more common in

nonelderly than elderly. Majority of patients, 105 (50.97%) had NSTEMI at presentation which was more common in elderly group. Elderly group also had significantly higher atypical symptoms (dyspnea and chest pain) and Killip class at presentation as compared to nonelderly. The post-MI complications as well as in hospital mortality was also more and statistically significant in higher mortality for elderly (20.6% vs 6.4%) which was attributed to late presentation, under use of thrombolysis resulting in more complications.

Bhatia et al conducted a prospective observational study at a tertiary care center in West India in 200 consecutive patients with AMI admitted in the ICCU who were divided as group I (107 patients) aged equal to or above 65 years and the group II (93 patients) aged below 65 years. The male female ratio was 1.27:1 and 3.43:1 in group I and group II respectively. This study showed that atypical presentations were more likely in the elderly, with shortness of breath as the most common presentation (40.18% versus 15.05%; $P < 0.05$), Hypertension, dyslipidemia and diabetes were equally present in both groups but obesity, smoking and family history of coronary artery disease was more prevalent in younger age group ($P < 0.05$). No risk factor was found in 34.58% cases in elderly with MI. Time from symptom onset to hospital admission was significantly longer in the case of elderly patients, they were significantly less frequently revascularized by PCI (4.67% vs 47.31%), more likely to have complications of cardiac failure (65.42% vs 36.56%) and arrhythmias especially atrio-ventricular (AV) blocks, also less likely to receive betablockers. In-hospital mortality was higher in the elderly (28.04% vs 8.6%, $P < 0.001$).

These results clearly highlight that elderly have a different clinical, risk, outcome profile in our population.

A similar study by Veeranna et al[77] reported that age and male sex, but not hypertension or dyslipidemia, represented an increased risk for CAD in elderly more than 70 years of age. Mogensen et al.[78] found that the prevalence of cardiovascular comorbidities increased with advancing age only until the seventh decade and then declined, resulting in the lowest prevalence of diabetes, hypertension, ischemic heart disease, and peripheral artery disease among the very elderly aged more than 85 years compared with patients aged less than 85 years. Female sex, hypertension, and

comorbidity were greater predictors of CAD in the elderly than in younger patients in this study.

Another study of very elderly (90 years or older),[79] who received a cardiac catheterization in Germany, within the study period of 2004–2013, there was no causal relationship between CAD and any traditional risk factors, except for hypertension despite being treated. The associations of most traditional risk factors with CAD were insignificant in the very elderly in a study reported by Odden et al.[80]

Despite conflicting results in various studies, optimal management of all cardiovascular risk factors in older patients with CAD has been found to reduce outcomes. Subgroup analysis of the SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated that older patients (>75 years of age) experienced a reduction in the primary endpoint of MI, ACS, stroke, heart failure, or cardiovascular death with intensive blood pressure control. Heart-healthy diet and lifestyle modifications were associated with reduced all-cause mortality in individuals >70 years of age in the 3C Study.[81]

Hence, the risk factors contributing to CAD in the elderly appear to be different and how it varies in our population needs to be studied. The current study aims to identify the risk factor profile of elderly patients diagnosed with significant CAD by coronary angiogram after 65 years of age and compare it with the population without CAD in a tertiary care hospital in South India. Furthermore, a subset analysis of patients more than 75 years would help contribute to the data on specific risk factors of CAD in this population so that targeted management can be applied to them.

Outcomes of CAD Management Strategies in Elderly:

Elderly with CAD have poorer outcomes as shown in previously mentioned studies. Guidelines recommend individualized decision making based on mode of presentation, bleeding risk vs benefit, frailty and comorbidities or patient/family preference especially in 75 years age and more as dedicated studies are few in this population.

MI in the elderly, is associated with poor short- and long-term prognosis in terms of both morbidity and mortality. The proportion of patients ≥70 years with recurrent MI, stroke, or HF within 5 years following a first MI is 1.5 to 3-fold greater and mortality within one year following a first MI is 2 to 3-fold higher than in those aged 40-69 years. [82]

Stable ischemic heart disease (SIHD):

In the CASS (Coronary Artery Surgery Study) registry,[83] 1,491 nonrandomized patients more than 65 years of age with SIHD were treated with CABG or medical therapy and the former was associated with improved rates of symptomatic angina relief and a survival benefit in higher-risk patients.

The only trial confined to an older population was the TIME (Trial of Invasive Versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary artery disease), in which 305 patients > 75 years of age (mean age 80 years) with chronic angina refractory to at least 2 antianginal agents were randomized to invasive angiography and revascularization (with PCI or CABG) versus GDMT. Quality-of-life indices and MACE (death, nonfatal MI, or readmission for ACS) were improved with the early invasive strategy at 6 months (19% vs. 49%; $p < 0.0001$) (163). At 4 years, however, MACE rates between the groups did not significantly differ, in part due to a high rate of treatment crossovers.[84]

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial found no differences in clinical outcomes (death, MI, or stroke) among 904 SIHD patients more than 65 years of age (mean age 72 years) randomized to PCI plus GDMT versus GDMT alone at median 4.6-year follow-up [85] while the APPROACH (Alberta Project for Outcomes Assessment in Coronary Heart Disease) registry reported significantly improved survival in 983 patients more than 80 years of age with SIHD and ACS in whom coronary revascularization with PCI or CABG was performed compared with medical management. [86]

Thus, it is uncertain whether revascularization in elderly patients with SIHD improves prognosis, although such therapy may reduce symptoms and improve quality of life.

Non–ST-segment elevation acute coronary syndrome:

The TACTICS–TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18) trial[87] found that the benefits of an early invasive therapy were greater in older than younger patients.

GDMT and cardiac catheterization were associated with improved survival in NSTEACS patients in the CRUSADE, GRACE registry[88] among elderly more than 75 years, although hemorrhagic complications were more frequent in nonagenarians. On the other hand, Savonitto et al.[89] randomized 313 patients (mean age 82 years) with NSTEACS to an early invasive strategy versus conservative management, showed no significant differences in 1-year outcomes but a trend towards reduced MACE was seen in the invasive approach (but not in UA).

The After Eighty trial[90] randomized 457 patients (mean age 85 years) with NSTEACS to an early invasive strategy versus conservative management also supported invasive arm despite elective revascularization in 50% of patients assigned to the conservative strategy. Hemorrhagic complications (2%) and contrast-induced acute kidney injury (2%) were infrequent, However, 89% of 4,187 screened patients were not randomized for reasons including short life expectancy, unstable presentation, refusal to participate, and logistic issues, challenging the generalizability of the results.

Thus, elderly patients with NSTEACS may benefit from revascularization, although the risk-benefit tradeoffs of aggressive therapies in the older patient must be carefully considered.

ST-segment elevation MI:

In an analysis of 9 randomized trials with 5,754 patients more than 75 years of age, 35-day mortality was not reduced with fibrinolytic therapy compared with placebo (24.3% vs. 25.3%) [91]. Nevertheless, fibrinolysis is still recommended for older patients without contraindications when primary PCI is not available.

In patients presenting within 3 h of symptom onset with a more than 1-h delay to PCI, the STREAM (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction) trial showed comparable efficacy in the composite 30- day rate of death, shock, congestive heart failure, or reinfarction with tenecteplase (half-dose in very elderly patients) followed by transfer to a PCI-capable hospital for rescue or routine delayed revascularization in those 75 years of age.[92]

The more recent TRIANA trial randomized STEMI patients with mean age 81 years to primary PCI versus fibrinolysis [93] with only 266 of 570 planned patients getting recruited. The primary endpoint of death, reinfarction, or disabling stroke at 30 days occurred in 18.9% of the PCI group versus 25.4% in the fibrinolysis arm (odds ratio [OR]: 0.69; 95% CI: 0.38 to 1.23; p ¼ 0.21). Recurrent ischemia was less common after PCI (0.8% vs. 9.7%; $p < 0.001$).

NORIN STEMI[55] showed that AWMI was the most common type, 46% of patients had an EF of less than 40%, 68% had single vessel disease and LAD was the most common culprit vessel (55%). Culprit vessels and the number of vessels with significant stenosis on angiography did not differ between the sexes.6% died during the index hospitalization,8% at 30 days, and 11% at 1 year. The overall rates of inpatient mortality were significantly higher in female patients. Lack of revascularization with PCI and being a female patients emerged as the strongest predictors of inpatient and 30-day, 1 year mortality.

Other studies comparing PCI and conservative management in older patients with STEMI also suggest lower mortality with revascularization[66,94]. Optimal GDMT may further improve survival after MI in older patients, regardless of reperfusion therapy. Finally, mortality is extremely high in elderly patients with STEMI and cardiogenic shock; whether early revascularization is beneficial in such patients is uncertain

PCI versus CABG:

Several studies have evaluated the comparative outcomes of PCI and CABG in older patient cohorts, with conflicting results. In general, younger patients with extensive CAD (e.g., SYNTAX scores >33) benefit to a greater degree from CABG compared with PCI. Whether this is true in older patients is uncertain.

In the APPROACH registry, [86] patients more than 80 years of age treated with CABG had higher adjusted survival rates and improved Seattle Angina Questionnaire scores compared with PCI whereas a systematic meta-analysis of 66 studies (most of which were also observational) that evaluated outcomes after PCI and CABG in octogenarians, CABG was a univariate predictor of 30-day and 1-year mortality but survival rates were similar between groups at 5 years, although they remained numerically higher in the CABG group compared with PCI (68% vs. 62%)[95]. Residual confounding in these studies cannot be excluded.

In a 10-study metanalysis of 2,386 older patients (mean age 75 years) with unprotected left main disease enrolled through 2013, no significant differences were observed between CABG and PCI (mostly with DES) in all-cause mortality, nonfatal MI, or MACE at 22 months. Patients who received PCI were more likely to have shorter hospital stays and lower rates of stroke compared with CABG, but more frequently required repeat revascularization.[96]

No randomized trials of PCI versus CABG restricted to older patients have been performed. However, insights from subgroup analyses from recent large, randomized trials like PRECOMBAT, SYNTAX (for less severe disease), BEST, EXCEL showed no significant difference in medium to long term outcomes while FREEDOM, NOBLE showed better outcomes in CABG group suggesting that the results in general appear to be comparable in older and younger patients. [97-102]

Although CABG more frequently achieves complete revascularization than PCI, with a lower requirement for repeat revascularization, the less invasive PCI approach may be appropriate in older adult patients who are often frail and prone to periprocedural complications, including stroke and neurocognitive decline.

Knowledge Gaps in Elderly patients:

Despite the high prevalence, morbidity, and mortality of CVD in older adults, most randomized clinical trials have either excluded older adults or have enrolled only relatively healthy older patients with few comorbidities or functional impairments.

In an analysis of recent late breaking clinical trials in Cardiology, 22 trials at the 2011 AHA Scientific Sessions were divided by category: coronary artery disease (5 trials), acute coronary syndromes (5 trials), chronic heart failure (3 trials), atrial fibrillation (3 trials), cardiac surgery and intervention (4 trials), peripheral artery disease (1 trial), and venous thromboembolism (1 trial). Among those trials, 8 did not include older adults of age 60 to 80 years, depending on the study. In trials in which the percentage of older adults were available, adults age more than 75 years constituted 9% to 55% of the enrolled subjects. In the remaining trials, the mean age was 54 to 66 years. Krishnan et al study population included 33% population of more than 60 years and only 9.7% more than 70 years of age.

This contrasts with the prevalence of older age among those with cardiovascular diseases in the general population, in which older adults represent one-third to one-half of patients with the cardiovascular diseases studied in these trials

The generalizability of these trial results to older age groups can be questioned. All recommendations extrapolated the positive results seen in younger individuals to the elderly also and have uniformly emphasized the need for more research with regard to the clinical characteristics and management of CVD in this population.

Aims and Objectives

Aim Of the Study:

To identify the risk factors in patients who were diagnosed with angiographically significant CAD after 65 years of age (Elderly)

Secondary Objectives:

1. To compare the risk factors between elderly with angiographically significant CAD and elderly without significant CAD
2. To identify and compare the risk factors for CAD in the older population of more than 75 years of age
3. To assess the Major Acute Cardiovascular and Cerebrovascular Events (MACCE) on follow up of patients more than 65 years of age with angiographically significant CAD

Materials and Methods

Study Design:

The current study is an observational retrospective study of elderly patients conducted between January 2022 to June 2023 at the Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, India

Participant Selection:

All consecutive elderly patients who attended the Department of Cardiology, SCTIMST and had undergone coronary angiogram (CAG) for suspected CAD or for a clinical diagnosis of CAD after 65 years of age from 2010 to June 2018 were identified from the hospital database and assessed for eligibility.

Inclusion Criteria:

All patients who underwent CAG for suspected CAD (or) for a clinical diagnosis of CAD after 65 years of age

Exclusion Criteria:

1. Patients who underwent CAG for other indications (Hypertrophic Cardiomyopathy, Restrictive Cardiomyopathy, Chronic Constrictive Pericarditis, Congenital Heart Disease, Valvular Heart Disease, CAG prior to Surgery)

2. Patients diagnosed with CAD before 65 years of age were excluded

Methodology:

The details of patients satisfying the eligibility criteria were recorded in detail for the study. Their baseline characteristics, risk factor profile, mode of presentation to the hospital, clinical parameters and investigations at admission, coronary angiogram details, mode of management planned post CAG were extensively collected from the hospital database. Their follow up data during outpatient visits till the end of study period and any hospitalization for occurrence of Major Adverse Cardiovascular and Cerebrovascular events including Acute Coronary Syndrome, Stroke, need for repeat interventions, Heart Failure hospitalization, Mortality as well all treatment details were recorded from the database. Available details of drug adherence, presence and control of risk factors during follow up were also collected from the hospital database and recorded in a detailed study proforma. Patients without follow up visits to this hospital were contacted by telephone for details on outcomes.

In this study, the presence of significant CAD was defined by the presence of 50 percent narrowing of intraluminal diameter of at least one of the major epicardial coronary arteries on coronary angiography.

Among the patients, those with significant CAD on CAG were then analyzed for risk factor profile and outcomes on follow up. Their risk factor profile was compared with those patients who had insignificant CAD or normal coronaries on CAG. The importance of these factors in assessing the risk for developing CAD in the elderly is uncertain. Hence, we attempted to gain further insight into this issue by comparing the prevalence of certain traditional coronary risk factors in patients diagnosed with significant CAD after 65 years of age with those who don’t in the same age group.

A subset analysis of angiographically significant CAD among those more than 75 years was also conducted. MACCE and Survival data analysis was planned for patients having angiographically significant CAD as secondary outcomes.

Data Analysis:

Data from study proforma was transferred to excel sheets and all analyses were carried out using **Stata 16.1 Stata Corp LLC.**

- Categorical baseline variables are presented as proportions and compared across the two CAD categories by using a Chi square test
- Distribution of continuous variables was checked, and normal distribution was ensured before applying parametric hypothesis testing
- Normally distributed continuous variables are presented as mean and standard deviation (SD) and non-normally distributed variables as median with inter quartile range (IQR)
- Group comparisons were made using Student's *t*-tests, Chi-square tests, Fisher exact tests and Mann–Whitney U tests as appropriate.
- Simple logistic regression and Multiple Logistic regression was performed to identify the risk factors associated with CAD
- Kaplan–Meier survival models were performed after checking the proportional hazards assumption using log-minus-log plots, and groups were compared using log-rank tests
- Multivariate Proportional Hazard Model Cox regression analysis was employed to assess the hazard ratio (HR) of all-cause mortality and MACCE
- All confidence intervals were calculated to the 95th percentile

Results

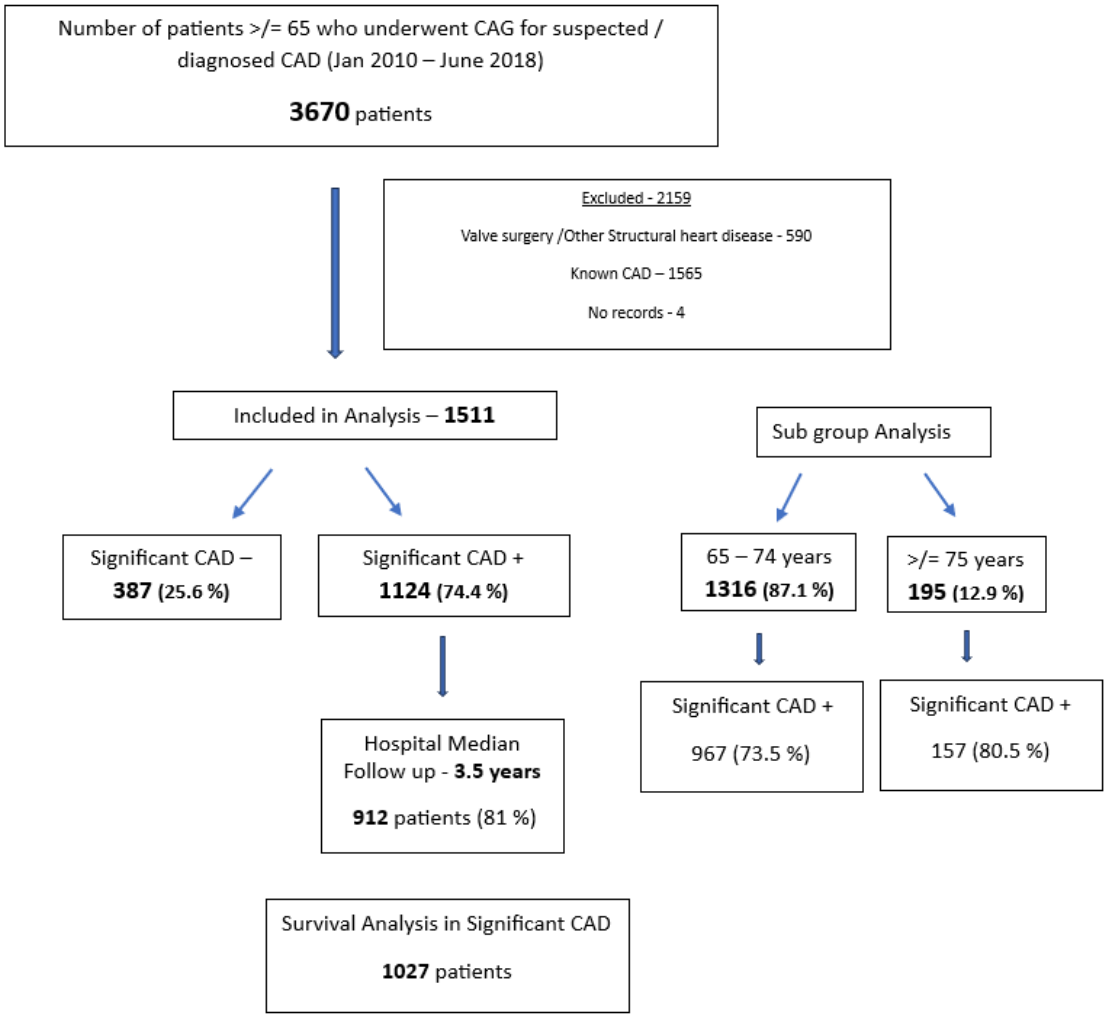

Figure 2: Patient flow diagram

Screening and Exclusion of patients: In this study, 3670 consecutive patients more than or equal to 65 years admitted in the Department of Cardiology and who underwent coronary angiogram for suspected CAD or clinical diagnosis of CAD between January 2010 and June 2018 were screened. Majority of them were excluded as they were diagnosed with CAD before 65 years of age followed by other structural heart disease as shown in the flow chart above (Figure 2).

1511 patients constituted the study group of which 195 (12.9%) were more than or equal to 75 years were included in the analysis. 1124 (74.4%) patients had angiographically significant CAD. Of these, 912 patients had regular hospital follow up and were analyzed for MACCE (median follow up 3.5 years). Telephonic contact yielded survival data for 1027 patients.

Table 2: Baseline characteristics and risk factor profile of patients

Characteristics	**Overall (N=1511)**	**65-74 years (n=1316)**	**>/= 75 years (n=195)**	**P value**
Age Mean (SD)	69.38 (4.03)	68.24 (2.74)	77.11 (2.55)	
Gender, n (%)				
Male	1043 (69.0)	906 (68.8)	137 (70.3)	0.691
Female	468 (31.0)	410 (31.2)	58 (29.7)	
Risk Factors				
Diabetes Mellitus, n (%)	861 (57.0)	751 (57.1)	110 (56.4)	0.863
Hypertension, n (%)	1032 (68.3)	904 (68.7)	128 (65.6)	0.393
Dyslipidemia, n (%)	752 (49.8)	659 (50.1)	93 (47.7)	0.534
Smoking, n (%)	227 (15.0)	208 (15.8)	19 (9.7)	0.080
Reformed Smoker	263 (17.4)	225 (17.1)	38 (19.5)	
Family History n (%)	177 (11.7)	156 (11.9)	21 (10.8)	0.660
CKD, n (%) (Cr > 1.4)	188 (12.4)	149 (11.3)	39 (20)	**0.001**
CVA, n (%)	68 (4.5)	63 (4.8)	5 (2.6)	0.162
PVOD, n (%)	71 (4.7)	62 (4.7)	9 (4.6)	0.953
Hypothyroidism, n (%)	86 (5.7)	76 (5.8)	10 (5.1)	0.716
Reactive airway disease, n (%)	160 (10.6)	142 (10.8)	18 (9.2)	0.509
Carcinoma, n (%)	24 (1.6)	21 (1.6)	3 (1.5)	0.952

BMI categories, n (%)	Overall (n=1308)	65-74 years (n=1157)	>/= 75 years (n=151)	P value
Underweight (<18.5)	36 (2.8)	31 (2.7)	5 (3.3)	0.218
Normal (18.5 – 22.9)	395 (30.2)	340 (29.4)	55 (36.4)	
Overweight (23 – 24.9)	305 (23.3)	280 (24.2)	25 (16.6)	
Obese I (25 – 29.9)	473 (36.2)	418 (36.1)	55 (36.4)	
Obese II (>/=30)	98 (7.5)	88 (7.6)	11 (7.3)	

Table 3: Baseline laboratory parameters of patients

	Overall	65-74 years	>/= 75 years	P Value
RBS Median (IQR)	132.00 (97.00)	132.00 (96.00)	130.00 (100.00)	0.295
SBP Mean (SD)	139.15 (61.34)	136.10 (20.20)	136.56 (17.94)	0.765
DBP Mean (SD)	79.74 (20.50)	79.42 (10.25)	78.26 (9.51)	0.139
Total Cholesterol Mean (SD)	147.05 (46.98)	147.37 (47.02)	144.99 (46.84)	0.580
LDL Median (IQR)	79.00 (53.00)	78.00 (53..00)	83.00 (57.00)	0.334
Triglycerides Mean (SD)	108.98 (49.69)	109.54 (49.70)	105.52 (49.69)	0.380
HDL Mean (SD)	39.53 (10.45)	39.47 (10.47)	39.90 (10.36)	0.654

Baseline Characteristics of patients: The mean age of total population was 69.38 (+/- 4.03) years with an age range of 65-86 years and a male preponderance (69%). Most patients belonged to the higher socioeconomic category “D” as per institutional classification (included patients eligible for re-imbursement). The age and gender distribution in the two age subgroups was comparable as shown in Table 2.

Risk factor profile: Prevalence of traditional and other risk factors is shown in the Table 2, 3 and all of them were found to be comparable between the subgroups except CKD which was higher in the older subgroup. At baseline, the mean RBS, SBP, DBP were controlled but LDL median value was more than 70 mg/dl (79.0 IQR 53.0). Nearly all of tobacco users were male (99%) with 15% having history of smoking at time of CAG. DM, HTN, Dyslipidemia were significantly more common in female patients whereas CKD was common in male. Family history of CAD was similar among the sexes. 43.7 % of patients were obese as per Asian standards. Only 1% of patients had none of the traditional risk factors.

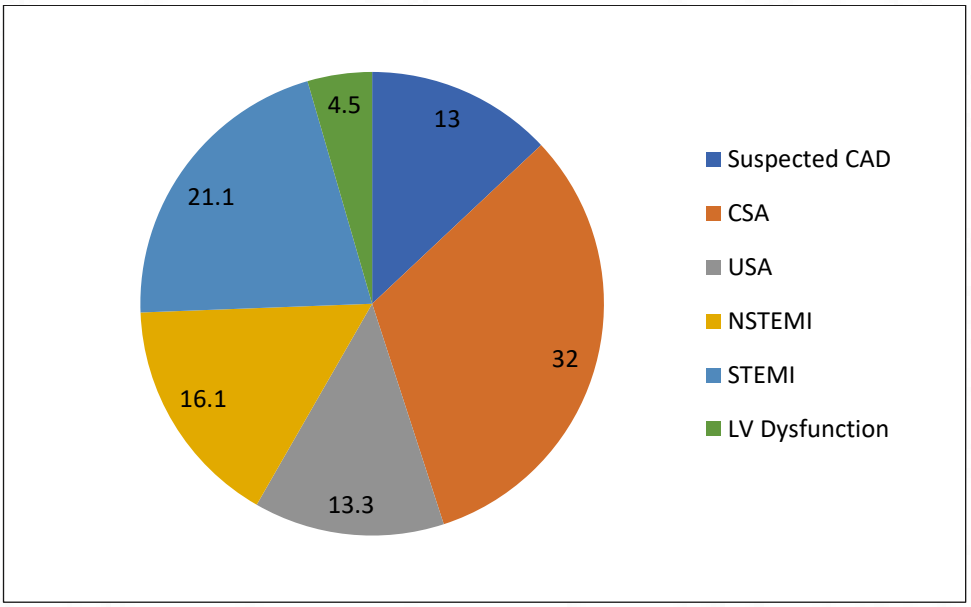

Figure 3: Mode of presentation of patients (N = 1511)

Mode of presentation: As depicted in Figure 2, most patients underwent CAG for CSA followed by NSTEACS. NSTEACS was significantly more common in the older > 75-year subgroup (Table 4). Classical angina was similar among both sexes, but atypical chest pain, dyspnoea on exertion and non-specific ECG changes were significantly more common in women.

Most patients had normal ejection fraction (Mean 60.92 +/-12.92) at baseline. 25.4% of patients had some LV systolic dysfunction and around 4% had severe LV dysfunction at presentation with no difference between the subgroups (Table 5). 56.3% of patients had some degree of diastolic dysfunction.

Of the STEMI patients, IWMI constituted 50% and was the most common type, however, AWMI was more common in 75 years and above age group. 42.6% of STEMI patients underwent thrombolysis and was higher in the younger subset (Table 6).

Table 4: Mode of presentation of patients

Mode of presentation, n(%)	**65 – 74 years (n= 1316)**	**>/= 75 years (n= 195)**	**P value**
Suspected CAD	182 (13.8)	14 (7.2)	0.023
CSA	428 (32.5)	55 (28.2)	
USA or /NSTEMI (NSTEACS)	372 (28.3)	73 (37.4)	
STEMI	273 (20.7)	46 (23.6)	
LV dysfunction/Heart Failure	61 (4.6)	7 (3.6)	

Table 5: Degree of LV dysfunction at the time of CAG

LV dysfunction, n(%)	**Overall (n=1510)**	**65-74 years (n=1315)**	**>/= 75 years (n=195)**	**P value**
None	1126 (74.6)	993 (75.5)	133 (68.2)	0.151
Mild	222 (14.7)	186 (14.1)	36 (18.5)	
Moderate	103 (6.8)	85 (6.5)	18 (9.2)	
Severe	59 (3.9)	51 (3.9)	8 (4.1)	

Table 6: Characteristics of STEMI patients

STEMI Type	**Overall (n=319)**	**65-74 years (n=273)**	**>/= 75 years (n=46)**
Anterior Wall	153 (47.9)	127 (46.4)	26 (56.5)
Inferior Wall	159 (50)	140 (51.5)	19 (41.3)
Lateral Wall	7 (2.1)	6 (2.1)	1 (2.2)
Thrombolysis, n (%)	**Overall (n=310)**	**65-74 years (n=264)**	**>/= 75 years (n=46)**
Done	127 (41.0)	113 (42.8)	14 (30.4)
Failed	5 (1.6)	5 (1.9)	0

CAG and Treatment details: Proportion of patients with angiographically significant CAD was 74.4% and was significantly higher in the older subgroup as shown in Table 7 and in males (79% vs 64.1% in female patients; P < 0.001). Triple vessel disease was the most common form of disease in this population which was comparable among the age subgroups (Table 8).

Significant left main involvement (> 50% stenosis) was present in 5.7% and LAD involvement (>70%stenosis) in 51.5% of cases which was also comparable among the subgroups.

Table 7: Proportion of patients with angiographically significant CAD on CAG

CAD, n(%)	**Overall (N=1511)**	**65-74 years (n=1316)**	**>/= 75 years (n=195)**	**P value**
Significant	1124 (74.4)	967 (73.5)	157 (80.5)	**0.036**

Table 8: Distribution of CAD extent on CAG

CAG Impression n (%)	Overall (N=1511)	65-74 years (n=1316)	>/= 75 years (n=195)	P value
Normal	125 (8.3)	115 (8.7)	10 (5.1)	0.168
Normal coronaries - Ectatic / Slow Flow	26 (1.7)	24 (1.8)	2 (1)	
Minor (< 50% plaque)	182 (12)	160 (12.2)	22 (11.3)	
Branch vessel disease	55 (3.6)	50 (3.9)	4 (2.1)	
SVD	261 (17.3)	229 (17.3)	33 (16.9)	
DVD	323 (21.4)	279 (21.2)	44 (22.6)	
TVD	539 (35.7)	459 (34.9)	80 (41)	

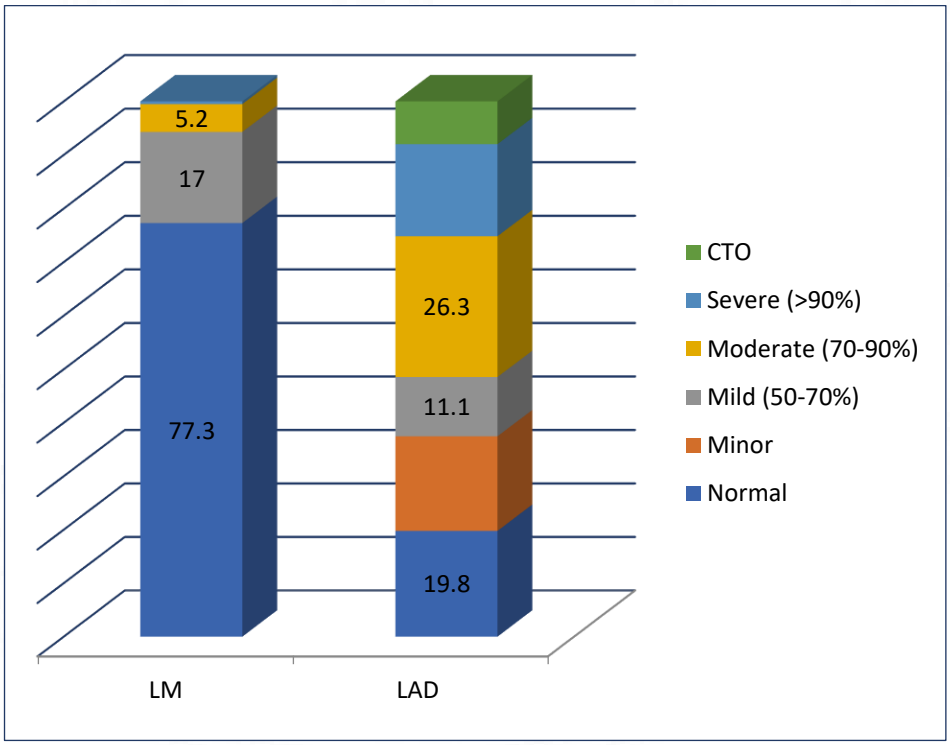

Figure 4: Extent of LM and LAD Involvement in all patients (N = 1492)

Most of the patients were kept on medical management which was comparable between age subgroups. Angioplasty was significantly more among older subgroup whereas CABG was significantly more in younger subgroup as shown in Figure 5. Male patients underwent significantly more angioplasties (35.9% vs 29.7%; P = 0.032) as well as CABG (19.4% vs 9.2%; P < 0.001) compared to female population.

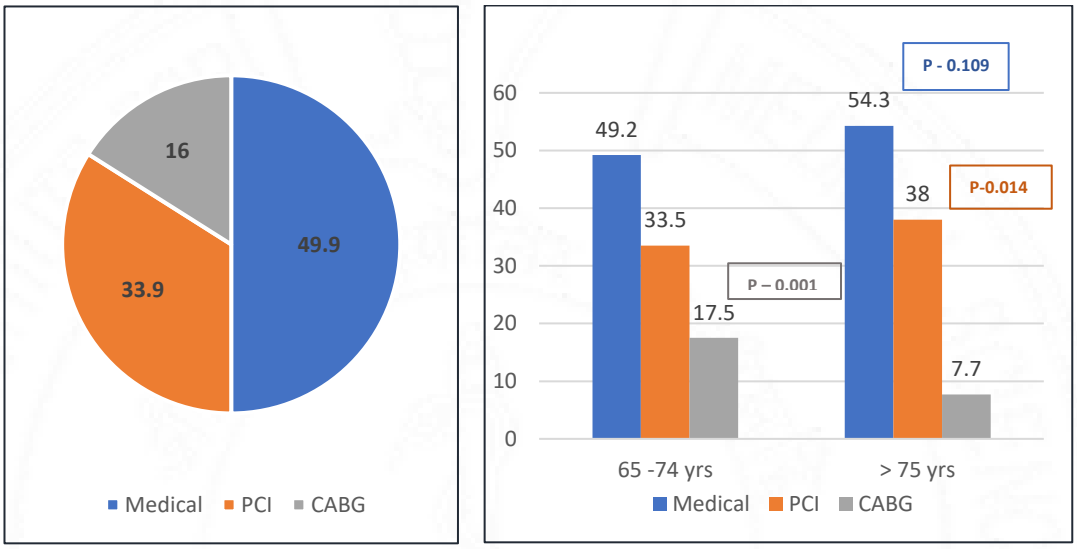

Figure 5: Distribution of modes of treatment overall (N=1511) and among age subgroups

Primary Outcome: Age, Male gender, Lower socioeconomic status (B, C), Diabetes mellitus, Dyslipidemia, Current and reformed tobacco use, Obesity category II but not Hypertension, Family history were associated with angiographically significant CAD in this study (Table 9). Multiple logistic regression suggested Male gender, Dyslipidemia, Current tobacco use were contributing to CAD (Table 10).

Table 9: Association of risk factors with angiographically significant CAD

(Simple logistic regression analysis)

Variables	**CAD not significant n (%)**	**CAD significant n (%)**	**Unadjusted Odds Ratio**	**OR 95% CI**	**P value**
Age Mean (SD)	68.70 (3.67)	69.62 (4.12)	**1.06**	**1.03-1.09**	**<0.001**
Male Gender	219 (56.6)	824 (73.3)	**2.10**	**1.65-2.68**	**<0.001**
Socio Economic Class					
A	6 (1.6)	11 (1.0)	0.73	0.26-1.99	0.5390
B	94 (24.4)	344 (30.9)	**1.46**	**1.11-1.91**	**0.006**
C	33 (8.6)	127 (11.4)	**1.53**	**1.02-2.31**	**0.041**
D	252 (65.5)	633 (56.8)	1		
DM	198 (51.2)	663 (59.0)	**1.37**	**1.09-1.73**	**0.007**
HTN	278 (71.8)	754 (67.1)	0.799	0.62-1.03	0.083
Dyslipidemia	173 (44.7)	579 (51.5)	**1.31**	**1.04-1.66**	**0.021**
Smoking	39 (10.1)	188 (16.7)	**1.91**	**1.32-2.77**	**0.001**
Reformed smoker	58 (15.0)	205 (18.2)	**1.40**	**1.02-1.93**	**0.039**
Family history	39 (10.1)	138 (12.3)	1.25	0.86-1.82	0.247
BMI					
Normal	91 (27.4)	304 (31.1)	1		
Underweight	7 (2.1)	29 (3.0)	1.24	0.53-2.92	0.623
Overweight	67 (20.2)	238 (24.4)	1.06	0.74-1.52	0.737
Obese I	128 (38.6)	345 (35.3)	0.80	0.59-1.09	0.175

Obese II	39 (11.7)	59 (6.0)	**0.46**	**0.29-0.73**	**0.001**
CVA	15 (3.9)	53 (4.8)	1.13	0.63-2.05	0.675
PVOD	8 (2.1)	63 (5.6)	2.81	1.33-5.93	0.007
Hypothyroidism	36 (9.3)	50 (4.4)	0.45	0.29-0.71	0.001
Reactive Airway Disease	51 (13.2)	109 (9.7)	0.70	0.49-1.01	0.056
Carcinoma	6 (1.6)	18 (1.6)	1.03	0.41-2.62	0.945

Table 10: Association of risk factors with angiographically significant CAD
(Multiple logistic regression analysis)

Variables	**CAD not significant n (%)**	**CAD significant n (%)**	**Adjusted Odds Ratio**	**OR 95% CI**	**p-value**
Male Gender	219 (56.6)	824 (73.3)	**1.67**	**1.09-2.55**	**0.017**
Dyslipidemia	173 (44.7)	579 (51.5)	**1.49**	**1.06-2.09**	**0.020**
Smoking	39 (10.1)	188 (16.7)	**2.39**	**1.37-4.19**	**0.002**

Secondary Outcomes: As shown in Tables 11 and 12, none of the studied risk factors were found to contribute to CAD in the older > 75-year age group. In the 65-74 age group, Male gender, Dyslipidemia, Socioeconomic Classes B, C and PVOD were associated with significant CAD.

Table 11: Association of risk factors with angiographically significant CAD among the two age subgroups (Simple logistic regression analysis)

Variables	65 – 74 yrs		Unadjusted Odds Ratio	OR 95% CI	P value	>/= 75 yrs		Unadjusted Odds Ratio	OR 95% CI	P value
	CAD not significant n (%)	CAD significant n (%)				CAD not significant n (%)	CAD significant n (%)			
Male Gender	195 (55.9)	711 (73.5)	**2.19**	**1.70-2.83**	**<0.001**	24 (63.2)	113 (72)	1.49	0.71-3.16	0.288
Socio Economic Class										
A	5 (1.4)	9 (0.9)	0.76	0.25-2.31	0.640	1 (2.6)	2 (1.3)	0.51	0.05-5.82	0.588
B	91 (26.2)	313 (32.6)	**1.47**	**1.10-1.94**	**0.007**	3 (7.9)	31 (19.9)	2.63	0.75-9.26	0.132
C	26 (7.5)	110 (11.5)	**1.81**	**1.15-2.84**	**0.011**	7 (18.4)	17 (10.9)	0.62	0.23-1.64	0.335
D	225 (64.8)	527 (55)	1			27 (71.1)	106 (67.9)	1		
DM	180 (51.6)	571 (59)	1.35	1.06-1.07	0.16	18 (47.4)	92 (58.6)	1.57	0.77-3.20	0.212
HTN	253 (72.5)	651 (67.3)	0.78	0.59-1.03	0.075	25 (65.8)	103 (65.6)	0.99	0.47-2.09	0.983
DLP	157 (45)	502 (51.9)	**1.32**	**1.03-1.69**	**0.027**	16 (42.1)	77 (49)	1.32	0.647-2.71	0.443
Smoking	37 (10.6)	171 (17.7)	**1.92**	**1.31-2.82**	**0.001**	2 (5.3)	17 (10.8)	2.46	0.54-11.25	0.245
Reformed smoker	53 (15.2)	172 (17.8)	1.35	0.96-1.89	0.086	5 (13.2)	33 (21)	1.91	0.69-5.31	0.214
Family history	36 (10.3)	120 (12.4)	1.23	0.83-1.83	0.300	3 (7.9)	18 (11.5)	1.51	0.42-5.42	0.527

Variables	65 – 74 yrs		Unadjusted Odds Ratio	OR 95% CI	p-value	>/= 75 yrs		Unadjusted Odds Ratio	OR 95% CI	P value
	CAD not significant n (%)	CAD significant n (%)				CAD not significant n (%)	CAD significant n (%)			
BMI										
Normal	6 (2)	25 (2.9)	1			1 (3.4)	4 (3.3)	1		
Underweight	81 (26.7)	259 (30.3)	1.3	0.52-3.29	0.058	10 (34.5)	45 (36.9)	0.89	0.09-8.83	0.920
Overweight	63 (20.8)	217 (25.4)	1.07	0.74-1.57	0.698	4 (13.8)	21 (17.2)	1.17	0.33-4.15	0.812
Obese I	115 (38)	303 (35.5)	0.82	0.59-1.14	0.249	13 (44.8)	42 (34.4)	0.72	0.28-1.81	0.483
Obese II	38 (12.5)	50 (5.8)	**0.41**	**0.25-0.67**	**<0.001**	1 (3.4)	10 (8.2)	2.22	0.25-19.4	0.470
CKD	27 (7.7)	122 (12.6)	**1.72**	**1.11-2.66**	**0.015**	8 (21.1)	31 (19.7)	0.92	0.38-2.21	0.857
Alcohol	3 (0.9)	20 (2.1)	2.19	0.64-7.48	0.210	1 (2.6)	3 (1.9)	0.24	0.02-3.93	0.317
CVA	15 (4.3)	48 (5)	1.06	0.9-1.9	0.834	0	5 (3.2)			
PVOD	7 (2)	55 (5.7)	**2.95**	**1.33-6.53**	**0.008**	1 (2.6)	8 (5.1)	1.99	0.24-16.38	0.524
Hypothy-roidism	35 (10)	41 (4.2)	**0.39**	**0.25-0.64**	**<0.001**	1 (2.6)	9 (5.7)	2.25	0.28-18.32	0.449
Reactive Airway Disease	48 (13.8)	94 (9.7)	0.68	0.47-0.98	0.038	3 (7.9)	15 (9.6)	1.23	0.34-4.49	0.752
Carcinoma	6 (1.7)	15 (1.6)	0.90	0.35-2.34	0.830	0	3 (1.9)			

Table 12: Association of risk factors with angiographically significant CAD among 65-74 years age subgroup (Multiple logistic regression analysis)

Variables	**CAD not significant n (%)**	**CAD significant n (%)**	**Adjusted Odds Ratio**	**OR 95% CI**	**P value**
Male Gender	195 (55.9)	711 (73.5)	**3.74**	**2.37-5.89**	**<0.001**
Dyslipidemia	157 (45)	502 (51.9)	**1.56**	**1.18-2.06**	**0.002**
SEC B Category	91 (26.2)	313 (32.6)	**1.59**	**1.16-2.18**	**0.004**
SEC C Category	26(7.5)	110 (11.5)	**1.78**	**1.08-2.93**	**0.023**
PVOD	7 (2)	55 (5.7)	**4.3**	**1.52-12.21**	**0.006**

Among those patients for whom laboratory parameters of major risk factors were available, it was found that many patients have uncontrolled risk factors especially DM (Table 13).

Table 13: Risk factor control on follow up*

Risk factors	**Uncontrolled n (%)**
DM (N =298)	174 (58.4)
HTN (N =835)	292 (35)
Dyslipidemia (N =213)	88 (41.3)

* Available data)

Follow up for MACCE: In-hospital follow up data of 912 patients with significant CAD over a median follow up of 3.5 years showed a MACCE rate of 14% (Table 14). 6.7% had ACS on follow up most common being NSTEMI, need for revascularization was 3.8% and 3.4% patients needed HF hospitalization. A higher event rate of 22.3% was recorded among those who completed 5 years follow up in the hospital (439 patients).

Table 14: MACCE in significant CAD patients on hospital follow up (N = 912)

Events n (%)	**Median Follow Up 3.5 years (N=912)**	**Completed 5 year follow up (N=439)**
MACCE	**128 (14)**	**98 (22.3)**
ACS	61 (6.7)	47 (10.7)
USA	21 (2.3)	
NSTEMI	30 (3.3)	
STEMI	10 (1.1)	
Revascularisation		
PCI	28 (3.1)	21 (4.8)
CABG	6 (0.7)	6 (1.4)
HF Hospitalisation	31 (3.4)	24 (5.5)
CVA	30 (3.3)	20 (4.5)
Mortality	20 (2.2)	17 (3.9)
Cardiac	12 (1.3)	
Non-Cardiac	8 (0.9)	
Re - CAG	63 (6.9)	50 (1.4)

*12 patients had events at zero time
** Censored data among all patients (N=912) – 473 (52%) who didn't complete hospital 5 year follow up

Kaplan Meier analysis showed that female gender and triple vessel disease were associated with greater MACCE (Figure 6A, 6B and Table 15). While worsening LV dysfunction showed a trend towards increased events, this was not significant (Supplementary figure 1A, 1B). There was no significant variation in events among various modes of presentation (Supplementary figure 1C). Revascularization (CABG or PCI), showed significant benefit over medical management for MACCE (Figure 6C).

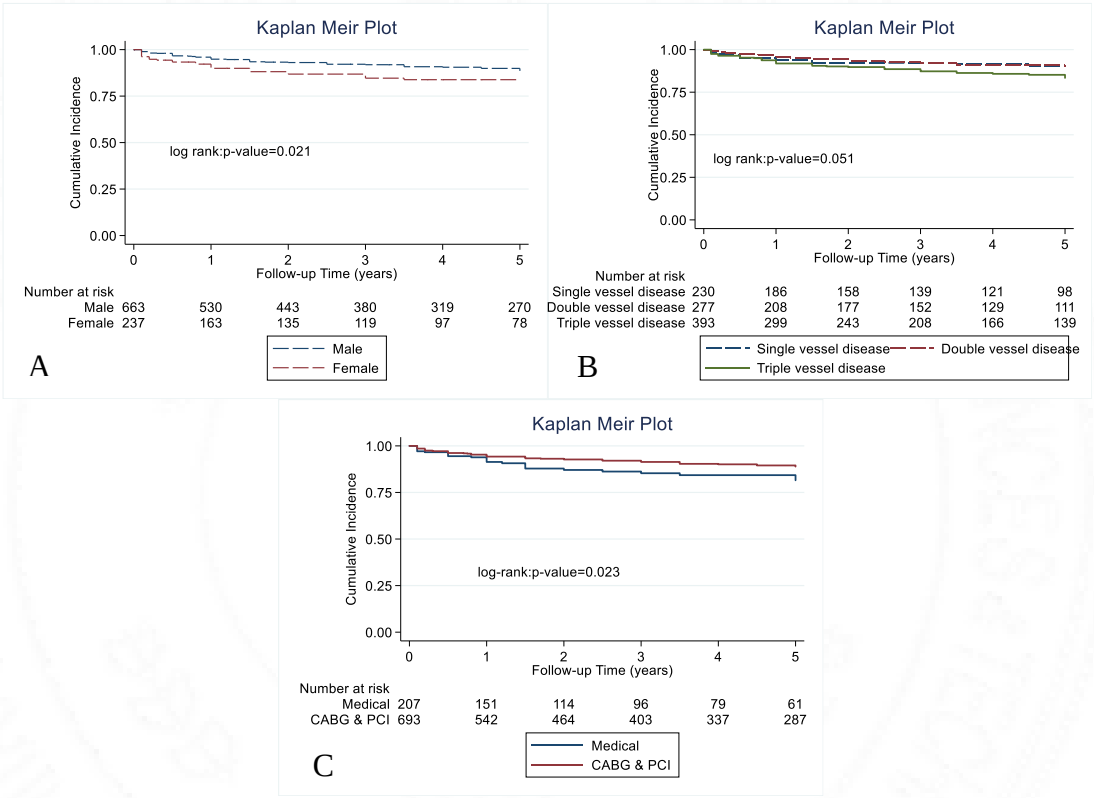

Figure 6: Kaplan Meier curves for 5-year MACCE in patients with angiographically significant CAD (N=912) based on A. Gender B. Extent of CAD C. Mode of treatment

In a sub-analysis of patients (Table 16) having significant LM (>50% lesion) or TVD (N= 195 after excluding those lost to follow up), the five-year MACCE rate was comparable for PCI versus medical management (26.7 % vs 45.2 %; p= 0.052), CABG and PCI (23.7 % vs 26.7 %; p= 0.674), However, CABG had significantly lower MACCE versus medical management (23.7 % vs 45.2 %; p= 0.012).

Table 15: Correlates of MACCE in elderly with significant CAD
(Multivariate proportional hazard model cox regression analysis)

Variables	**Adjusted HR (95 % CI)**	**P value**
Female Gender	1.73 (1.10 – 2.72)	**0.018**
LV dysfunction	1.22 (0.72 – 2.07)	0.452
DVD	1.08 (0.57 – 2.06)	0.815
TVD	2.17 (1.22 – 3.85)	**0.008**
PCI	0.69 (0.42 – 1.14)	0.149
CABG	**0.45 (0.24 – 0.84)**	**0.013**
Revascularization	**0.596 (0.37-0.95)**	**0.029**
NSTEMI	1.55 (0.84 – 2.86)	0.161
STEMI	1.78 (0.96 – 3.30)	0.066

Table 16: Five-year MACCE among patients with significant LM or triple vessel disease based on treatment

	Five-year MACCE (N=195) *		
	Medical N=42	**PCI** N=60	**CABG** N=93
Event rate n (%)	19 (45.2)	16 (26.7)	22 (23.7)

*Patients lost to follow up were excluded

Follow up for Mortality: Survival analysis of 1027 significant CAD patients over a median follow up of 6 years showed a 1, 3, 5, 10-year mortality of 44(4.3%), 71(6.9%), 111(10.8%), 187(18.2%) respectively. Kaplan Meier survival analysis (5 year) showed that LV dysfunction and triple vessel disease were associated with greater mortality (Figure 7A, 7B and Table 16) and worsening LV dysfunction showed a trend towards increased mortality (Supplementary figure 2C). There was no significant variation among age subgroups, gender, various modes of presentation (Supplementary figure 2A, 2B, 2D and Table 17). None of the major risk factors showed correlation with survival. Those who underwent revascularization (CABG or PCI) had better survival compared to medical management (Figure 7C). Similar results were obtained on 10-year survival analyses also (Supplementary figure 3 and Supplementary table 1).

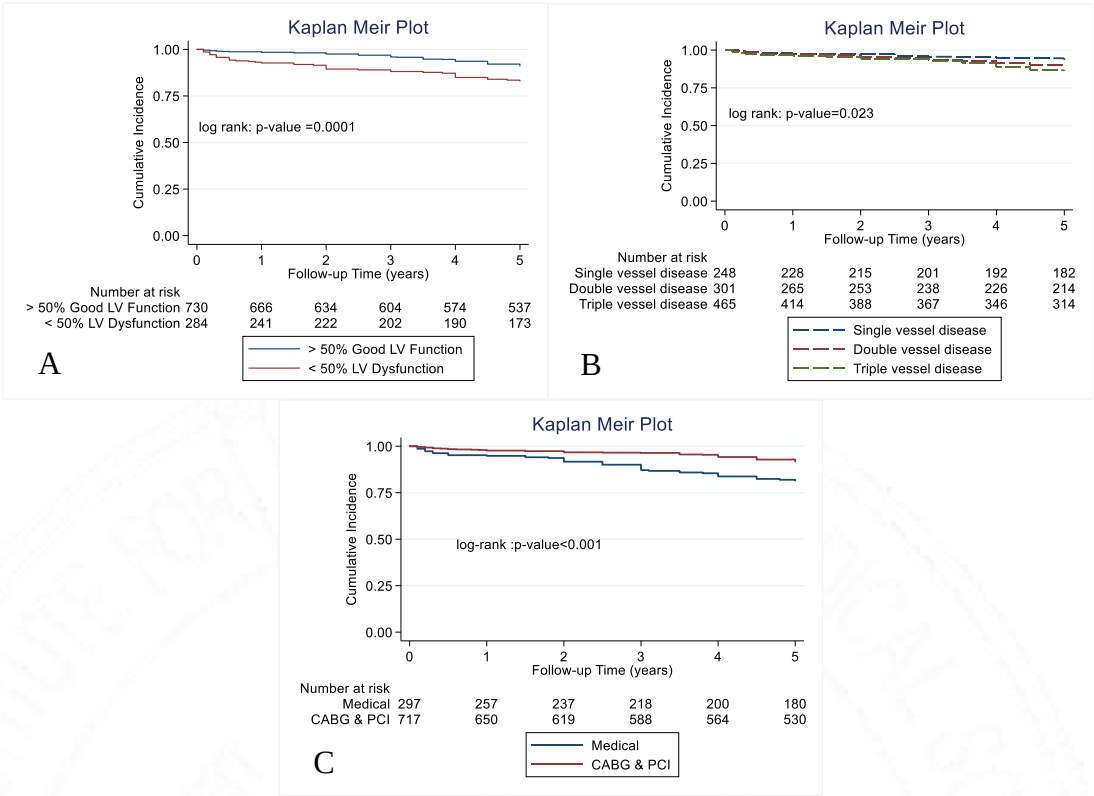

Figure 7: Kaplan Meier curves for 5-year survival in patients with angiographically significant CAD (N=1027) based on A. LV Dysfunction B. Extent of CAD C. Revascularization

*13 patients had events at zero time.

**Censored data - 213 (17.6%) patients lost to follow up (didn't complete 5 years follow up)

Table 17: Correlates of 5-year mortality in elderly with significant CAD (Multivariate proportional hazard model cox regression analysis)

Variables	**Adjusted HR (95 % CI)**	**P value**
Female Gender	1.19 (0.66 – 2.15)	0.556
> 75 years	0.78 (0.39 – 1.53)	0.466
LV Dysfunction	2.12 (1.23 – 3.65)	**0.007**
DVD	1.71 (0.86 – 3.40)	0.126
TVD	2.26 (1.18 – 4.32)	**0.014**
PCI	**0.55 (0.33 – 0.92)**	**0.022**
CABG	**0.29 (0.14 – 0.57)**	**< 0.001**
Revascularization	**0.41 (0.27 - 0.62)**	**< 0.001**
NSTEMI	1.91 (0.98 – 3.77)	0.059
STEMI	1.67 (0.83 – 3.36)	0.154
DM	1.29 (0.81 – 2.07)	0.285
HTN	1.64 (0.96 – 2.79)	0.070
Dyslipidemia	0.74 (0.47 – 1.16)	1.191
Smoking	1.15 (0.60 – 2.19)	0.669
Reformed smoker	1.23 (0.67 – 2.26)	0.503
Obesity	0.66 (0.12 – 3.75)	0.636

In a sub-analysis of patients (Table 18) having significant LM (>50% lesion) or TVD (N=389 after excluding those lost to follow up), the 5-year mortality rate was significantly lower among those who underwent PCI versus medical management (12.5 % vs 27.1 %; p= 0.006) and also for CABG versus medical management (12.8% vs 27.1%; p=0.002). CABG however had no significant difference compared to PCI in this group of patients (12.8% vs 12.5%; p=0.939).

Table 18: Five-year mortality rate among patients with significant LM or triple vessel disease based on treatment

	Five-year mortality rate (N=389)*		
	Medical N=129	**PCI** N=104	**CABG** N=156
Event rate n (%)	35 (27.1)	13 (12.5)	20 (12.8)

*Patients lost to follow up were excluded

Discussion

The present study was conducted at a tertiary care center in South India among elderly patients (more than or equal to 65 years of age) admitted for CAG for either suspected CAD or a clinical diagnosis of CAD with an intention to determine the risk factors contributing to CAD in this population.

A total of 3670 elderly patients who underwent CAG in our institute between January 2010 and June 2018 were screened of which 1511 patients satisfying eligibility criteria were analyzed for risk factor profile and clinical characteristics. A subset analysis among those more than or equal to 75 years was also done. Patients with angiographically significant CAD were followed up for occurrence of 5-year MACCE and survival outcomes.

The major findings in this study were that, there was a high prevalence of traditional risk factors in this cohort compared to other similar studies. Male gender, dyslipidemia and current tobacco use were significantly found to be contributing to angiographically significant CAD in elderly whereas none of the risk factors were found to be significant in the subgroup of 75 years or more. Fourteen percent of patients with significant CAD developed MACCE over a median 3.5-year hospital follow up. Female patients had significantly less revascularization and higher MACCE on follow up. Triple vessel disease and LV dysfunction were found to significantly predict 5-year mortality rate in elderly. MACCE and survival were significantly better among those who underwent revascularization compared to medical management.

The mean age of this patient population was 69.38 (+/- 4.03) years which is similar to other similar Indian studies[70,74,76] Most of the CAD studies [2,55,64] had a mean age between 50 to 60 years and hence their results cannot be generalised to elderly. Krishnan et al study done in Kerala had 33% of patients above 60 years and only 9.7% of the patients more than 70 years. Our study having all patients above 65 years and 12.9% of them in >75-year age group (mean age 77.1 +/- 2.55 years) aimed to generate data in this group of patients so that targeted management can be offered. 69% of the patients were men which is the predominant pattern worldwide

in CAD studies. Even among the >75-year subgroup, male preponderance persisted (70%). Studies have shown that post menopause, women have equal risk for CAD which was not reflected in elderly studies. This could be due decreased access to health care, low socioeconomic status especially in developing countries.

Table 19: Comparison of Indian studies on prevalence of risk factors and their association with CAD

Parameters	**ICMR INDIAB[47]**	**Krishnan et al[2]**	**NORIN STEMI[55]**	**LASI wave I[64]**	**Present study**
Study Setting	Population survey	Community based	Hospital based	Community based	Hospital based retrospective observational
Participants	113043	5167	3635	65562	1511
Year	2008-2020 (in stages)	2016	2019-2020	2017-2018	2010-2018
Mean age (years)	43	51 (33.28% above 60)	55	35.2% were > 65 years	69.38
CAD	Not studied	12.% Any CAD 3.5% Definite CAD	STEMI patients	Self-reported CVD and risk factors	Suspected or diagnosed with CAD
Prevalence of risk factors	DM 11.4% HTN 35.5% DLP 81.2% Obesity 28.6%	DM 33% HTN 51.3% High T.Ch 41% Low HDL 43% Smoking 15.7% Family history 25.3% (In definite CAD)	DM 24% HTN 29% Tobacco use 53% Obesity 11%	DM 66.3% High T.Ch 68% Physical inactivity 34.8% Family history 43.8% (In CVD)	DM 57% HTN 68% DLP 50% Smoking 33% Family history 12% Obesity 7.5%
Risk factors found to be associated with CAD	Not studied	HTN, Low HDL, Family history (with Any CAD)	Not studied	DM, T.Ch, Physical Inactivity (with CVD)	Male gender, DLP, Smoking

The prevalence of risk factors in this study was high in comparison to other population-based studies like ICMR INDIAB[47] as all patients had CAD or suspected

to have CAD. Even compared to studies done among CAD patients in India[2,55,70,76], this cohort showed very high prevalence of DM, HTN, Dyslipidemia, Obesity. Most of the patients were in Obese I category by Asian standards. Moreover, these four risk factors were significantly higher among female patients. This reflects the growing prevalence of risk factors in our country especially among elderly women in urban and higher socioeconomic population like in Kerala. Hence, we should make more efforts to control these risk factors in these patients. Smoking was similar but family history was lesser than previously reported. Smoking history was present in 33% among which 15% were current smokers contrary to what was shown earlier that prevalence decreases with age. This indicates the need to aggressively bring down modifiable causes for CVD even in elderly patients in our country. Only 1% had none of the traditional risk factors similar to the 2-7% reported in INTERHEART Study versus 34.58% in the study by Bhatia et al. Unexpectedly, all major risk factors were comparable between the two subgroups except CKD which was significantly high in the > 75-year subgroup and didn't show increasing prevalence with age. This highlights that multimorbidity increases with age making it difficult to make management decisions in them.

In the overall cohort, 74.4% had angiographically significant CAD and there was a significantly higher prevalence in > 75-year group vs 65-74 years (80.5% vs 73.5%; P 0.036) indicating that CAD continues to increase in prevalence. The AHA had also reported that incidence of CVD in US men and women is ~40% from 40–59 years, ~75% from 60–79 years, and ~86% in those above the age of 80.[57] Elderly patients need equal or rather more attention with respect to modifying risk factors, clinical management and formulating guidelines.

Few studies have looked into whether the same traditional risk factors leading to CVD till 60 years continue to play a role. They all show conflicting results and there is still uncertainty. Mukherji et al.[74] had used similar study design to our study and showed that male gender, cigarette smoking and DM (even if controlled) contributed to significant CAD among elderly while HTN did not. More recently, Sharma et al.[76] compared risk factor prevalence between elderly and non-elderly in acute MI and found that only HTN was significantly higher in elderly whereas Bhatia

et al.[70] showed that DM, HTN, DLP was similar between the two groups. Our findings stating that Male gender, DLP, Smoking are significantly associated with angiographically significant CAD in elderly are more in line with Mukherji et al.[74] despite being conducted nearly three decades apart. Some studies done in very elderly showed that only hypertension [78,79] or none of the major risk factors[80] contributed to CAD. Our sub analyses among 75 year and older also suggests the same.

Table 20: Comparison of Indian studies on association of risk factors with CAD in elderly

Parameters	**Mukherji et al.[74]**	**Sharma et al.[76]**	**Bhatia et al.[70]**	**Present study**
Study Setting	Hospital based	Hospital based	Hospital based	Hospital based retrospective observational
Participants	128	206	200	1511
Year	1989	2011-2012	2006-2008	2010-2018
Mean age (years)	67	67.28 (Elderly) 50.54 (Non Elderly)	73 (Elderly) 47.2 (Non Elderly)	69.38
CAD Sub groups	Angiographically Significant CAD Vs < 30% stenosis or Normal coronaries on CAG	>/= 60 years Vs < 60 years	>/= 65 years Vs < 65 years	Angiographically Significant CAD Vs < 50% stenosis or Normal coronaries on CAG
Prevalence of risk factors	-	DM 7% HTN 56.7% DLP 24.7% Smoking 43.3% Obesity 37%	DM 16.8% HTN 42.9% DLP 22.4% Smoking 16.8% Obesity 5.6% Family history 2.8%	DM 57% HTN 68% DLP 50% Smoking 33% Family history 12% Obesity 7.5%
Risk factors found to be associated with CAD	Male gender, Cigarette smoking, DM (even controlled)	HTN (Elderly) DLP, Family history (Non Elderly)	None (Elderly) Smoking, Obesity, Family history (Non Elderly)	Male gender, DLP, Smoking

The lack of a significant difference in the prevalence of DM, HTN, family history of CAD, and Obesity between the significant CAD and insignificant CAD/Normal coronary groups may suggest that these risk factors contribute less to the development of coronary atherosclerosis in the elderly than in younger individuals. Another important explanation is that significant proportion of patients with these risk factors have expired before reaching this age. Thus, by enrolling only elderly patients, we may have inadvertently selected a healthier population compared to younger counterparts with similar risk factor profiles. In view of conflicting results in various studies, we can only suggest that traditional risk factors don't seem to predict the presence of CAD with the same degree as in younger individuals but they continue to play a role and need to be addressed. As shown here, more than one third of patients with available data had uncontrolled DM, HTN, DLP on follow up despite being in a tertiary set up.

We also found that despite women having higher prevalence of most major risk factors, female gender was not significantly associated with angiographically significant CAD. This supports the theory that women are more prone to Non – obstructive CAD spectrum of conditions.

Most of the patients underwent CAG for Chronic stable angina. Among ACS, UA/NSTEMI (29.4%) was the most common which is similar to previous studies[65,66,76,79]. IW was most involved in STEMI which was also the pattern observed in other elderly studies[70,76] while in NORIN STEMI study which had a younger cohort, AWMI was the most common. Thrombolysis was performed in only 42.6% of patients and was significantly less in > 75-year age group (30.4%) which could be explained by higher contraindications or higher rates of Primary PCI in our setup. Unlike other studies indicating that atypical symptoms are more common in elderly [70,76], there was no difference between the two age subgroups in this study. However, women had significantly higher rates of atypical symptoms and non-specific ECG changes and hence, lower threshold to diagnosed CAD in them should be maintained. Multivessel disease was the more common as shown in previous registries in elderly indicating more extensive atherosclerosis with age.

Half of the patients were kept on medical follow up while PCI (33.9%) was the more common form of revascularisation. Age related factors like frailty, co-morbidities and unwillingness to undergo intervention could be the reasons. Also, female patients were significantly more likely to be kept on medical management (61.3% vs 44.8% in males; $P < 0.001$) and lesser women underwent PCI 29.7% vs 35.9%; $P = 0.032$) or CABG (9.2% vs 19.4%; $P < 0.001$). Among the age strata, PCI was significantly more in older elderly which may be due to avoidance of surgery in view of age-related factors.

On follow-up, MACCE occurred in 14% patients. Women had significantly higher MACCE which however didn't reflect in survival rates. Higher bleeding events, vascular complications, decreased compliance to follow up and medication could be factors. Among those who completed 5-year hospital follow up, the MACCE was higher (22.3%) which could be more reflective.

CAD in the elderly is associated with poor prognosis. Previous studies have shown that mortality rates in older patients with STEMI have ranged from 13% to 30% at 30 days and as high as 52% at 3 years, depending on the median age, study setting, and type and frequency of interventions. Among patients >80 years of age with NSTEACS, 30-day mortality rates have ranged between 12% and 16%, and 1-year mortality rates exceeding 25% have been reported.[68] NORIN STEMI Study in which 66% had undergone PCI too had shown 11% 1-year mortality which was significantly contributed by female patients (12% vs 5% in males). Sharma et al [76] and Bhatia et al [70] conducted in acute MI patients had significantly higher in hospital Mortality in the elderly compared to non-elderly of 20.6% and 28.04% respectively. Survival rates in this study reflected very good outcomes among elderly with 1 year Mortality Rate of 4.3%, 3-year Mortality Rate of 6.9% and 5-year Mortality Rate 10.8% with no difference between men and women. Both MACCE and mortality which were significantly predicted by triple vessel disease and LV dysfunction but not the mode of presentation.

This being a tertiary center in a state with higher socioeconomic indices could have resulted in better compliance to management and follow up and hence leading to better outcomes.

Studies in elderly have shown that revascularization has better prognosis for STEMI patients while taking age-related factors into account. However, this is not clear for SIHD, NSTEACS. TIME study which recruited only elderly patients >/=75 years with SIHD showed that QOL, MACCE was better at 6 months but there no difference on longer follow up of 4 years. While GRACE, CRUSADE, TACTICS TIMI showed that invasive management is better in NSTEACS, Savonitto et al.[89] showed that there was no difference in 1-year outcomes with invasive vs conservative management. In the current study, MACCE over 3.5 year follow up and survival was significantly better with revascularization than medical management. This could be the result of revascularization leading to better outcomes among ACS patients which constituted 50 % of cases (NSTEACS 29.4% and STEMI 21.1%) while CSA was in 32 % patients. These results support revascularization in elderly patients.

In a sub-analysis of patients having significant LM (>50% lesion) or TVD, the 5 year mortality rate was significantly lower among those who underwent PCI versus medical management (12.5 % vs 27.1 %; p= 0.006) and also for CABG versus medical management (12.8% vs 27.1% ; p=0.002). CABG however had no significant difference compared to PCI in this group of patients (12.8% vs 12.5% ; p=0.939). While there was no difference in MACCE in PCI versus medical management groups but CABG had lower MACCE. This also supports revascularization over medical management.

In large studies like ISCHEMIA trial, medical management was non-inferior to revascularization in SIHD. Medical management in our population could have been sub-optimal due to various issues in elderly like decreased compliance, polypharmacy due to multimorbidity, drug-drug interactions and side effects of medication leading to suboptimal GDMT. Hence, further dedicated research in elderly is needed to decide on the optimal mode of management.

The limitations of our study were, this was a single center retrospective observational study. The risk factors contributing to CAD in elderly were not compared with a younger age group. Patients with borderline lesions on CAG which don't exactly reflect insignificant CAD were also included for comparison. Patients who were lost to follow up were contacted over telephone for outcomes which may be unreliable data and hence these patients were included only in survival analysis.

Summary

- Elderly patients are the fastest growing cohort of patients who significantly contribute to CAD mortality and morbidity especially in low- and middle-income countries like India
- Most of the patients included in the large epidemiologic and clinical studies were middle-aged. The risk factors contributing to CAD and their impact on CAD causation in the elderly appear to be different and how it varies in our population is unclear
- Our study was an observational retrospective study conducted at a tertiary care center in South India among elderly patients of more than or equal to 65 years of age admitted for CAG between 2010 and 2018 for either suspected CAD or a clinical diagnosis of CAD with an intention to determine the risk factors contributing to CAD
- A total of 3670 elderly patients who underwent CAG were screened of which 1511 patients satisfying eligibility criteria were analyzed for risk factor profile and clinical characteristics
- The mean age of total population was 69.38 (+/- 4.03) years with a male preponderance (69%)
- Prevalence of traditional risk factors were found to be high and they were comparable between the subgroups except CKD which was higher in the older subgroup of more than 75 years
- Angiographically significant CAD was present in 74.4% of patients and was significantly higher in the older subgroup of more than 75 years
- Male gender, dyslipidemia and current tobacco use were found to be contributing to angiographically significant CAD in elderly by multiple logistic regression analysis
- None of the studied risk factors were found to contribute to CAD in the older subgroup of more than 75 years

- Nearly half of the patients were kept on medical management. While angioplasty was significantly more among older subgroup, CABG was significantly more in younger subgroup
- Female patients had more atypical presentation, more prevalent risk factors, underwent significantly less revascularization and had higher MACCE
- Fourteen percent of patients with angiographically significant CAD (912 patients) developed MACCE over a median 3.5-year hospital follow up
- Survival analysis of 1027 patients with significant CAD showed a one, three, five and ten-year mortality rate of 4.3%, 6.9%, 10.8%, and 18.2% respectively
- Multivariate proportional hazard model cox regression analysis showed that left ventricular dysfunction and triple vessel disease were associated with worse survival
- Overall, MACCE and survival were significantly better among those who underwent revascularization compared to medical management
- In a sub-analysis of patients having significant left main disease (>50% lesion) or triple vessel disease also (N=389), the five-year mortality rate was significantly lower among those who underwent revascularization compared to medical management while CABG and PCI were comparable
- These results support revascularization in elderly patients but further dedicated research is needed to decide on the optimal mode of management.

Conclusion

- This retrospective observational study showed a high prevalence of traditional risk factors in elderly patients among which male gender, dyslipidaemia, current tobacco use were found to predict angiographically significant CAD.
- None of the traditional risk factors were significantly associated with CAD in the older subgroup of more than 75 years.
- MACCE and survival rates were better when compared to previous studies in this cohort of patients and were predicted by the presence of triple vessel disease and left ventricular dysfunction.
- Mortality was significantly lower among elderly who underwent revascularization compared to medical management in this study.

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Annexures

Curriculum Vitae

CV : Dr. Garikapati Vrandha, DM Trainee

Last Name **Garikapati**	First Name **Vrandha**	Middle Name
Date of Birth (dd/mm/yy) - 11/12/1992		Sex - Female
Study Site Affiliation - Principal Investigator		
Professional Mailing Address		Study Site Address
Senior Resident, Department of Cardiology, SCTIMST, Trivandrum		SCTIMST, Trivandrum
Mobile Number - 9182861314		
Email – gvrandha@gmail.com		

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, State
MD (Medicine)	2019	JIPMER, Puducherry
MBBS	2015	JIPMER, Puducherry

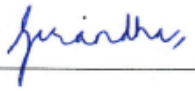
Details of professional registration:
TNMC/114612 Year of registration – 2016
TCMC/ 80834 Year of registration – 2021

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, State
January 2021	Senior Resident (Cardiology)	SCTIMST, Trivandrum
July 2016	Junior Resident (Medicine)	JIPMER, Puducherry

Brief summary of relevant research experience:
MD Thesis: The Effect of Probiotics on Ventilator Associated Pneumonia – A Randomized Controlled Trial

Current project/s at hand:

Signature: 	Date: 06/01/2022 Place: Trivandrum

IEC Approval Certificate

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1877/MAY/2022 23.03.2023

Dr. Garikapati Vrandha
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Garikapati Vrandha,

The Institutional Ethics Committee held on 13th May, 2022, reviewed and discussed your application to conduct the study titled "**RISK FACTORS FOR CORONARY ARTERY DISEASE IN THE ELDERLY**" (IEC/1877).

The following members of the Ethics Sub-committee were present at the meeting held on 13th May, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
2.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
4.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
5.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
3. *IEC Application Form*
4. *Study Proposal*
5. *Declaration form*
6. *CV of PI and Co-PIs*
7. *Proforma*
8. *SRC Recommendation*

Revised submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
3. *IEC Application Form*
4. *Study Proposal*
5. *Proforma*
6. *Patient Information Sheet in English and Malayalalam*
7. *Study Consent Form in English and Malayalam*
8. *Telephone Recruitment and Interview Script in English and Malayalam*
9. *Declaration form*
10. *CV of PI and Co-PIs*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

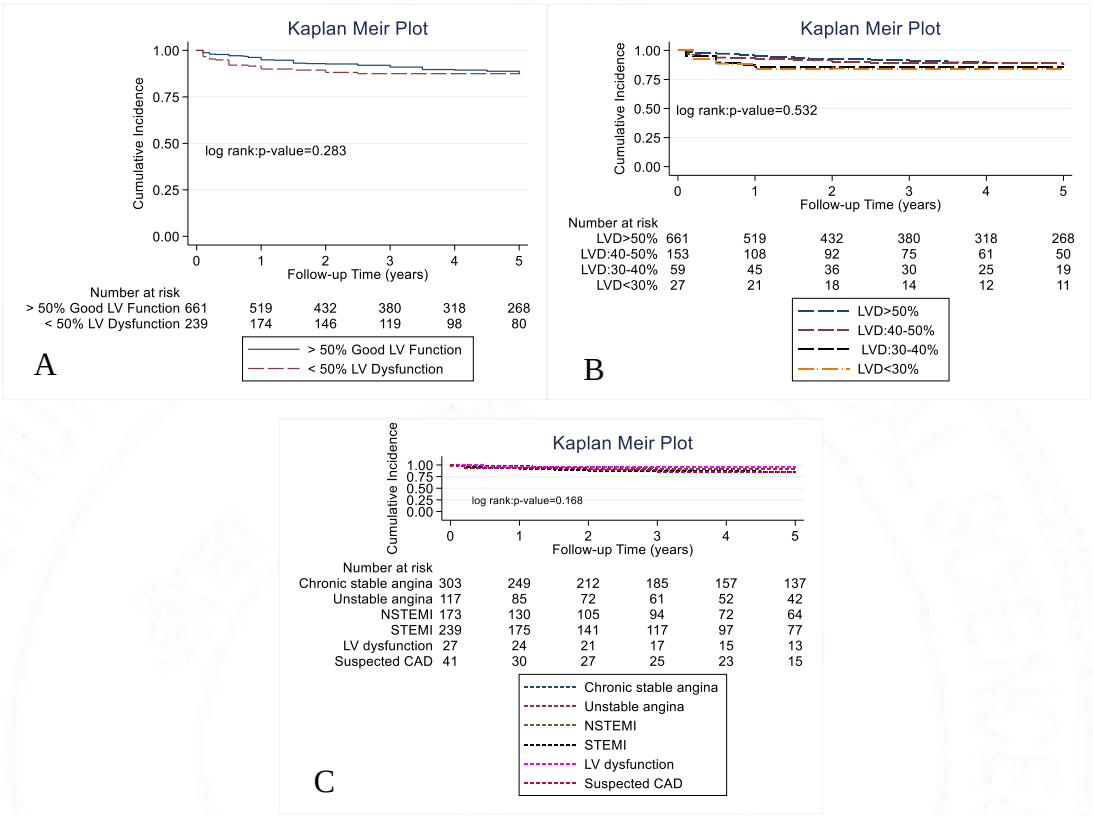
Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

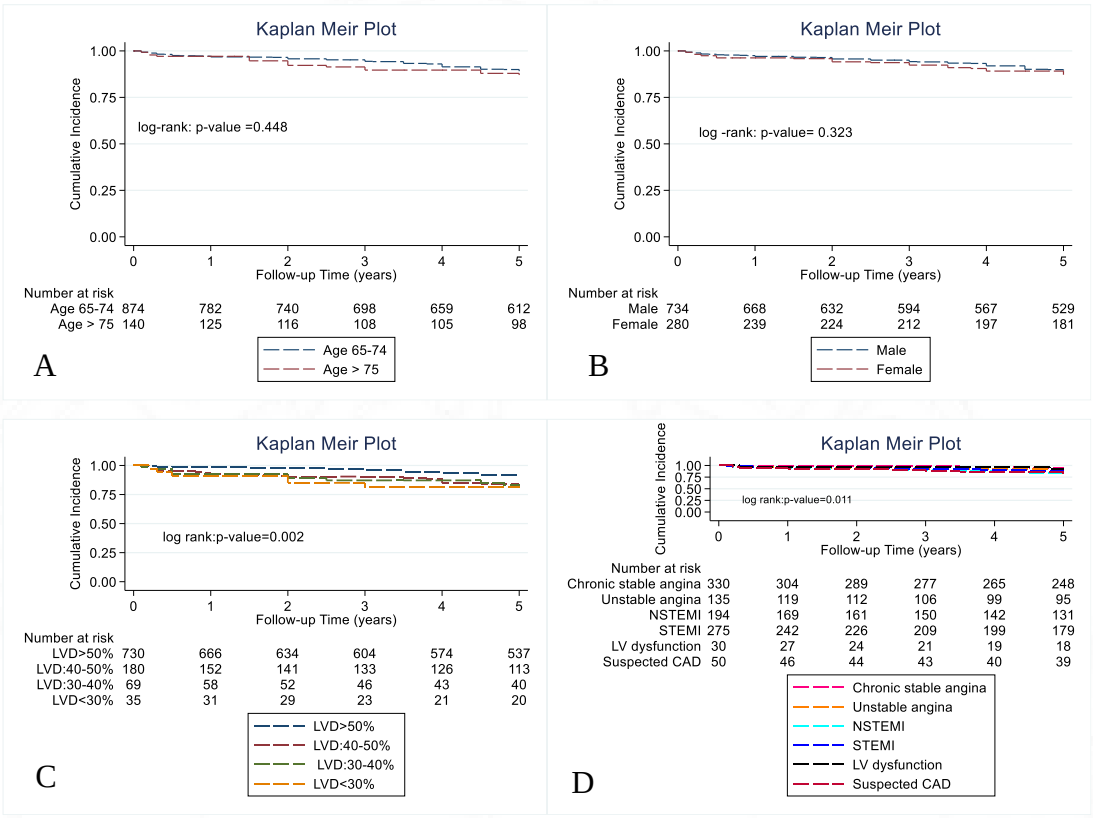
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

Supplementary Figures and Tables



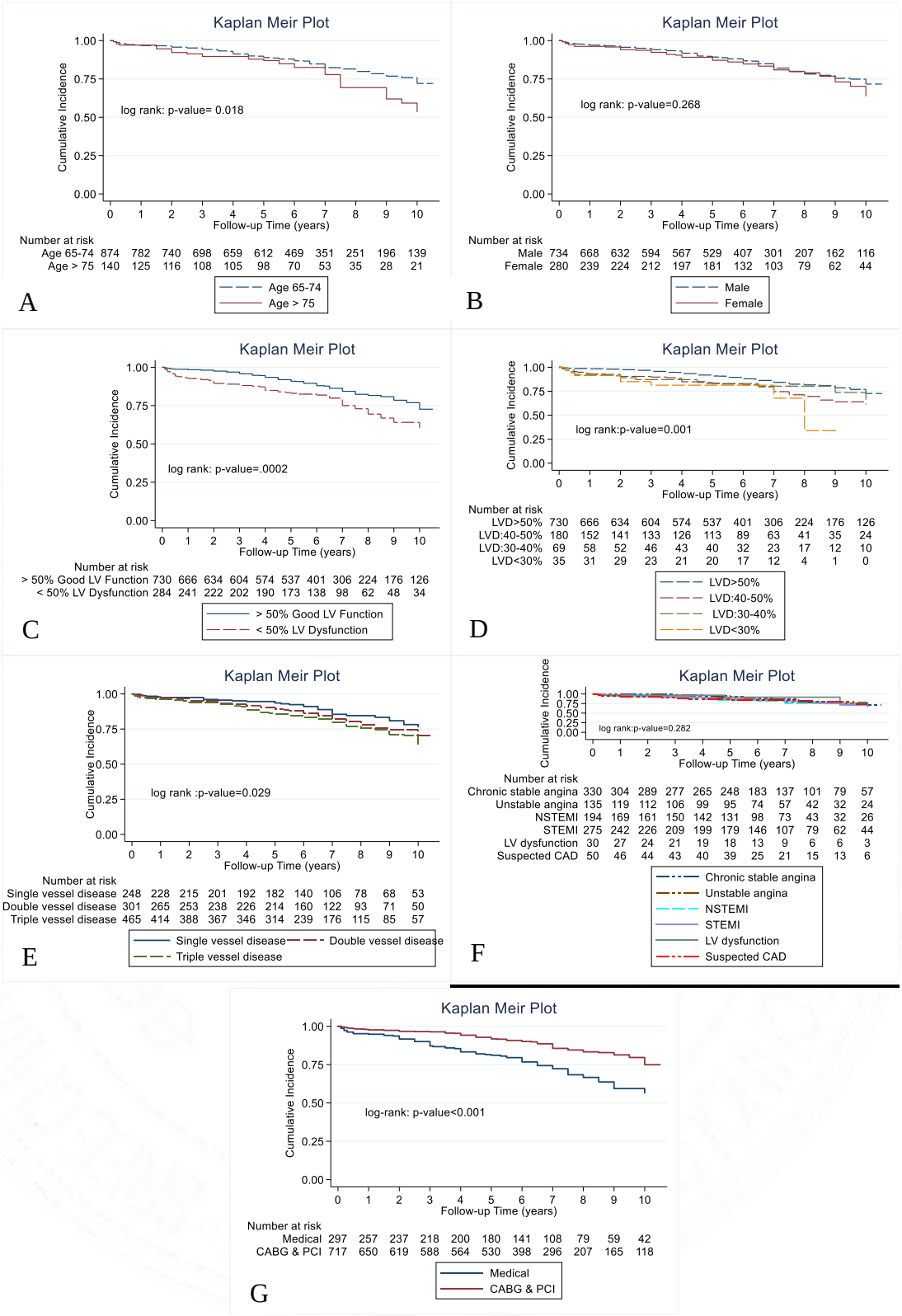
Suppl. Figure 1: Kaplan Meier curves for 5-year MACCE in patients with angiographically significant CAD (N=912) based on A. LV Dysfunction B. Degree of LV Dysfunction C. Mode of presentation



Suppl. Figure 2: Kaplan Meier curves for 5-year survival in patients with angiographically significant CAD (N=1027) based on A. Age subgroups B. Gender C. Degree of LV Dysfunction D. Mode of presentation E. Treatment strategy F. Mode of Revascularization

*13 patients had events at zero time.

**Censored data - 213 (17.6%) patients lost to follow up (didn't complete 5 years follow up)



Suppl. Figure 3: Kaplan Meier curves for 10-year survival in patients with angiographically significant CAD (N=1027) based on A. Age subgroups B. Gender C. LV Dysfunction D. Degree of LV Dysfunction E. Extent of CAD F. Mode of presentation G. Mode of treatment

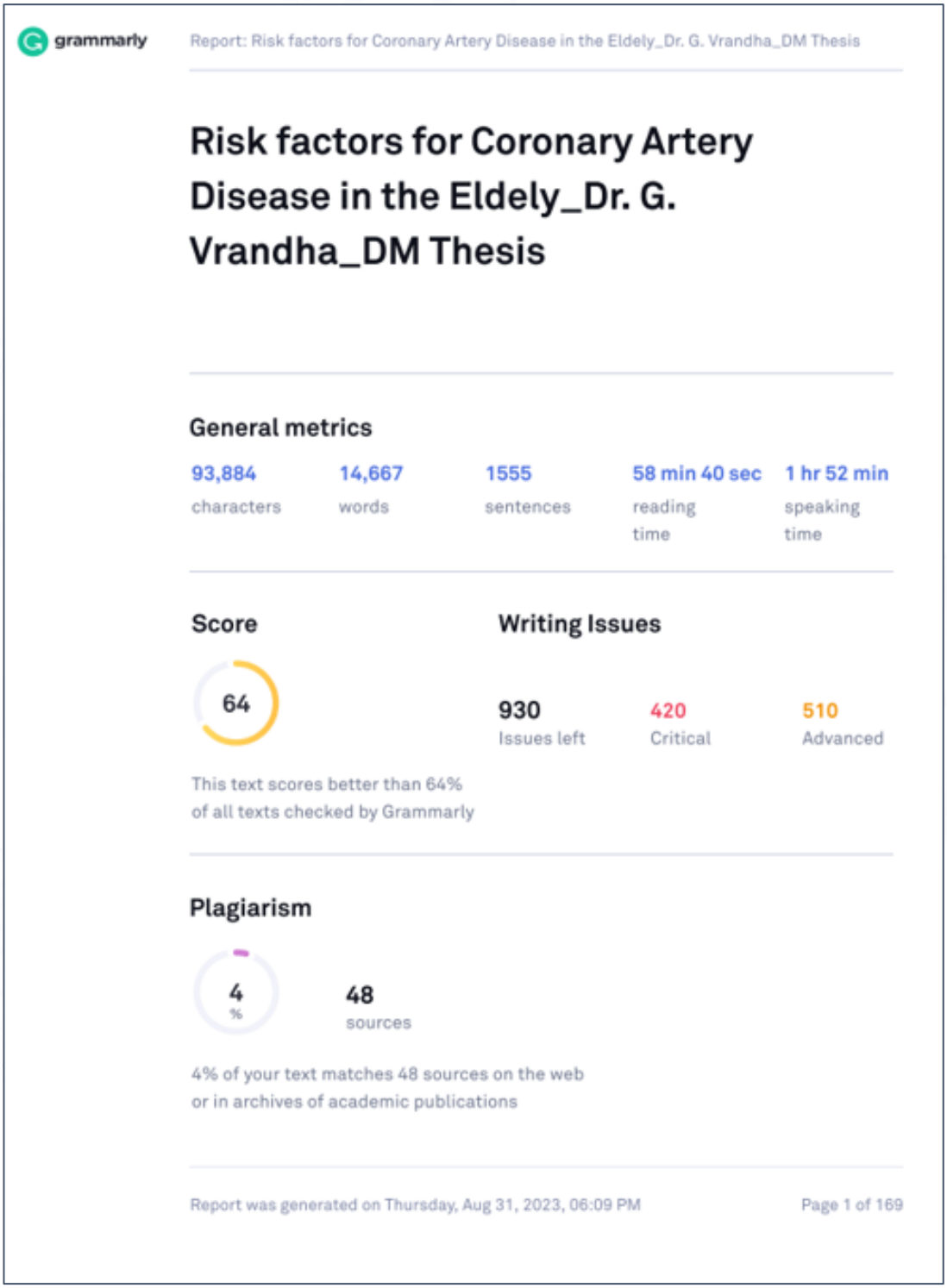
*13 patients had events at zero time.

**Censored data - 689 (57%) patients lost to follow up (didn't complete 10 years follow up)

Suppl. Table 1: Correlates of 10-year mortality in elderly with significant CAD
(Multivariate Proportional Hazard Model Cox regression analysis)

Variables	**Adjusted HR (95 % CI)**	**P value**
Female Gender	1.23 (0.78 – 1.93)	0.370
> 75 years	1.20 (0.76 – 1.90)	0.441
LV Dysfunction	1.81 (1.17 – 2.80)	**0.007**
DVD	1.44 (0.87 – 2.38)	0.151
TVD	1.65 (1.03 – 2.65)	**0.038**
PCI	**0.50 (0.33 – 0.75)**	**0.001**
CABG	**0.42 (0.26 – 0.68)**	**< 0.001**
Revascularization	**0.45 (0.33 - 0.61)**	**< 0.001**
NSTEMI	1.27 (0.77 – 2.11)	0.347
STEMI	1.14 (0.68 – 1.93)	0.612
DM	1.26 (0.89 – 1.80)	0.196
HTN	1.40 (0.95 – 2.08)	0.090
DLP	0.71 (0.50 – 1.01)	0.054
Smoking	1.31 (0.81 – 2.12)	0.276
Reformed smoker	1.16 (0.73 – 1.86)	0.524
Obesity	0.76 (0.23 – 2.48)	0.652

Plagiarism Report



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Report: Risk factors for Coronary Artery Disease in the Eldely_Dr. G. Vrandha_DM Thesis

Risk factors for Coronary Artery Disease in the Eldely_Dr. G. Vrandha_DM Thesis

General metrics

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Page 1 of 169

Consent Forms

SREE CHITRA THIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

PATIENT INFORMATION SHEET

Title: Risk Factors for Coronary Artery Disease in the Elderly

Name of Investigators: Dr. Garikapati Vrandha, Dr. Ajit Kumar V.K., Dr. Abhilash S.P.

Dear Patient/Relative/Guardian,

We welcome you and thank you for your interest in this research project titled "RISK FACTORS FOR CORONARY ARTERY DISEASE (CAD) IN THE ELDERLY". Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

CAD is a major cause of morbidity and preventable death worldwide. Increased rate of traditional risk factors with age like diabetes, hypertension, abnormal lipid profile, smoking contributes to this. In addition to this, factors associated with aging are also now found to contribute and are being studied as potential targets to prevent CAD in elderly. As older patients are the fastest growing cohort dying of CAD, further improvements in prevention, diagnosis, and treatment of CAD in this population needs attention. Despite the high prevalence, death rate of cardiovascular disease in older adults, most randomized clinical trials have either excluded older adults or have enrolled only relatively healthy older patients with few comorbidities or functional impairments. Hence, the risk factors contributing to CAD in the elderly appear to be different and needs to be studied. The current study aims to identify the risk factor profile of elderly patients more than 65 years of age with significant CAD identified by Coronary Angiogram and compare it with the population without CAD. Furthermore, a subset analysis of patients more than 75 years would help would contribute to the data on specific risk factors contributing to CAD in this population so that targeted

management can be applied to them. You will be required to have ongoing medication and follow up with a Cardiologist after your procedure.

WHAT DOES THE PRESENT STUDY INVOLVE?

The records of the Coronary Angiogram that you have undergone and other clinical follow up details will be collected from the hospital database. You will be contacted by phone/ by mail to give details of latest follow up details. You will usually come in to hospital on the day of appointment. A specialist doctor will explain the proposed study design to you and ask you to sign the consent form to confirm that you understand the procedure and agree to go ahead with it. Please ask any questions you want.

Following enrolment into the study, you will undergo the following tests- usually done as part of routine follow up evaluation:

- Functional status- History
- Electrocardiogram
- Echocardiogram
- Any other test deemed necessary as part of evaluation

HOW LONG DOES IT TAKE?

The hospital visit will be a routine consultation, and the tests done will be part of routine follow up. This may take up to 2-3 hours. Please be prepared to be in the hospital OPD during that time.

WHAT ARE THE RESPONSIBILITIES OF PARTICIPANTS?

Your decision to participate in this study is voluntary, your own personal choice. You may choose not to continue at any time, for any reason, without notice.

WHAT ARE THE EXPECTED RISKS FOR THE PARTICIPANTS?

The study involves collection of previous data from case records, and a follow up evaluation to assess the functional status and outcome of prior surgery. There will be no risks for the participants because of participation in the study. They will be managed according to the hospital protocol. No specific intervention will be done.

WHAT ARE THE EXPECTED BENEFITS OF THE RESEARCH TO THE PARTICIPANTS?

The participants are evaluated in detail for any cardiac cause for functional impairment. A follow up examination and evaluation may be helpful in identification of any risk factors for poor outcomes or functional deterioration. It may be helpful in detecting patients who require early intervention or addition of medical therapy. The data derived from the study may be helpful in planning appropriate risk prevention and medical /interventional strategies for patients with similar conditions in the future.

WILL PARTICIPANTS BE COMPENSATED FOR PARTICIPATION IN THIS TRIAL?

You will not be paid for participation in the study.

WILL MY PARTICIPATION IN THIS STUDY BE KEPT CONFIDENTIAL?

All records of your study will be kept confidential. Your identity will not be revealed in any publication or release of results. Study records will be kept indefinitely for analysis and follow-up.

CAN I WITHDRAW FROM THE STUDY AT ANY TIME DURING THE STUDY PERIOD?

Yes, you can. Your decision will not affect your regular medical care.

IF THERE ARE ANY NEW FINDINGS / INFORMATION, WOULD I BE INFORMED?

Yes.

WHAT HAPPENS IN CASE OF A STUDY RELATED INJURY?

There will be no study related injury.

IS THERE ANY ALTERNATIVE TO THE TREATMENT MENTIONED?

Not applicable.

If you have any further questions, please ask: Dr. Garikapati Vrandha (Principal investigator), Senior Resident, Department of Cardiology (Email: gvrandha@sctimst.ac.in Ph No: 9182861314). For any technical clarifications, please contact Dr. G. Srinivas, Member Secretary, IEC, SCTIMST (Email: iec.mem.sec@sctimst.ac.in, Phone no. 0471-2524234)

ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി
തിരുവനന്തപുരം

രോഗിക്കുള്ള കാര്യവിവരണപത്രം

ശീർഷകം: കൊറോണറി ആർട്ടറിരോഗത്തിന്റെ പ്രായമായവരിലെ അപായ ഘടകങ്ങൾ.
ഗവേഷകരുടെ പേര്:

ഡോ. ഗരികപതി വ്യന്ദ, ഡോ. അജിത് കുമാർ വി. കെ, ഡോ. അഭിലാഷ് എസ് പി

പ്രിയ രോഗി/ ബന്ധു/രക്ഷകർത്താവ്
കൊറോണറി ആർട്ടറിരോഗത്തിന്റെ പ്രായമായവരിലെ ആപായ ഘടകങ്ങൾ എന്ന പഠനത്തിലേയ്ക്ക് താങ്കളെ സ്വാഗതം ചെയ്യുകയും, താങ്കൾ കാണിച്ച താത്പര്യത്തിന് നന്ദിപ്രകാശിപ്പിക്കുകയും ചെയ്യുന്നു. ഈ ഗവേഷണ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കൾ തീരുമാനിക്കുന്നതിനു മുൻപ് എന്തുകൊണ്ടാണ് ഈ പഠനം നടത്തുന്നത് എന്ന് മനസ്സിലാക്കേണ്ടത് പ്രധാനമാണ്. പഠനത്തിന്റെ പ്രസക്തമായ വിവരങ്ങൾ കാര്യവിവരണ പത്രം നൽകും. എങ്ങനെ നടത്തുന്നു, പഠനത്തിന്റെ സ്വഭാവം, ഉദ്ദേശം, നേട്ടങ്ങൾ അപായങ്ങൾ, അസ്വസ്ഥതകൾ മുൻകരുതലുകൾ എങ്ങനെയാണ് ഈ പദ്ധതി നടപ്പിലാക്കുന്നത് എന്നതിന്റെ വിവരങ്ങൾ എന്നിവ അത് വിശദീകരിക്കും. താങ്കൾ ഇത് ശ്രദ്ധയോടെ വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടത് പ്രധാനമാണ്. ഈ പത്രികയിൽ ചില ശാസ്ത്രീയ പദങ്ങളുണ്ടായേക്കാം, ആകയാൽ പഠനത്തിന് സമ്മതം നൽകുന്നതിന് മുമ്പോ പഠനകാലത്ത് ഏതുസമയത്തുമോ, താങ്കൾക്കെന്തെങ്കിലും സംശയങ്ങളുണ്ടെങ്കിലോ കൂടുതൽ ചോദ്യങ്ങളുണ്ടെങ്കിലോ താങ്കൾക്ക് പഠനം നടത്തുന്നവരോടോ, താഴെ ബന്ധപ്പെടാനായി നൽകിയിരിക്കുന്നവരോടോ ചോദിക്കുന്നതിന് സ്വാതന്ത്ര്യമുണ്ട്.

ലോകത്തെമ്പാടും രോഗാവസ്ഥയുടെയും തടയാനാകുന്ന മരണത്തിന്റെയും ഒരു പ്രധാനകാരണമാണ് സിഎഡി. പ്രായാധിക്യത്തോടൊപ്പമുള്ള പ്രമേഹം, രക്താതിസമ്മർദ്ദം, അസാധാരണമായ ലിപിഡ് രൂപരേഖ, പുകവലി എന്നീ പരമ്പരാഗത അപായങ്ങളുടെ വർദ്ധനവ് എന്നിവ ഇതിന് സഹായകമാകുന്നു. അതിനൊപ്പം, പ്രയമാകുന്നതുമായി ബന്ധപ്പെട്ട ഘടകങ്ങളുംഇതിൽ പങ്കുവഹിക്കുന്നു എന്ന് കണ്ടെത്തപ്പെട്ടത് സിഎഡി തടയാൻ ഉദ്ദേശിക്കുന്ന പഠനലക്ഷ്യമാകുന്നതിന് സാദ്ധ്യതയുണ്ട്. സിഎഡിയാൽ മരണപ്പെടുന്നവരുടെ സംഘത്തിൽ പ്രായമായവരുടെ എണ്ണമാണ് ഏറ്റവും വേഗം വർദ്ധിക്കുന്നത് എന്നതിനാൽ, സിഎഡി തടയുന്നതിലും, രോഗനിർണ്ണയത്തിലും ചികിത്സയിലും ഈ വിഭാഗത്തിൽ കൂടുതൽ ശ്രദ്ധ ആവശ്യമാണ്. പ്രായമായവരുടെ മരുണ നിരക്കിൽ ഉയർന്ന വ്യാപനമുണ്ടായിട്ടും മിക്ക് ക്രമാനുഗതമല്ലാത്ത പരീക്ഷണങ്ങളും പ്രായമായവരെ ഒഴിവാക്കുകയോ താരതമ്യേനെ ആരോഗ്യമുള്ള കുറച്ചുമാത്രം അനുബന്ധരോഗങ്ങളോ പ്രവർത്തനപരമായ വൈകല്യങ്ങളോ മാത്രം ഉള്ള പ്രായമായവരെമാത്രം ഉൾപ്പെടുത്തുകയോചെയ്തു. ആകയാൽ പ്രായമായവരിലെ സിഎഡിക്ക് ആക്കം കൂട്ടുന്ന അപായഘടകങ്ങൾ വ്യത്യസ്ഥമാണെന്ന് കാണുന്നതിനാൽ അത് പഠിക്കേണ്ടതുണ്ട്. കൊറോണറി ആൻജിയോഗ്രാം വഴി കണ്ടെത്തിയ

നിർണ്ണായകമായ സിഎഡിയുള്ള 65 വയസ്സിലേറെ പ്രായമുള്ള രോഗികളുടെ അപായ ഘടക രൂപരേഖ കണ്ടെത്തുകയും അത് സിഎഡിയില്ലാത്ത ജനവിഭാഗവുമായി താരതമ്യം ചെയ്യുകയും ലക്ഷ്യമിടുന്നതാണ് ഈ പഠനം. തന്നെയുമല്ല, 75 വയസ്സിലേറെ പ്രായമുള്ള രോഗികളെ വിലയിരുത്തുന്ന ഒരു ഉപവിഭാഗം പ്രത്യേകമായ അപായഘടകങ്ങളെപ്പറ്റിയുള്ള വിവരങ്ങളെ ശക്തിപ്പെടുത്തുകയും സിഎഡിയുള്ള ജനവിഭാഗത്തിൽ കൈകാര്യംചെയ്യാൻ നടപ്പാക്കുകയും ചെയ്യാനാകും. താങ്കളുടെ ചികിത്സയ്ക്ക് ശഷം തുടരെയുള്ള മരുന്നും ഒരു കാർഡിയോളജിസ്റ്റിന്റെ തുടർ ചികിത്സയും ചെയ്യേണ്ടതാവശ്യമാണ്.

ഈ പഠനത്തിൽ ഉൾക്കൊള്ളുന്നവയെന്ത്?
ആശുപത്രിയുടെ വിവരശേഖരണിയിൽ നിന്നും താങ്കൾ വിധേയമായ കൊറോണറി ആൻജിയോഗ്രാം വിവരങ്ങളും, ക്ലിനിക്കൽ, തുടർചികിത്സാ വിവരങ്ങളും ശേഖരിക്കും. താങ്കളെ ഫോൺ/ഇമെയിൽ വഴി് പുതിയ തുടർചികിത്സാ വിവരങ്ങൾക്കായി ബന്ധപ്പെടും. താങ്കളുടെ അപ്പോയിന്റ്മെന്റ് ദിവസം സാധാരണ താങ്കൾ ആശുപത്രിയിൽ വരും. ഒരു സ്പെഷ്യലിസ്റ്റ് ഡോക്ടർ ഉദ്ദേശിക്കുന്ന പഠനപരിപാടി വിശദീകരിക്കുകയും നടപടികളെപ്പറ്റി താങ്കൾക്ക് മനസ്സിലായി എന്നും പങ്കെടുക്കുന്നതിന് സമ്മതം എന്നുമുറപ്പിക്കാൻ ഒരു സമ്മതപത്രം ഒപ്പിടാൻ ആവശ്യപ്പെടും. താങ്കൾക്കാവശ്യമുള്ള ഏതു ചോദ്യവും ദയവായി ചോദിക്കുക.

പഠനത്തിൽ ഉൾപ്പെടുത്തപ്പെട്ടശേഷം സാധാരണയായി താങ്കളുടെ തുടർചികിത്സാ വിലയിരുത്തലിന്റെ ഭാഗമായി ചെയ്യുന്ന താഴെപ്പറയുന്ന പരിശോധനകൾക്ക് താങ്കൾ വിധേയമാകും.
പ്രവർത്തന നിലവാരം- ചരിത്രം
ഇലക്ട്രോകാർഡിയോഗ്രാം
എക്കോകാർഡിയോഗ്രാം
വിലയിരുത്തലിന്റെ ഭാഗമായി ആവശ്യമാകുന്ന മറ്റ് പരിശോധനകൾ

ഇതിനെത്ര സമയമെടുക്കും?
ആശുപത്രി സന്ദർശനവും, പരിശോധനകളും തുടർ ചികിത്സയുടെ ഭാഗമാണ്. ഇതിന് 2-3 മണിക്കൂറെടുത്തേക്കാം. ആസമയത്ത് ഒപിഡിയിലുണ്ടാകാൻ ദയവായി തയ്യാറാകുക.

പങ്കെടുക്കുന്നവരുടെ ഉത്തരവാദിത്തങ്ങളെന്തെല്ലാം?
താങ്കളുടെ പഠനത്തിലെ പങ്കാളിത്തം സ്വമേധയാ ആണ്, താങ്കളുടെ വ്യക്തിപരമായ തീരുമാനം. മുന്നറിയിപ്പില്ലാതെ ഏതു കാരണത്താലും ഏതു സമയത്തും താങ്കൾക്ക് പിൻമാറാം.

പങ്കാളികൾക്ക് പ്രതീക്ഷിക്കുന്ന അപായങ്ങളെന്തെല്ലാം?
മുൻകാലത്തെ വിവരങ്ങളും, പ്രവത്തന നിലവാരവും മുൻപ് നടത്തിയ ശസ്ത്രക്രിയയുടെ നേട്ടങ്ങളും വിലയിരുത്താനുള്ള അപഗ്രഥനത്തിനന്റെ വിവരങ്ങളും ശേഖരിക്കുകയാണ് പഠനത്തിൽ ചെയ്യുന്നത്. പഠനത്തിൽ പങ്കെടുക്കുന്നതു കൊണ്ട് പങ്കാളികൾക്ക് ഈ പഠനത്തിന്റെ ഭാഗമായി അപായമൊന്നുമുണ്ടാകുന്നില്ല. അവരെ ആശുപത്രി നടപടിക്രമമനുസരിച്ച് കൈകാര്യം ചെയ്യും. പ്രത്യേകമായ ഒരു ഇടപെടലും നടത്തില്ല.

പങ്കാളികൾക്ക് ഗവേഷണത്തിൽനിന്നും പ്രതീക്ഷിക്കുന്ന നേട്ടങ്ങളെന്തെല്ലാം?
പങ്കെടുക്കുന്നവരുടെ പ്രവർത്തനപരമായ തകരാറുകൾക്കുള്ള ഹൃദയപരമായ കാരണങ്ങൾ വിശദമായി വിലയിരുത്തപ്പെടും.മോശം നേട്ടങ്ങളോ പ്രവർത്തനപരമായ തകരാറുകളോ

കണ്ടെത്തുന്നതിന് തുടർ പരിശോധനയും വിലയിരുത്തലും സഹായകമായേക്കാം. ഇത് നേത്തേയുള്ള ഇടപെടലോ മരുന്നു ചികിത്സയോ ആവശ്യമുള്ള രോഗികളെ തിരിച്ചറിയുന്നതിന് സഹായകമായേക്കാം. പഠനത്തിൽനിന്നും ഉരുത്തിരിയുന്ന വിവരങ്ങൾ, സമാനമായ അവസ്ഥയുള്ള രോഗികൾക്ക് അനുഗുണമായ ശസ്ത്രക്രിയാതന്ത്രങ്ങൾ ഭാവിയിൽ രൂപപ്പെടുത്താനും സഹായകമാകും.

ഈ പരീക്ഷണത്തിൽ പങ്കെടുക്കുന്നവർക്ക് നഷ്ടപരിഹാരം നൽകുമോ?
പഠനത്തിൽ പങ്കെടുക്കുന്നതിന് താങ്കൾക്ക് പണം നൽകില്ല.

എന്റെ പങ്കാളിത്തം രഹസ്യമായി സൂക്ഷിക്കുമോ?
താങ്കളുടെ എല്ലാ രേഖകളും രഹസ്യമായി സൂക്ഷിക്കും. പ്രസിദ്ധീകരണങ്ങളിലോ പ്രസിദ്ധീകരിക്കുന്ന ഫലങ്ങളിലോ താങ്കളുടെ കുട്ടിയുടെ വ്യക്തിവിവരങ്ങൾ പ്രസിദ്ധീകരിക്കില്ല. പഠനരേഖകൾ വിശകലനത്തിനും തുടർച്ചക്കുമായി നീണ്ടകാലത്തേക്ക് സൂക്ഷിക്കും.

പഠനകാലയളവിലെപ്പോൾ വേണമെങ്കിലും എനിക്ക് പഠനത്തിൽനിന്നും പിൻവാങ്ങാനാകുമോ?
താങ്കൾക്ക് കഴിയും. താങ്കളുടെ തീരുമാനം താങ്കളുടെ പതിവ് വൈദ്യപരിചരണത്തെ ബാധിക്കില്ല.

പുതിയ കണ്ടെത്തലുകൾ/വിവരങ്ങൾ എന്തെങ്കിലുമുണ്ടെങ്കിൽ അറിയിക്കുമോ?
അറിയിക്കും.

പഠനസംബന്ധമായ പരിക്കുണ്ടായാലെന്ത് സംഭവിക്കും?
പഠനസംബന്ധമായി പരിക്കൊന്നുമുണ്ടാവില്ല.

സൂചിതമായ ചികിത്സക്ക് പകരമെന്തെങ്കിലുമുണ്ടോ?
ബാധകമല്ല

താങ്കൾക്ക് കൂടുതലെന്തെങ്കിലും ചോദിക്കാനുണ്ടെങ്കിൽ ചോദിക്കാവുന്നതാണ്. ഡോ ഗരികാപടി വൃന്ദ (പ്രധാന ഗവേഷകൻ) സീനിയർ റസിഡന്റ്, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് കാർഡിയോളജി (ഇമെയിൽ. gvrandha@sctimst.ac.in, ഫോൺ. 9182861314

എന്തെങ്കിലും സാങ്കേതിക വിശദീകരണങ്ങൾക്ക് ദയവായി ബന്ധപ്പെടുക. ഡോ. ശ്രീനിവാസ് ജി, മെമ്പർസെക്രട്ടറി, SCTIMST, അഡീഷണൽ പ്രൊഫസർ AMCHSS, ഇമെയിൽ. iec.memsec.@sctimst.ac.in ഫോൺ 04712524689

STUDY CONSENT FORM

Title Of The Study: Risk Factors for Coronary Artery Disease in the Elderly

Participant's name:

Date of Birth / Age (in years):

I_____, son/daughter of

[ ] Declare that I have read the above information provided to me regarding the study: "Risk Factors for Coronary Artery Disease in the Elderly" and have clarified any doubts that I had.

[ ] I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights.

[ ] I understand that the study staff and institutional ethics committee members may not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.

[ ] I understand that my identity may not be revealed in any information released to third parties or published.

[ ] I voluntarily agree to take part in this study.

[ ] I received a copy of this signed consent form.

Name: Name of witness:

Signature: Relation to participant:

Date: Date:

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name and Signature of Person Obtaining Consent

Dr. Garikapati Vrandha
Senior resident
Dept. of Cardiology SCTIMST

For any technical clarifications, please contact Dr. G. Srinivas, Member Secretary, IEC, SCTIMST (Email: iec.mem.sec@sctimst.ac.in, Phone no. 0471-2524234)

പഠന സമ്മതപത്രം

ശീർഷകം: കൊറോണറി ആർട്ടറിരോഗത്തിന്റെ പ്രായമായവരിലെ അപായ ഘടകങ്ങൾ.
ഗവേഷകരുടെ പേര്:

ഡോ. ഗരികപടി വ്യന്ദ, ഡോ. അജിത് കുമാർ വി. കെ, ഡോ. അഭിലാഷ് എസ് പി

പങ്കാളിയുടെ പേര്. ജനനതീയതി/വയസ്സ്(വർഷത്തിൽ)

ഞാൻ..... (മകൻ/മകൾ.....
..... (ദയവായി ബോക്സുകളിൽ ശരിയടയാളമിടുക)

- കൊറോണറി ആർട്ടറിരോഗത്തിന്റെ പ്രായമായവരിലെ ആപായ ഘടകങ്ങൾ. എന്ന പഠനവുമായി ബന്ധപ്പെട്ട മുകളിൽ നൽകിയ വിവരങ്ങൾ ഞാൻ വായിക്കുകയും എനിക്കുണ്ടായിരുന്ന സംശയങ്ങൾ പരിഹരിക്കുകയും ചെയ്തു [ ]
- എന്റെ ഈ പഠനത്തിലുള്ള പങ്കാളിത്തം പൂർണ്ണമായും സ്വമേധയായാണെന്നും അനുവാദം എനിക്ക് ഏതുസമയത്തും എന്റെ ചികിത്സയെയും നിയമപരമായ അവകാശങ്ങളെയും ബാധിക്കാതെ പിൻവലിക്കാൻ അവകാശമുണ്ടെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.[ ]
- ഞാൻ ഈ പഠനത്തിൽ നിന്നും പിൻമാറിയാലും പഠനം നടത്തുന്നവർക്കും സ്ഥാപനത്തിലെ നൈതിക കമ്മിറ്റി അംഗങ്ങൾക്കും എന്റെ ആരോഗ്യരേഖകൾ പരിശോധിക്കുന്നതിന് എന്റെ അനുവാദം ആവശ്യമില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. അതിനോട് ഞാൻ യോജിക്കുന്നു.[ ]
- എന്നെ തിരിച്ചറിയാനുതകുന്ന വിവരങ്ങൾ ഒന്നും മറ്റുള്ളവർക്കു നൽകുകയോ പ്രസിദ്ധീകരിക്കുകയോ ചെയ്യില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- ഞാൻ സ്വമേധയാ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുന്നു [ ]
- സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു കോപ്പി എനിക്കു കിട്ടി [ ]

പങ്കെടുക്കുന്നയാളുടെപേര് സാക്ഷിയുടെ പേര്

ഒപ്പ്
തീയതി

സാക്ഷിയുടെ ഒപ്പ്
തീയതി

രോഗിയുമായുള്ള ബന്ധം

(സമ്മതം വാങ്ങുന്നയാൾ)

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതപത്രം വാങ്ങുന്ന ആളുടെ പേര്
ഡോ. ഗരികാപടി വൃന്ദ
സീനിയർ റെസിഡന്റ്
ഡിപ്പാർട്ട്മെന്റ് ഓഫ് കാർഡിയോളജി
എന്തെങ്കിലും സാങ്കേതിക വിശദീകരണങ്ങൾക്ക് ദയവായി ബന്ധപ്പെടുക. ഡോ. ശ്രീനിവാസ് ജി, മെമ്പർസെക്രട്ടറി, SCTIMST, അഡീഷണൽ പ്രൊഫസർ AMCHSS, ഇമെയിൽ. iec.memsec.@sctimst.ac.in ഫോൺ 04712524689

Sree Chitra Tirunal Institute of Medical Science and Technology, Thiruvananthapuram, Kerala

TELEPHONE RECRUITMENT AND INTERVIEW SCRIPT

Title of the Study: Risk Factors for Coronary Artery Disease in the Elderly

Hello, my name is Dr. G. Vrandha. I'm calling from Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) about a research study. Am I speaking to _____ (name of recruit) or his/ her relative?

If "no," wait for recruit to pick up, leave a message, or ask for a time to call back.
If "yes":
I got your phone number from the hospital records. Is this a good time to talk?

Arrange to call at another time, if appropriate.
I'm calling about a research study of a condition that you/your family member has entitled " Risk Factors for Coronary Artery Disease in the Elderly
The purpose of this research study is to learn more about the risk factors contributing to Coronary Artery Disease in the older age group, long term outcome of the condition in you/ your family member. Joining a research study is completely voluntary. If it's alright with you I'd like to take about 2-3 minutes to explain the basic idea of the study and to see if you would be interested in you/your family member taking part.

If you agree to participate, we will analyze the data of you or your family member stored in our hospital record and when you to come to the Cardiology OPD for your regular follow up, we would like to interview about your current clinical status i.e, symptoms, risk factor control, drug usage and also would like to assess for the presence of any co morbidities or new complications. If you or your family member have lost to our follow up, we would like to know if you could come for a repeat visit at your convenience. If it is not possible for you to come for a visit, we would like to take a telephonic interview about your current status with your consent at your convenient time. We will access and analyze your hospital data if you will give your consent for the same. As we will analyze your data with your consent without any intervention, there will be no risks for the participants because of participation in the study. No specific intervention will be done. The participants data will be analyzed in detail for more knowledge in Coronary Artery Disease risk factors – long term follow up status. A follow up examination and evaluation may be helpful if you have symptomatic recurrence or co existing other diseases and this follow up will be a routine assessment.

We will do our best to keep your information confidential by not mentioning your identity and keeping the records on a password-protected computer. If you do not want to give permission to analyze your medical records at any point of time you can choose to stop at any time without penalty. If you have questions about the study, you can call me at 9182861314. If you have questions about your rights as a research subject or technical clarifications, you can call Dr. G. Srinivas, Member Secretary, IEC, SCTIMST (Email: iec.mem.sec@sctimst.ac.in, Phone no. 0471-2524234)
If accepting: Document eligibility response and make appointment, if appropriate.

If the patient has expired and relative replies that "He/ She is no more/ has expired"
I'm sorry to hear about his/her demise. Can you tell me the time of death and the details about the cause of death? If you are agreeable, can we go through the hospital records of this person?
If yes: Thank you. The details might be helpful in preventing similar complications in other people. Thank you for your time.
If *no*: That's perfectly understandable. Thank you for your time.

TELEPHONIC SCRIPT FOR FOLLOW UP		
Serial No		
Date of Assessment		
Name		Age
Hospital Number		Sex
Date of registration		Age at registration
Risk factor profile:	• DM • CKD • Cerebrovascular Disease • Malignancy • Dementia • Anemia • Alcohol use • HTN • Lipid profile • Smoking status • Family history • Obesity / BMI / Other co-morbidities	
Follow up details	• Drug adherence	

	• Risk Factor Control and latest lab results • Events after last follow up visit and their time of occurrence: Acute Coronary event / Need for repeat revascularisation / Heart Failure hospitalisation / Stroke
Details about Mode of Presentation for any Recent Coronary events	• Symptoms at presentation – Typical / Atypical • Diagnosis – CSA/USA/NSTEMI/STEMI • HF / Cardiogenic Shock • Trop T • Pro-BNP
CAG Details if done	• Significant / Not • Vessel Involvement • Severity, LAD / LM Involvement
Management details	• Thrombolysis done or not • PCI / CABG / Medical

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, തിരുവനന്തപുരം

പഠന സമ്മതപത്രം

ശീർഷകം: കൊറോണറി ആർട്ടറിരോഗത്തിന്റെ പ്രായമായവരിലെ അപായ ഘടകങ്ങൾ.

ഗവേഷകരുടെ പേര്:

ഹലോ, എന്റെ പേര് ഡോ. ഗരികപടി വൃന്ദ എന്നാണ്. ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജിയിൽ നിന്നും ഒരു ഗവേഷണപഠനത്തിനായി വിളിക്കുകയാണ്. എനിക്ക് ..... (പഠനത്തിലുൾപ്പെടുത്താനദ്ദേശിക്കുന്നയാളുടെ പേര്) ആയോ അല്ലെങ്കിൽ അവരുടെ രക്ഷിതാക്കളുമായോ സംസാരിക്കാനാകുമോ?
ഇല്ലെങ്കിൽ പങ്കെടുപ്പിക്കാനുദ്ദേശിക്കുന്നയാൾ ഫോണെടുക്കുന്നതുവരെ കാക്കുക, അല്ലെങ്കിൽ വീണ്ടും വിളിക്കാൻ പറ്റിയ സമയം ചോദിക്കുക
ആണെങ്കിൽ:
ആശുപത്രി രേഖകളിൽനിന്നാണ് എനിക്ക് താങ്കളുടെ ഫോൺ നമ്പർ കിട്ടിയത്. ഇത് സംസാരിക്കാൻ പറ്റിയ സമയമാണോ.
അനുയോജ്യമെങ്കിൽ, മറ്റൊരു സമയത്ത് വിളിക്കാൻ ഏർപ്പാടുചെയ്യുക.

താങ്കളോ താങ്കളുടെ കുടുംബാംഗത്തിനോ ഉള്ള ഒരു രോഗാവസ്ഥയുമായി ബന്ധപ്പെട്ട കൊറോണറി ആർട്ടറിരോഗത്തിന്റെ പ്രായമായവരിലെ അപായ ഘടകങ്ങൾ **എന്ന** ഒരു ഗവേഷണ പഠനത്തിനായാണ് ഞാൻ വിളിക്കുന്നത്.

പ്രായമായവരിലെ കൊറോണറി ആർട്ടറി രോഗത്തിന് കാരണമാകുന്ന അപായഘടകങ്ങളെപ്പറ്റിയും താങ്കൾക്ക് താങ്കളുടെ കുടുംബാംഗത്തിന് ആ അവസ്ഥയ്ക്ക് ഉണ്ടായ ദീർഘകാല നേട്ടങ്ങളെപ്പറ്റി യും ഇപ്പോഴത്തെ അവസ്ഥയെപ്പറ്റിയും കൂടുതലറിയുക എന്നതാണ് ഈ ഗവേഷണ പഠനത്തിന്റെ ഉദ്ദേശം. ഗവേഷണന പഠനത്തിൽ പങ്കെടുക്കുന്നത് പൂർണ്ണമായും സ്വമേധയായാണ്. താങ്കളോ /താങ്കളുടെ കുടുംബാംഗമോ പഠനത്തിൽ പങ്കെടുക്കാൻ താത്പര്യപ്പെടുന്നുണ്ടോ എന്നറിയാൻ, പഠനത്തിന്റെ അടിസ്ഥാന ആശയം വിശദീകരിക്കാൻ ഞാൻ 2-3 മിനിട്ട് എടുക്കുന്നതിൽ കുഴപ്പമില്ലല്ലോ.

താങ്കൾ പതിവ് തുടർചികിത്സയ്ക്കായി കാർഡിയോളജി ഒപിയിൽ വരുമ്പോൾ താങ്കളുടെ ഇപ്പോഴത്തെ അവസ്ഥയെപ്പറ്റിയറി, അതായത്, ലക്ഷണങ്ങൾ, അപായ ഘടകങ്ങളുടെ നിയന്ത്രണം, മരുന്നിന്റെ ഉപയോഗം എന്നിവ സംബന്ധമായി ഒരു അഭിമുഖം നടത്തുകയും അനുബന്ധരോഗങ്ങളോ പുതിയ സങ്കീർണ്ണതകളോ ഉണ്ടോയെന്ന് വിലയിരുത്തുകയും ചെയ്യും. താങ്കളുടെ/ താങ്കളുടെ കുടുംബാംഗത്തിന്റെ തുടർ ചികിത്സ നഷ്ടപ്പെട്ടിട്ടുണ്ടെങ്കിൽ, താങ്കൾക്ക് സൗകര്യപ്രദമായി വീണ്ടുമുള്ള പരിശോധനയ്ക്ക് വരാനാകുമോ എന്നറിയാൻ ഞങ്ങൾക്ക് താത്പര്യമുണ്ട്. അതിന് കഴിയില്ലെങ്കിൽ, താങ്കൾ സമ്മതിക്കുമെങ്കിൽ ഇപ്പോഴത്തെ അവസ്ഥയെപ്പറ്റി താങ്കളുടെ സൗകര്യത്തിനനുസരിച്ച് ടെലിഫോൺ വഴി താങ്കളുമായി ഒരഭിമുഖം നടത്താൻ ഞങ്ങൾക്ക് താത്പര്യമുണ്ട്. താങ്കൾ സമ്മതിക്കുകയാണെങ്കിൽ, ആശുപത്രിയിലെ താങ്കളുടെ ചികിത്സാവിവരങ്ങൾ ഞങ്ങൾ വിശകലനം ചെയ്യും. ഞങ്ങൾ വിവരങ്ങൾ വിശകലനംചെയ്യുന്നത് ഇടപെടലുകളൊന്നുമില്ലാതെയാകയാൽ ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് ഒരപായവുമുണ്ടാകില്ല. പ്രത്യേകിച്ച് ഒരിടപെടലുമുണ്ടാകില്ല. കൊറോണറി ആർട്ടറി രോഗത്തിന്റെ അപായഘടകങ്ങളെപ്പറ്റിയും ദീർഘകാല തുടർചികിത്സാ നിലവാരത്തെത്തപ്പറ്റിയും കൂടുതൽ അറിയാൻ പങ്കെടുക്കുന്നവരുടെ വിവരങ്ങൾ വിശദമായി വിലയിരുത്തും. താങ്കൾക്ക് ലക്ഷണങ്ങൾ വീണ്ടുമുണ്ടാകുകയോ, മറ്റ് രോഗങ്ങളുണ്ടെങ്കിലോ ഒരു തുടർ ചികിത്സാ പരിശോധനയും വിലയിരുത്തലും താങ്കൾക്ക് സഹായകരമാകും, ഇത് പതിവ് തുടർചികിത്സയും വിലയിരുത്തലുമാകും,.

താങ്കളുടെ വ്യക്തിവിവരങ്ങൾ രേഖപ്പെടുത്താതെ രേഖകൾ പാസ്‌വേർഡിനാൽ സംരക്ഷിക്കപ്പെട്ട കമ്പ്യൂട്ടറിൽ സൂക്ഷിച്ച് താങ്കളെപ്പറ്റിയുള്ള വിവരങ്ങൾ രഹസ്യമാക്കിവയ്ക്കാൻ ഞങ്ങൾ പരമാവധി പരിശ്രമിക്കും. പിഴയൊന്നും കൂടാതെ താങ്കൾക്ക് ഏതുസമയത്തും പങ്കാളിത്തം അവസാനിപ്പിക്കാം. പഠനത്തെപ്പറ്റി ചോദ്യങ്ങളുണ്ടെങ്കിൽ താങ്കൾക്ക് എന്നെ 9182861314 എന്ന നമ്പറിൽ ബന്ധപ്പെടാം. ഗവേഷണപങ്കാളിയെന്നനിലയിലുള്ള താങ്കളുടെ അവകാശങ്ങളെപ്പറ്റിയുള്ള ചോദ്യങ്ങൾക്കോ, സാങ്കേതിക വിശദീകരണങ്ങൾക്കോ താങ്കൾക്ക് ബന്ധപ്പെടാഡോ. ശ്രീനിവാസ് ജി മെമ്പർ സെക്രട്ടറി, IEC, SCTIMST,. ഫോൺ നമ്പർ 0471-2524689, ഇമെയിൽ iec.mem.sec@sctimst.ac.in

സമ്മതിക്കുന്നെങ്കിൽ, അനയോജ്യമാണെങ്കിൽ യോഗ്യത രേഖപ്പെടുത്തുക,

രോഗി മരിക്കുകയും ബന്ധു "അദ്ദഹം മരിച്ചു" എന്നു മറുപടി നൽകിയാൽ
അദ്ദേഹത്തിന്റെ മരണത്തിൽ ഞാൻ അനുശോചിക്കുന്നു. താങ്കൾക്ക് മരണമടഞ്ഞ സമയം പറയാനാകുമോ, മരണകാരണത്തിന്റെ വിശദാംശങ്ങൾ നൽകാനാകുമോ?
താങ്കൾ സമ്മതിക്കുമെങ്കിൽ ഈ വ്യക്തിയുടെ ആശുപത്രി രേഖകൾ പരിശോധിക്കാമോ.സമ്മതമെങ്കിൽ. നന്ദി. മറ്റുള്ളവരിൽ സമാനമായ സങ്കീണ്ണതകൾ തടയാൻ വിശദാംശങ്ങൾ സഹായിച്ചേക്കാം. താങ്കളുടെ സമയത്തിന് നന്ദി.
വേണ്ടായെങ്കിൽ. അത് മനസ്സിലാക്കാനാകും. താങ്കളുടെ സമയത്തിന് നന്ദി.

ടെലിഫോണിലൂടെ തുടരന്വേഷണത്തിനുള്ള കുറിപ്പ്		
ക്രമനമ്പർ		
വിലയിരുത്തലിനുള്ള തീയതി		
പേര്		വയസ്സ്
ആശുപത്രി നമ്പർ		ലിംഗം
രജിസ്റ്റർചെയ്ത തീയതി		രജിസ്റ്റർ ചെയ്യുമ്പോഴുള്ള പ്രായം
അപായഘടകങ്ങളുടെ രൂപരേഖ	• ഡിഎം • സികെഡി • കാർഡിയോവാസ്ക്കുലാർ രോഗം • അലിഗ്നൻസി • ഡിമൻഷ്യ • അനീമിയ	

	• മദ്യപാനം • എച്ച്ടിഎൻ • ലിപിഡ് രൂപരേഖ • പുകവലിയുടെ അവസ്ഥ • കുടുംബചരിത്രം • അമിതവണ്ണം/ബിഎംഐ/മറ്റ് അനുബന്ധരോഗങ്ങൾ
തുടർചികിത്സാ വിവരങ്ങൾ	• മരുന്നിനോടുള്ള അവലംബം • അപായഘടകങ്ങളുടെ നിയന്ത്രണവും പുതിയ ലാബ് ഫലങ്ങളും • അവസാനത്തെ തുടർചികിത്സാ സന്ദർശനത്തിനു ശേഷമുള്ള സംഭവങ്ങളും അവയുണ്ടായ സമയവും ഗുരുതരമായ കൊറോണറി സംഭവങ്ങൾ/ വിണ്ടുമുള്ള ശസ്ത്രക്രിയയുടെ ആവശ്യകത/ ഹാർട്ട് ഫെയിലുവർ ആശുപത്രി പ്രവേശനം/ മസ്തിഷ്ക്കാഘാതം
അടുത്തകാലത്തുണ്ടായ കൊറോണറി സംബന്ധമായ സംഭവങ്ങളുടെ പ്രദർശന രീതി	• പ്രദർശനത്തിലുള്ള - ടിപ്പിക്കൽ/എടിപ്പിക്കൽ • രോഗനിർണ്ണയം- – CSA/USA/NSTEMI/STEMI • HF / കാർഡിയോജനിക് ഷോക്ക് • Trop T • Pro-BNP
CAG ചെയ്തിട്ടുണ്ടെങ്കിൽ വിശദാംശങ്ങൾ	• നിർണ്ണായകം / നിർണ്ണായകമല്ല • ധമനിയുടെ പങ്കാളിത്തം • ഗുരുതരാവസ്ഥ, LAD / LM പങ്കാളിത്തം
കൈകാര്യം ചെയ്തതിന്റെ വിശദാംശങ്ങൾ	• ത്രോമ്പോളിസിസ് ചെയ്തോ ഇല്ലയോ • PCI / CABG / മരുന്നുചികിത്സ

Data Collection Proforma

Baseline characteristics:

- Age
- Gender

Risk factor profile:

- DM
- HTN
- Lipid profile
- Smoking status
- Family history
- Obesity / BMI
- Other co-morbidities
- Alcohol use
- CKD
- Cerebrovascular Disease
- Malignancy
- Dementia
- Anemia

Mode of presentation:

- Symptoms at presentation – Typical / Atypical
- Diagnosis – CSA/USA/NSTEMI/STEMI
- Killip Class
- HF / Cardiogenic Shock
- ECG Changes
- ECHO parameters
- Trop T

- Pro-BNP

CAG Details:

- Significant / Not
- Vessel Involvement
- Severity
- LAD / LM Involvement

Management:

- Thrombolysis done or not
- PCI / CABG / Medical

Follow up:

- Drug adherence
- Risk Factor Control
- MACCE Events and their time of occurrence

ACS
Need for repeat revascularization
HF
CVEA
Mortality