Dissertation on

A STUDY ON
PREVALANCE OF ELEVATED HsCRP IN ACUTE VASCULAR EVENTS

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON PREVALANCE OF ELEVATED HIGHLY SENSITIVE C-REACTIVE PROTEIN IN ACUTE VASCULAR EVENTS"** submitted by **Dr. JEGAN. A** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2010 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I, **Dr.A.JEGAN** solemnly declare that dissertation titled **"A STUDY ON PREVALANCE OF ELEVATED HIGHLY SENSITIVE C-REACTIVE PROTEIN IN ACUTE VASCULAR EVENTS"** is a bonafide work done by me at Madras Medical College and Govt. General Hospital from January 2008 to September 2009 under the guidance and supervision of my unit chief **Prof. A.RADHAKRISHNAN, M.D.,** Professor of Medicine.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulation for the award of M.D. Degree (Branch – I) in General Medicine.

Place : Chennai **(Dr. A. JEGAN)**

Date :

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INTRODUCTION

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GLOBAL TRENDS IN CARDIOVASCULAR DISEASE

Estimating global trends in the burden of disease, particularly CVD, is aided by examining regional trends. Because 85 percent of the world's population lives in the low- and middle-income countries, global rates of CVD are largely driven by rates in these countries. Even as rates fall in high-income countries, worldwide CVD rates are accelerating because most low- and middle-income countries are entering the second and third phases of the epidemic transition, marked by rising CVD rates.

The economic impact of chronic diseases could be substantial as this transition proceeds. Over the next decade or so, countries such as China, India, and Russia could forego between $200 billion and $550 billion in national income as a result of heart disease, stroke, and diabetes.

In 1990 CVD accounted for 28 percent of the world's 50.4 million deaths and 9.7 percent of the 1.4 billion lost DALYs. By 2001, CVD was responsible for 29 percent of all deaths and 14 percent of the 1.5 billion lost DALYs.

By 2020, the population will grow to 7.8 billion and 32 percent of all deaths will be due to CVD, and by 2030, when the population is expected to reach 8.2 billion, 33 percent of all deaths will be caused by CVD. By 2030, the WHO predicts that worldwide CVD will cause 24.2 million deaths. Of these, 14.9 percent of deaths in men and 13.1 percent of deaths in women will be due to CHD. Stroke will be responsible for 10.4 percent of all male deaths and 11.8 percent of all female deaths.

TABLE

Contribution of Various Disease Categories to Global Mortality

			Total Deaths (%)					
	Population (Millions)	**Total Deaths (Millions)**	***CMPN***	***Injury***	***Non-CMPN Non-CVD***	***All CVD***	***CHD***	***Stroke***
1990								
World	5267	50.4	34.2	10.1	27.4	28.4	12.4	8.7
High income	798	7.12	6.4	6.2	42.8	44.6	23.4	11.1
Low and middle income	4470	43.3	38.7	10.7	24.8	25.7	10.6	8.3
2001								
World	6148	56.2	32.3	9.2	29.3	29.1	12.5	9.6
High income	929	7.9	7.0	6.0	48.5	38.5	17.3	9.9
Low and middle income	5219	48.3	36.4	9.7	26.2	27.6	11.8	9.5
2020[*]								
World	7800	65.1				31.5	13.6	10.6
2030[*]								
World	8200	74.5				32.5	14.0	11.1

CHD = coronary heart disease; CMPN = communicable diseases, maternal and perinatal conditions, and nutritional deficiency; CVD = cardiovascular disease.

* Modified from Mackay J, Mensah G: Atlas of Heart Disease and Stroke. Geneva, World Health Organization, 2004.

HIGH-INCOME COUNTRIES

In the high-income countries, population growth will be fueled by emigration from the low- and middle-income countries, but as a proportion of the world's population, the high-income segment is gradually shrinking. In the high-income countries, the modest decline in CVD death rates begun in the latter third of the 20th century will continue, but the rate of decline appears to be slowing. However, these countries are expected to see an increase in the prevalence of CVD, as well as the absolute number of deaths, predicted to increase between 30 percent and 60 percent, as populations age.

LOW- AND MIDDLE-INCOME COUNTRIES

Of the 7.1 million individuals who died from ischemic heart disease in 2001, 5.7 million lived in low- and middle-income countries. And of the 5.4 million people who died from a stroke in 2001, less than 1 million lived in high-income countries. From 1990 to 2001, the percentage of deaths from communicable diseases decreased from 38.7 percent to 36.4 percent and continued substantial declines are expected. Although some countries are still in the first and second phases of the epidemiological transition, large portions of the population living in low- and middle-

income countries have entered the third phase and some are entering the fourth.

Today, in most of the regions, the pattern is typical, with CHD rates exceeding stroke rates. Exceptions include sub-Saharan Africa and China, home to the vast majority of East Asia and Pacific residents. In sub-Saharan Africa, which is in an earlier stage of the transition, this ratio is currently about 1:1, but the balance is likely to shift in favor of CHD over time.

In China, however, the ratio is reversed, with stroke rates exceeding CHD rates, but this is also likely to change. In urban China, CHD rates are rapidly increasing as stroke rates fall. Changing demographics play a significant role in future predictions for CVD throughout the world. For example, between 1990 and 2001, the population of Europe and Central Asia grew by 1 million people per year, whereas South Asia added 25 million people each year

In their report *A Race Against Time: The Challenge of Cardiovascular Disease in Developing Economies,* Leeder and colleagues compare the role of CVD in the death patterns of one low-income country (India) and four middle-income countries (Russia, Brazil, China, and South Africa) in 2000 and in the future. Portugal and the United States were used

as high-income comparator countries. Even assuming no increase in CVD risk factors, the authors predict that all five study countries, but especially India and South Africa, will see a dramatic number of working-age people (35 to 64 years old) die of CVD over the next 30 years, as well as an increasing level of morbidity among middle-aged people related to heart disease and stroke. In China, they estimate that there will be 9 million deaths from CVD in 2030—up from 2.4 million in 2002—with half occurring in individuals between 35 and 64 years old.

Because of a growing population of younger people at risk for CVD in the five study countries, they predict that the proportion of CVD deaths occurring in the prime labor years will greatly exceed the experience of the United States and Portugal. Predictions of the increase in the number of productive years lost due to CVD between 2000 and 2030 are: South Africa, 28 percent; China, 57 percent; Brazil, 64 percent; and India, 95 percent. (In South Africa and Brazil, the predicted rates per 100,000 population actually decrease slightly as a result of anticipated demographic changes.)

In Russia, the number is predicted to decrease because the size of the population at risk is falling. For comparison, the number of years of productive life lost is expected to increase by 20 percent in the United States and by 30 percent in Portugal by 2030.

The ultimate promise of an improved understanding of cardiovascular risk is the concept of "personalized medicine," in which targeted interventions can get the right drug to the right patient at the right time.

By the mid-1960s, investigators in the Framingham Heart Study had defined the major risk factors of age, hypertension, smoking, and hyperlipidemia, and coined the term *coronary risk factors*. Over time, these four biomarkers, along with gender, have generated global risk prediction scores for the assessment of cardiovascular risk. However, as also described earlier, one vascular event in five occurs in the absence of any of these major risk factors and one in two in the absence of hyperlipidemia. From a research perspective, the past 50 years has seen a remarkable expansion in our understanding of atherothrombosis to include the biology of hemostasis, thrombosis, inflammation, and endothelial dysfunction. Despite this changing view of pathophysiology, the variables in current risk assessment algorithms remain largely unchanged from those evaluated a half-century ago.

An expanded and updated approach to vascular risk detection is needed so that primary care physicians can be guided by the most modern biological constructs. New risk prediction algorithms must involve rigorous evaluation, with particular care given not only to the concepts of discrimination but also calibration and reclassification. This change in focus for prevention must include an understanding that reliance on the C-statistic as a traditional method for selecting variables for inclusion in risk prediction models is outmoded and subject to considerable error. Indeed, careful investigation has shown that inappropriate reliance on the C-statistic would actually eliminate LDL cholesterol, HDL cholesterol, and blood pressure from most global prediction models. Furthermore, continued reliance on 10-year risk estimates rather than estimates of lifetime risk may actually restrain more effective prevention efforts.

In an effort to move beyond traditional risk variables, a few recent investigations have ascertained wide panels of biomarkers in large cohorts of initially healthy individuals who were then followed prospectively for incident vascular events. For example, using such data in the Women's Health Study, nine variables—age, current smoking, systolic blood pressure, hemoglobin A_{1c} among diabetics, hsCRP, apo B-100, apo A-I, Lp(a), and a parental history of premature atherosclerosis—were found to improve risk prediction substantially when compared with traditional

Framingham covariates. Importantly, use of this novel algorithm reclassified nearly 50 percent of those otherwise considered to be at intermediate risk on the basis of usual risk factors, an effect that was also seen for a simplified prediction model that substituted non-HDL cholesterol for apo B-100 and HDL cholesterol for apo A-I. Moreover, this reclassification was correct in over 90 percent of cases

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. To determine the **PREVALANCE OF ELEVATED HsCRP IN 50 PATIENTS WITH ACUTE VASCULAR EVENTS**
2. To compare with 50 controls of non vascular acute event.
3. To determine role of HsCRP in determining the morbidity and mortality.
4. To study the prognostic implication of HsCRP in acute vascular events.
5. To analyse the levels in patient with out any other specific CVS risk factors.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ATHEROSCLEROTIC RISK FACTORS

Despite the importance of blood lipids, 50 percent of all myocardial infarctions and stroke occur in individuals without overt hyperlipidemia. In a major prospective study of healthy American women, 77 percent of all future cardiovascular events occurred in patients with LDL cholesterol levels less than 160 mg/dl and 46 percent occurred in those with LDL cholesterol levels less than 130 mg/dl.[1]

Although the use of global prediction models like those developed in Framingham greatly improves the detection of heart disease risk, as many as 20 percent of all events occur in the absence of any of the major classic vascular risk factors. This fact challenges several basic issues related to current screening programs for risk detection and disease prevention. However, clinical data continue to accurate demonstrating the hazard of relying solely on classic risk factors.

In one analysis more than 120,000 patients with coronary heart disease, 15 percent of the women and 19 percent of the men had no evidence of hyperlipidemia, hypertension, diabetes, or smoking and more than 50 percent had only one of these general risk factors.[2]

In another large analysis, between 85 and 95 percent of participants with coronary disease had at least one conventional risk factor, but so too did those participants without coronary disease despite follow-up for as long as 30 years[3]. Thus, because of the considerable need to improve vascular risk detection, much research over the past 10 or 15 years has focused on the identification and evaluation of novel atherosclerotic risk factors[4].

When evaluating any novel risk factor as a potential new screening tool, clinicians need to consider whether:

1. There is a standardized and reproducible assay for the marker of interest.

2. There is a consistent series of prospective studies demonstrating that a given parameter predicts future risk.

3. The novel marker adds to the predictive value of lipid screening.

4. There is evidence that the novel marker adds to global risk prediction scores, such as that in the Framingham Heart Study. The following section applies these basic epidemiological requirements to a series of novel risk factors, including hsCRP and other markers of inflammation, lipoprotein(a), homocysteine, and markers of fibrinolytic and hemostatic function, such as fibrinogen, D-dimer, tissue plasminogen activator (t-PA), and plasminogen activator inhibitor 1 (PAI-1) antigens. Shows data describing the relative efficacy of several variables measured at baseline in two large cohorts of initially healthy middle-aged men and women.

TABLE 1

Clinical Epidemiology of Proposed Plasma-Based Biomarkers for Prediction of Future Cardiovascular Events

Biomarker	Prospective Studies Convincing?	Standardized Commercial Assay?	Additive to Lipid Screening?	Additive to Framingham Risk Score?
Inflammation				
hsCRP	++++	+++	+++	+++
sICAM-1	++	±	+	-
SAA	++	-	+	-

Biomarker	Prospective Studies Convincing?	Standardized Commercial Assay?	Additive to Lipid Screening?	Additive to Framingham Risk Score?
IL-6/IL-18	++	-	+	-
Myeloperoxidase	+	-	±	-
sCD40L	+	-	-	-
Altered thrombosis				
t-PA/PAI-1	++	±	-	-
Fibrinogen	+++	±	++	-
Homocysteine	++++	+++	±	-
D-dimer	++	+	-	-
Oxidative stress-oxidized LDL	±	-	-	-
Altered lipids				
Lipoprotein(a)	+++	±	±	-
LDL particle size	++	±	±	-

High-Sensitivity C-Reactive Protein

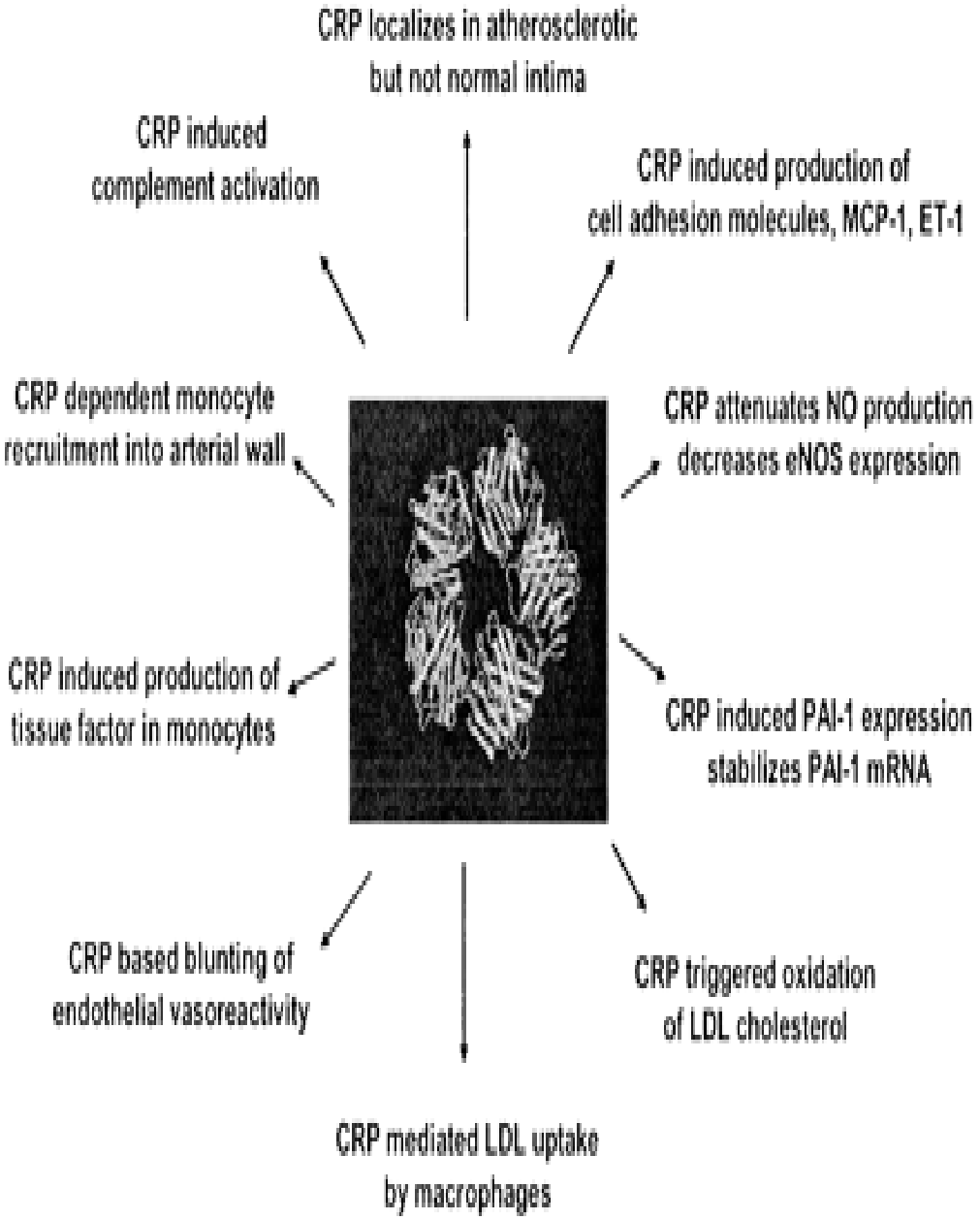
Inflammation characterizes all phases of atherothrombosis and provides a critical pathophysiological link between plaque formation and acute rupture, leading to occlusion and infarction[5]. Formation of the fatty streak, the earliest phase of atherogenesis, involves recruitment of leukocytes caused by the expression of adhesion molecules on endothelial cells, in turn triggered by inflammatory cytokines such as interleukin-1 and tumor necrosis factor-alpha. Subsequent migration of inflammatory cells into the subendothelial space requires chemotaxis controlled by chemokines induced by the primary cytokines. Mononuclear cells within this initial infiltrate, as well as intrinsic vascular cells, subsequently release growth factors that stimulate proliferation of the smooth muscle cells and lead to plaque progression. The thrombotic complications of plaques often involve physical disruption, usually associated with signs of local and systemic inflammation.

Other proinflammatory cytokines such as CD40 ligand can in turn induce tissue factor expression and promote thrombus formation. Moreover, the primary proinflammatory cytokines result in the expression of messenger cytokines such as interleukin-6, which can travel from local sites of inflammation to the liver, where a change in the program of protein synthesis characteristic of the acute phase response is thereby triggered.

The acute-phase reactant, CRP, a simple downstream marker of inflammation, has now emerged as a major cardiovascular risk factor.[6]

Composed of five 23-kDa subunits, CRP is a circulating member of the pentraxin family that plays a major role in the human innate immune response. Although derived primarily from the liver, studies have found that cells within human coronary arteries, particularly in the atherosclerotic intima, can also elaborate CRP.

More than simply a marker of inflammation, CRP may influence directly vascular vulnerability through several mechanisms, including enhanced expression of local adhesion molecules, increased expression of endothelial PAI-1, reduced endothelial nitric oxide bioactivity, altered LDL uptake by macrophages, and colocalization with complement within atherosclerotic lesions. Moreover, expression of human CRP in CRP-transgenic mice was found to directly enhance intravascular thrombosis.[7]



The evidence for direct proinflammatory effects of CRP has less strength at present than the consistent data regarding its ability to predict risk. In primary prevention, a large series of prospective epidemiological studies has demonstrated convincingly that CRP, when measured with high-sensitivity assays, strongly and independently predicts risk of myocardial infarction, stroke, peripheral arterial disease, and sudden

cardiac death among apparently healthy individuals. These data apply to women as well as men across all age levels and have been consistent in diverse populations. Most importantly, hsCRP adds prognostic information at all levels of LDL cholesterol and at all levels of risk, as determined by the Framingham Risk Score. [8]

In other major studies from the United States and Europe, hsCRP levels predicted subsequent risk better than LDL cholesterol level. [9] [10] However, because hsCRP levels reflect a component of vascular risk different from that of cholesterol, the addition of hsCRP to lipid evaluation provides a major opportunity to improve global risk prediction.

In clinical terms, absolute vascular risk is higher in individuals with elevated hsCRP levels and low levels of LDL cholesterol than in those with elevated levels of LDL cholesterol but low levels of hsCRP, but current guidelines consider only the latter group to be at high risk Even in studies that have reported the effect of hsCRP as modest, the magnitude of effect was at least as large as that of hypertension and smoking, data demonstrating the importance of inflammation in atherogenesis.[11]

Largely on the basis of these data, the American Heart Association and the Centers for Disease Control and Prevention issued guidelines in 2003 for the use of hsCRP in clinical practice.[11]

Briefly,

HsCRP levels **<1mg/dl LOW RISK**

1 to 3mg/dl INTERMEDIATE

> 3 mg/liter HIGHER relative vascular risk

respectively, when considered along with traditional markers of risk. This critical finding has corroborated studies conducted worldwide; all studies of adequate sample size have found the risk of hsCRP to be independent of and additive to traditional risk factors [12] [8] [13] [14] [15] [16] [17]. Screening for hsCRP should be done at the discretion of the physician as part of global risk evaluation, not as a replacement for LDL and HDL testing.

Although hsCRP predicts risk across the entire population spectrum, its greatest usefulness is likely to be for those at intermediate risk—that is, individuals with anticipated 10-year event rates between 5 and 20 percent. In a recent analysis of the impact that CRP makes on clinical risk prediction, global risk prediction models that included hsCRP reclassified approximately 20 percent of those otherwise considered to be at

intermediate risk; moreover, the impact of hsCRP on risk prediction was at least as large as that of lipid screening.[18]

Values of hsCRP in excess of 8 mg/liter may represent an acute-phase response caused by an underlying inflammatory disease or intercurrent infection and should lead to repeat testing in approximately 2 to 3 weeks; consistently high values, however, represent very high risk of future cardiovascular disease, because risk appears to be linear across the full range of hsCRP levels.[19] Because hsCRP levels are stable over long periods, have no circadian variation, and do not depend on prandial state, screening can easily be done on an outpatient basis at the time of cholesterol evaluation.

All these data support the concept that inflammation plays a critical role throughout the atherothrombotic process. Additionally, hsCRP has prognostic usefulness in cases of acute ischemia, even without troponin level elevation, suggesting that an enhanced inflammatory response at the time of hospital admission can determine subsequent plaque rupture.[20] These findings help explain why individuals with elevated hsCRP levels are also more likely to benefit from aggressive interventions compared with those with low hsCRP levels.

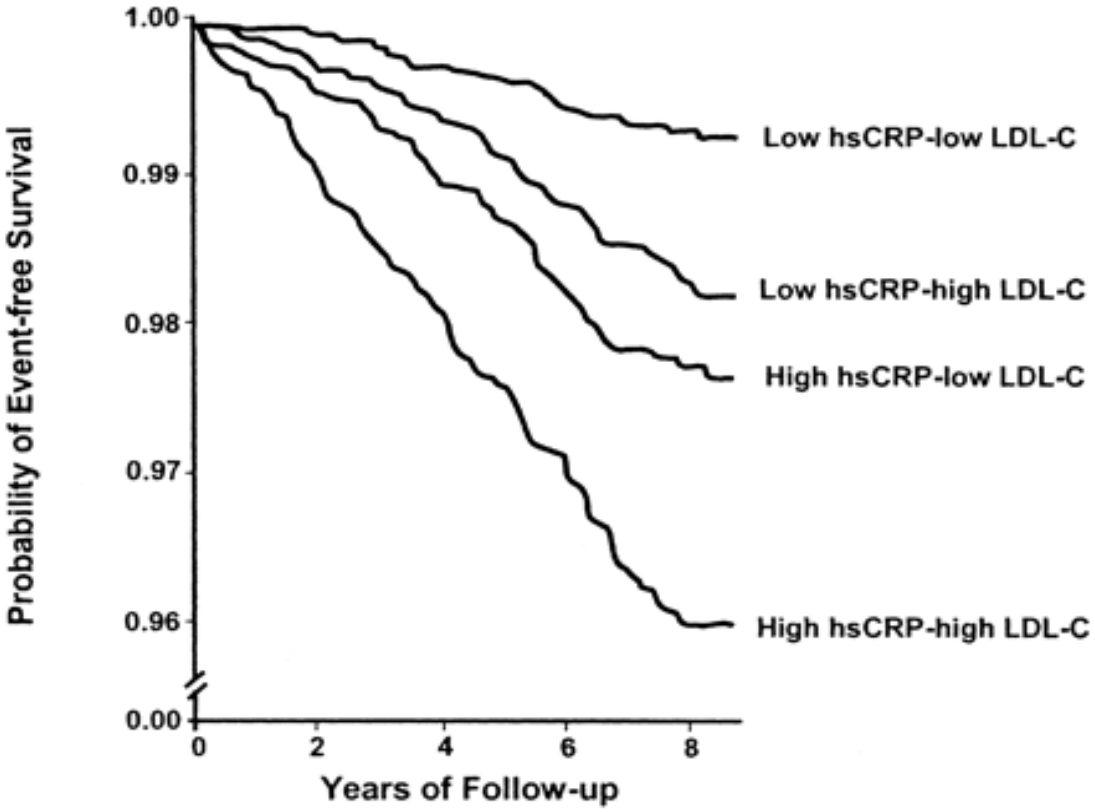
Elevated levels of hsCRP predict not only cardiovascular events but also the onset of type 2 diabetes mellitus, [21] [22] perhaps because hsCRP

levels correlate with several components of the metabolic syndrome, including those not easily measured in clinical practice such as insulin sensitivity, endothelial dysfunction, and hypofibrinolysis. Thus, hsCRP assessment also adds prognostic information at all levels of the metabolic syndrome. [23] [24]

In the AFCAPS/TexCAPS trial, for example, statin appeared to lower cardiovascular event rates, even for those with below-median levels of LDL cholesterol but above-median levels of hsCRP.[25]

In the PROVE IT-TIMI 22 clinical trial conducted in patients with acute coronary syndromes treated with statin therapy, achieving levels of hsCRP less than 2 mg/liter was as important for long-term event-free survival as was achieving levels of LDL cholesterol less than 70 mg/dl; in fact, the best long-term outcomes were found in those who achieved both these goals [26]. This new concept of "dual goals" for statin therapy, which includes both CRP andLDL level reduction, has been corroborated in the A-to-Z clinical trial,[27]

According to AFCAPS trial



Although hsCRP is by far the best-characterized and most reliable inflammatory biomarker for clinical use, several other markers of inflammation have shown promise in terms of predicting vascular risk. These include cytokines such as interleukin-6, soluble forms of certain cell

adhesion molecules such as intercellular adhesion molecule (sICAM-1), P-selectin, or the mediator CD40 ligand, as well as markers of leukocyte activation such as myeloperoxidase.

Other inflammatory markers associated with lipid oxidation such as lipoprotein-associated phospholipase A_2 and pregnancy-associated plasma protein A have also shown promise. However, each of these biomarkers has analytical issues that need careful evaluation before routine clinical use.

For example, some have too short a half-life for clinical diagnostic testing, whereas the ability of others to predict risk in settings of broad populations has proved marginal thus far. Nonetheless, several of these inflammatory biomarkers can shed critical pathophysiological light on the atherothrombotic process, particularly at the time of plaque rupture. For example, soluble CD40 ligand (probably released from activated platelets) may provide insight into the efficacy of specific antithrombotic agents independently of CRP.

Similarly, myeloperoxidase may provide prognostic information in cases of acute ischemia over and above that associated with troponin or CRP.Thus, continued evaluation of other inflammatory biomarkers may

well provide targets for or monitors of therapy, particularly in the setting of acute coronary ischemia.

Homocysteine

Homocysteine is a sulfhydryl-containing amino acid derived from the demethylation of dietary methionine. Patients with rare inherited defects of methionine metabolism can develop severe hyperhomocysteinemia (plasma levels higher than 100μmol/liter) and have markedly elevated risk of premature atherothrombosis as well as venous thromboembolism. Mechanisms suggested to account for these effects include endothelial dysfunction, accelerated oxidation of LDL cholesterol, impairment of flow-mediated endothelium-derived relaxing factor with subsequent reduction in arterial vasodilation, platelet activation, and oxidative stress.

In contrast to severe hyperhomocysteinemia, mild to moderate elevations of homocysteine (plasma levels higher than 15μmol/liter) are more common in the general population, primarily because of insufficient dietary intake of folic acid. Other patient groups who tend to have elevated levels of homocysteine include those receiving folate antagonists such as

methotrexate and carbamazepine and those with impaired homocysteine metabolism caused by hypothyroidism or renal insufficiency.

Despite reduced enthusiasm and lack of evidence that homocysteine reduction lowers risk, there remain a few specific patient populations for whom homocysteine evaluation may prove appropriate, including those lacking traditional risk factors, with renal failure, or with markedly premature atherosclerosis or a family history of myocardial infarction and stroke at a young age. It is also crucial to continue folate supplementation in the general population to reduce the risk of neural tube defects, an inexpensive practice that has been in place in the United States for over a decade yet remains a public health challenge for much of Europe and the developing world

Fibrinogen and Fibrin D-Dimer

Plasma fibrinogen influences platelet aggregation and blood viscosity, interacts with plasminogen binding and, in combination with thrombin, mediates the final step in clot formation and the response to vascular injury. In addition, fibrinogen associates positively with age, obesity, smoking, diabetes, and LDL cholesterol level, and inversely with

HDL cholesterol level, alcohol use, physical activity, and exercise level. Fibrinogen, like CRP, is an acute-phase reactant and increases during inflammatory responses.

Given these relationships, it is not surprising that fibrinogen was among the first "novel" risk factors evaluated. Early reports from the Gothenburg, Northwick Park, and Framingham heart studies all found significant positive associations between fibrinogen levels and future risk of cardiovascular events. Since then, a number of other prospective studies have confirmed these findings and, in recent meta-analyses, there was an approximately linear logarithmic association between usual fibrinogen level and the risk of coronary heart disease and stroke. In one analysis, the age- and gender-adjusted hazard ratio per 1-g/liter increase in fibrinogen was 2.4 for coronary heart disease and 2.1 for stroke.

Interestingly, these effects were largely unaffected in those studies in which further adjustment for hsCRP was possible. In more recent studies, hsCRP and fibrinogen levels appeared to be additive in their ability to predict risk, although the absolute effect of hsCRP appeared to be larger. Other studies have suggested that the predictive usefulness of

fibrinogen is highest in those with other concomitant elevations of lipoprotein(a) or homocysteine.

MATERIALS AND METHODS

MATERIAL AND METHODS

STUDY POPULATION

A total of 50 patients were enrolled for the study from who attended the in patient clinics of the institute of Internal Medicine and department of cardiology.

Patients are selected for the study who satisfied all the inclusion and exclusion criteria. Written consent was obtained from all patients participating in the study.

Age and sex matched controls (50) were also studied for comparison and meaningful interpretation of data. The controls were recruited from other acute cases that were recruited from the wards; appropriate controls

were recruited from the wards. All patients and controls were not from a single ethnic background.

STUDY DURATION

This study was conducted for a period of eighteen months from January 2008 to September 2009.

STUDY DESIGN

A single centre matched care- control study design was chosen.

METHODS

Detailed clinical history were taken from each patients and a completes review of their case notes performed. A complete clinical examination of the nervous system and cardiovascular system was done for each patient.

LABORATORY METHODS

To all selected patients, following investigations were taken.

- **ECG**
- **ECHO**

- **CPK MB**
- **CT BRAIN**
- **FBS**
- **FLP**
- **HsCRP**
- **Other relevant investigations**

INCLUSION CRITERIA

FOR CASES

1. Age more than 12 years.
2. Acute myocardial infarction

   Evidenced by ECG, elevated CK MB, or ECHO
3. Ischemic stroke

   Two CT BRAIN taken at least 3 days gap showing signs of ischemia
4. Unstable angina

   Evidenced by ECG or elevated CK MB
5. Those who are willing for study

FOR CONTROL

1. Age more than 15 less than 60.
2. Presence of any illness
3. Event should be acute
4. No cardiovascular risk factors

EXCLUSION CRITERIA

1. Age less than 15 and more than 60
2. Smoking
3. Alcoholism
4. Patient with previous attacks
5. Other inflammatory conditions
    a. SLE
    b. Scleroderma
    c. Rheumatoid arthritis
    d. Other Connective Tissue Disorders
6. Immunosuppresant therapy
7. Patient lost followup

STATISTICAL ANALYSIS

The significance of difference between two proportions was indicated by the chi-square (x^2) statistic. The significance of difference in mean between two groups was calculated by student t-test. Variables were considered to be significant if ($P<0.05$).

OBSERVATION AND RESULTS

OBSERVATIONS AND RESULTS

In our study of 50 patients were selected and 50 control where selected to analyzed for the following

- To determine the **PREVALANCE OF ELEVATED HsCRP PATIENTS WITH ACUTE VASCULAR EVENTS**
- To compare with 50 controls of non vascular acute event.
- To determine role of HsCRP in determining the morbidity and mortality.
- To study the prognostic implication.

ACCORDING TO VARIOUS REFERENCES QUOTED ABOVE THE LEVEL OF HsCRP determines prognosis as well as mortality.

When we divide and analyze as follows

Sl.No	Baseline Features	Cases	Control

1. **With risk factors and elevated HsCRP.**
2. **Without risk factors only elevated HsCRP.**
3. **Control**

OBSERVATIONS ARE AS FOLLOWS

TABLE – 1

BASELINE CHARACTERS

1.	**Male**	**34**	**25**
2.	**Female**	**16**	**25**
3.	**Hindu**	**43**	**40**
4.	**Muslim**	**2**	**4**
5.	**Christian**	**5**	**6**
6.	**Family History**	**18**	**0**
7.	**Hypertension**	**29**	**0**
8.	**Diabetes Mellitus**	**26**	**0**
9.	**LDL >100**	**25**	**0**
10.	**HDL <50 for Female <40 for Male**	**20**	**0**
11.	**TGL**	**20**	**0**
12.	**FBS**	**26**	**0**
13.	**ECHO**	**7**	**0**
14.	**Death**	**5**	**1**

No. of Diseases

TABLE – 2

CONTROLS

Patients	
14	Fever
4	LRI
10	Trauma
3	Post operative
8	DKA
2	Acute abdomen
1	Haemorrhagic stroke
1	SLE
3	UTI
1	Dengue
1	ARF
1	Myocarditis

GENDER	No of Patients

TABLE – 3

SEX WISE DISTRIBUTION

MALE	**34**
FEMALE	**16**

COMMUNITY	**No. of Patients**

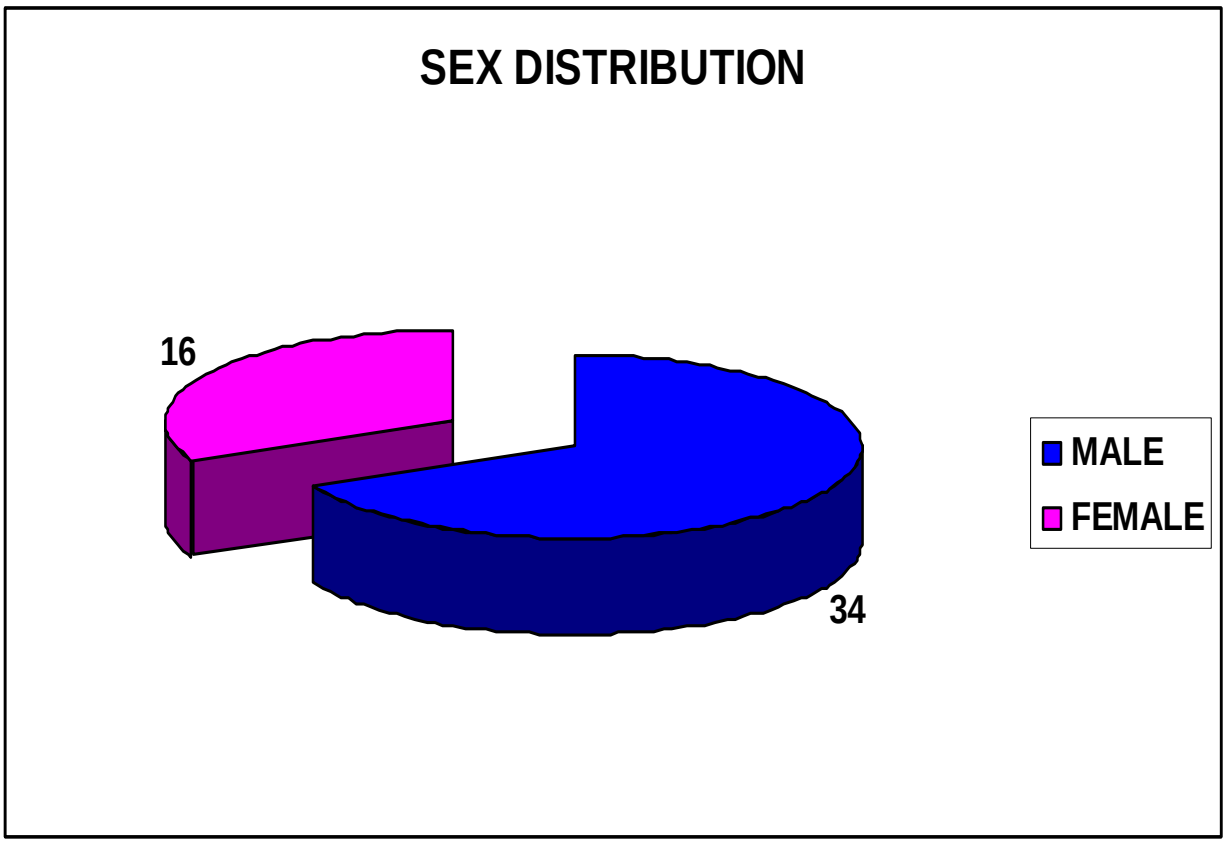


TABLE – 4

COMMUNITY WISE DISTRIBUTION

HINDU	**43**
MUSLIM	**2**
CHRISTIAN	**5**

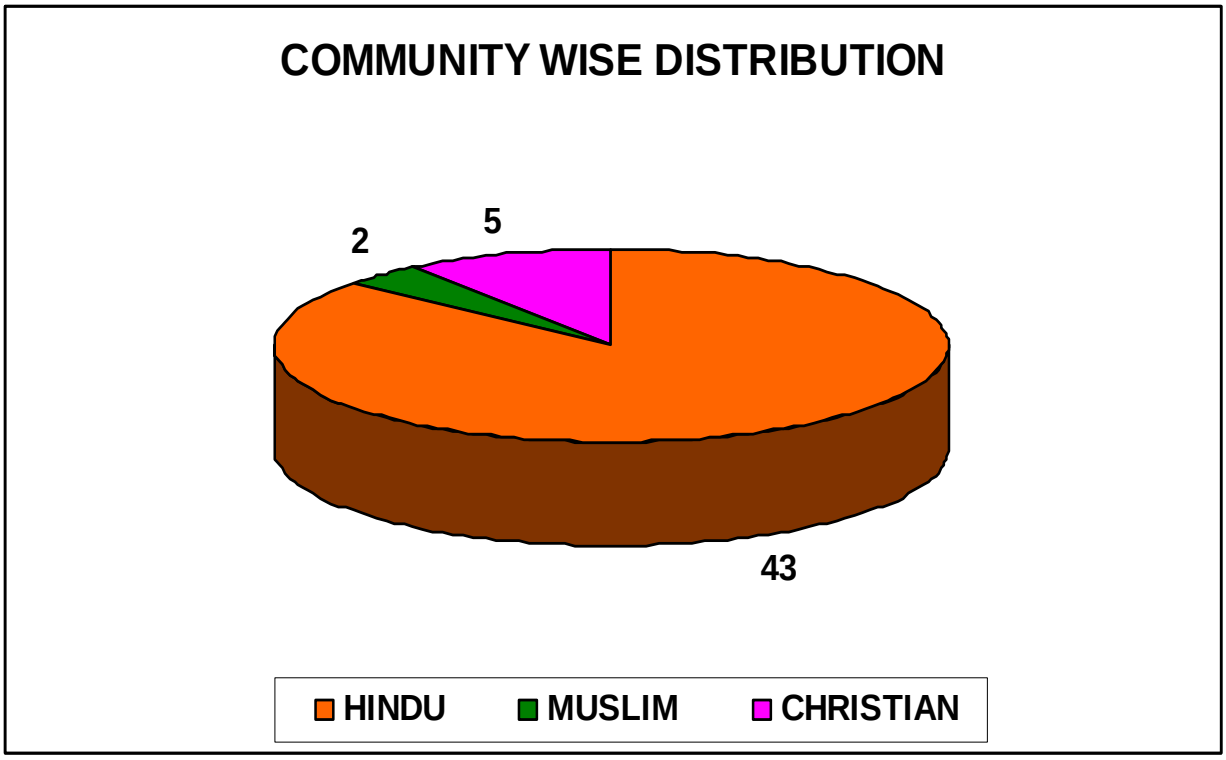


TABLE – 5

RISK FACTOR DISTRIBUTION

Total No. of Patients	**50**
RISK FACTOR	
HYPERTENSION	**29**
DIABETES MELLITUS	**26**
LDL >100	**25**
HDL <50 for Female **<40 for Male**	**20**
TGL >150	**20**
WITHOUT RISK FACTOR	**15**

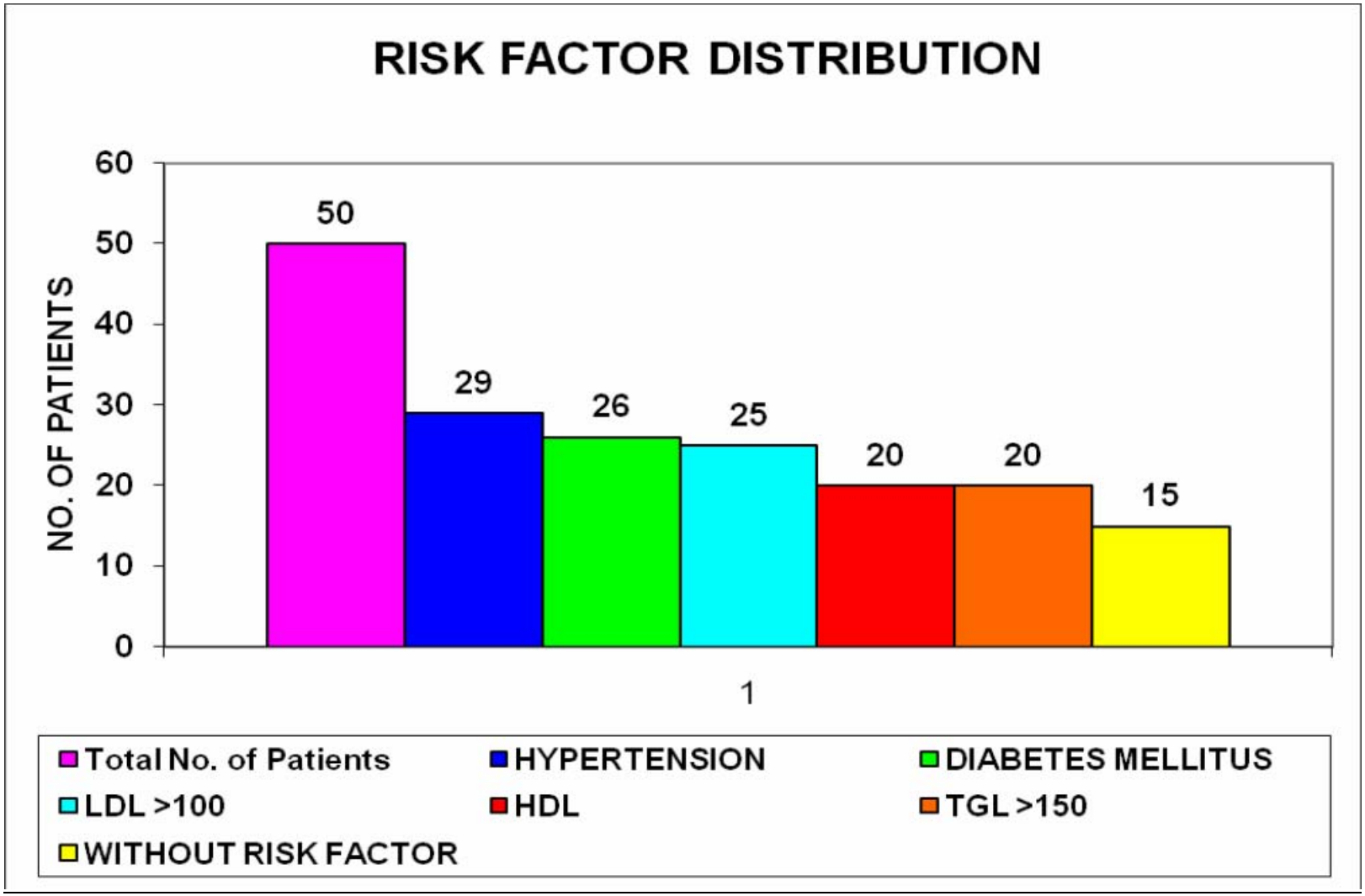

RISK FACTOR DISTRIBUTION
NO. OF PATIENTS
60
50
40
30
20
10
0
50
29
26
25
20
20
15
1
Total No. of Patients
HYPERTENSION
DIABETES MELLITUS
LDL >100
HDL
TGL >150
WITHOUT RISK FACTOR

TABLE – 6

AVERAGE ELEVATED CRP

Normal	Cases	Cases with risk factor	Cases without risk factor	Controls
<0.3	2.59	1.81	2.91	1.66

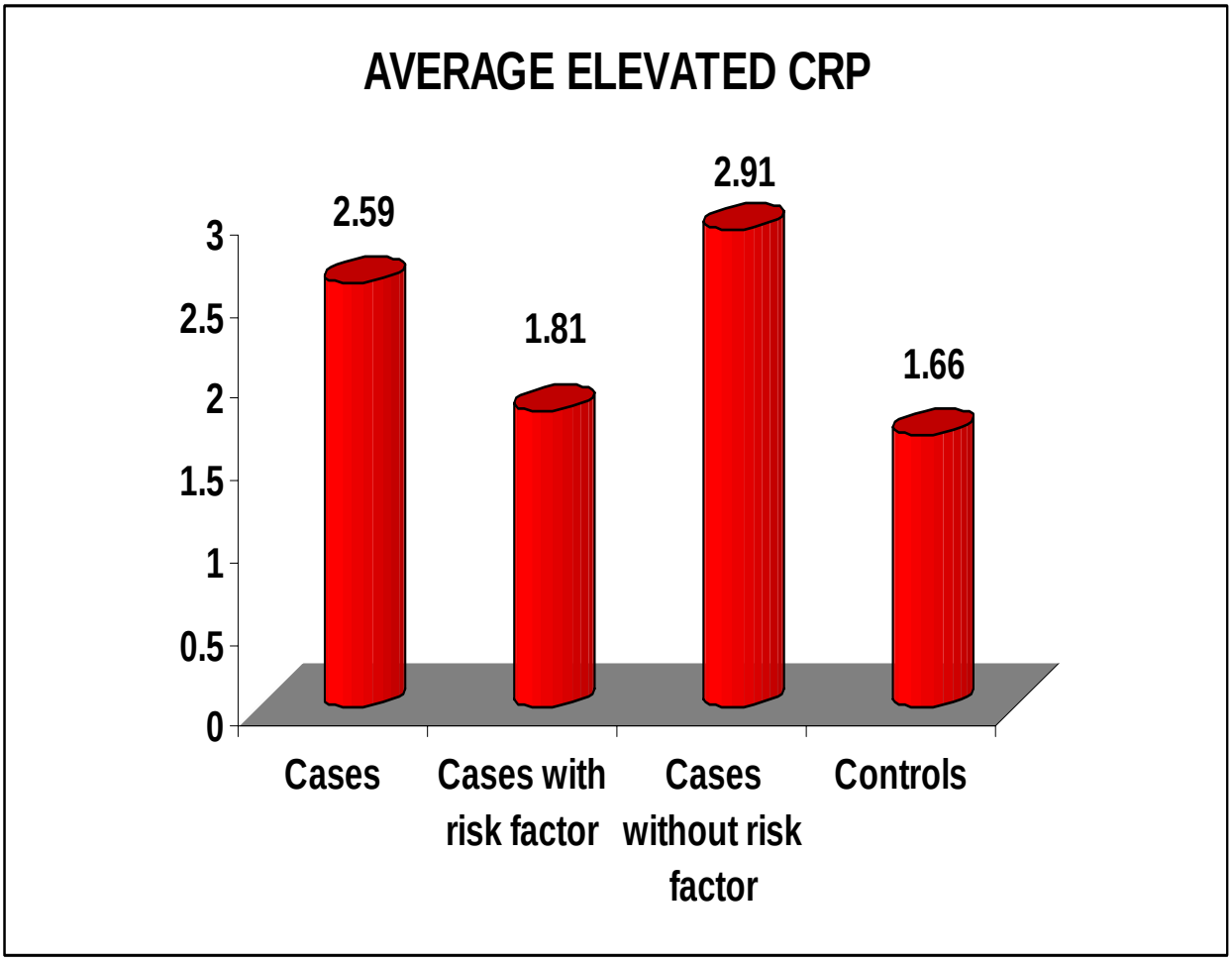


TABLE – 7

CLASS WISE DISTRIBUTION WITHOUT RISK FACTORS

TYPE OF DISEASE	LOW	INTERMITTANT	HIGH
MYOCARDIAL INFARCTION	0	2	0
UNSTABLE ANGINA	4	6	0
STROKE	2	1	0

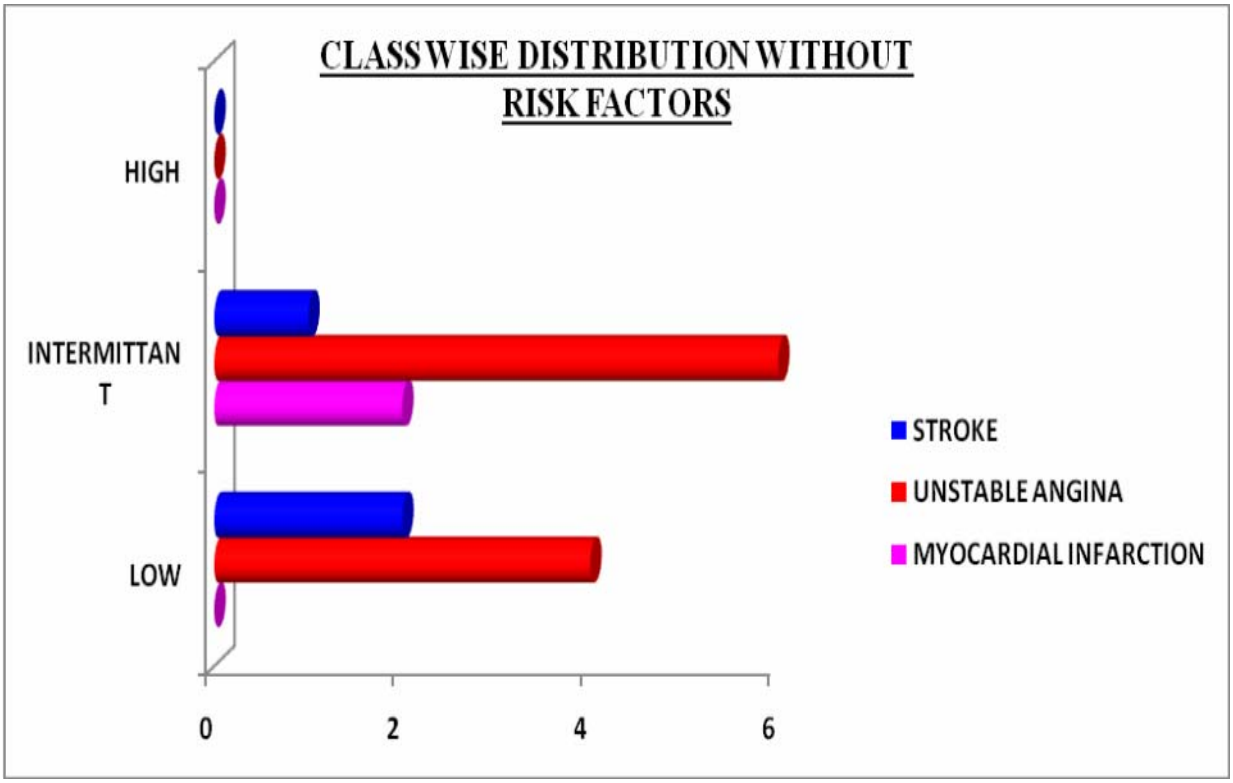


TABLE –8

CLASS WISE DISTRIBUTION FOR ALL CASES

TYPE OF DISEASE	LOW	INTERMITTANT	HIGH	TOTAL
MYOCARDIAL INFARCTION	1	14	2	17
UNSTABLE ANGINA	5	13	0	18
STROKE	9	5	1	15

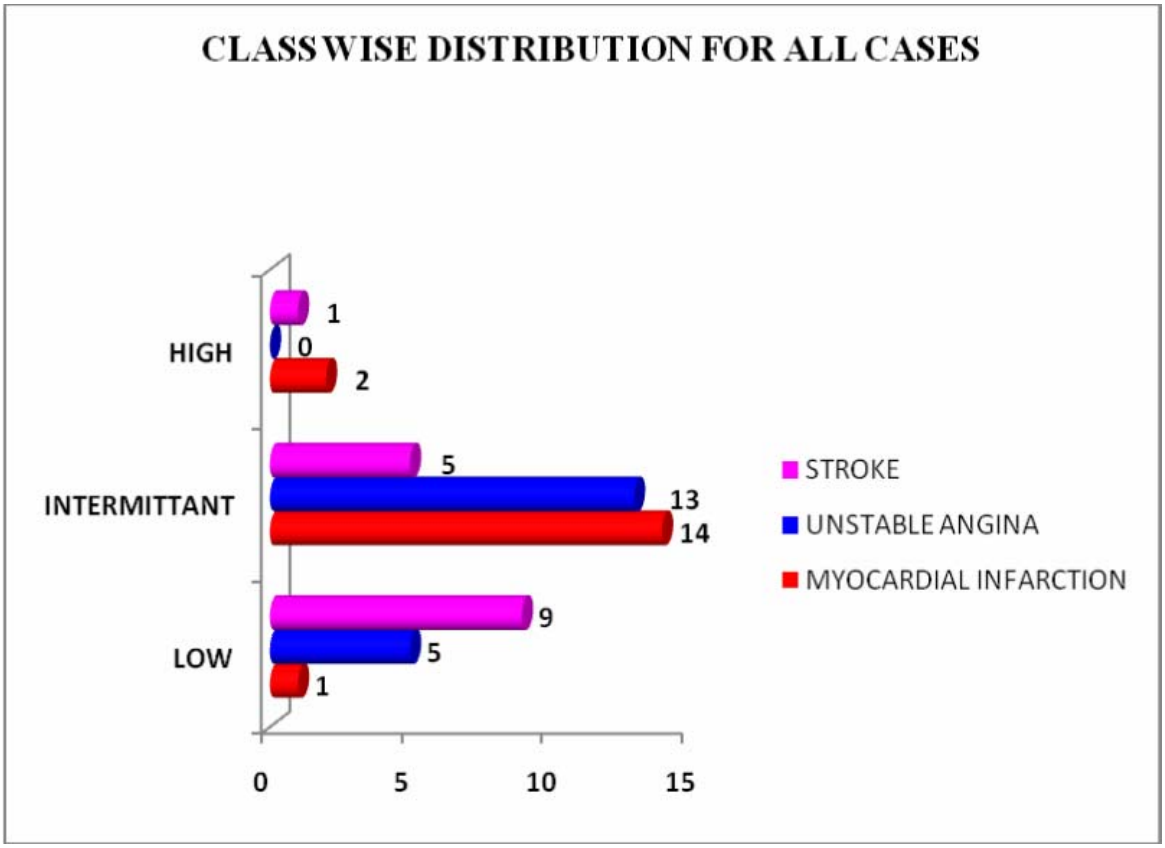


TABLE –9

MORTALITY AND ASSOCIATED RISK FACTORS

Type	No. of patients
DEATH	5
ASSOCIATED RISK FACTORS HYPERTENSION	3
DIABETES MELLITUS	3
HYPERLIPIDEMIA	4

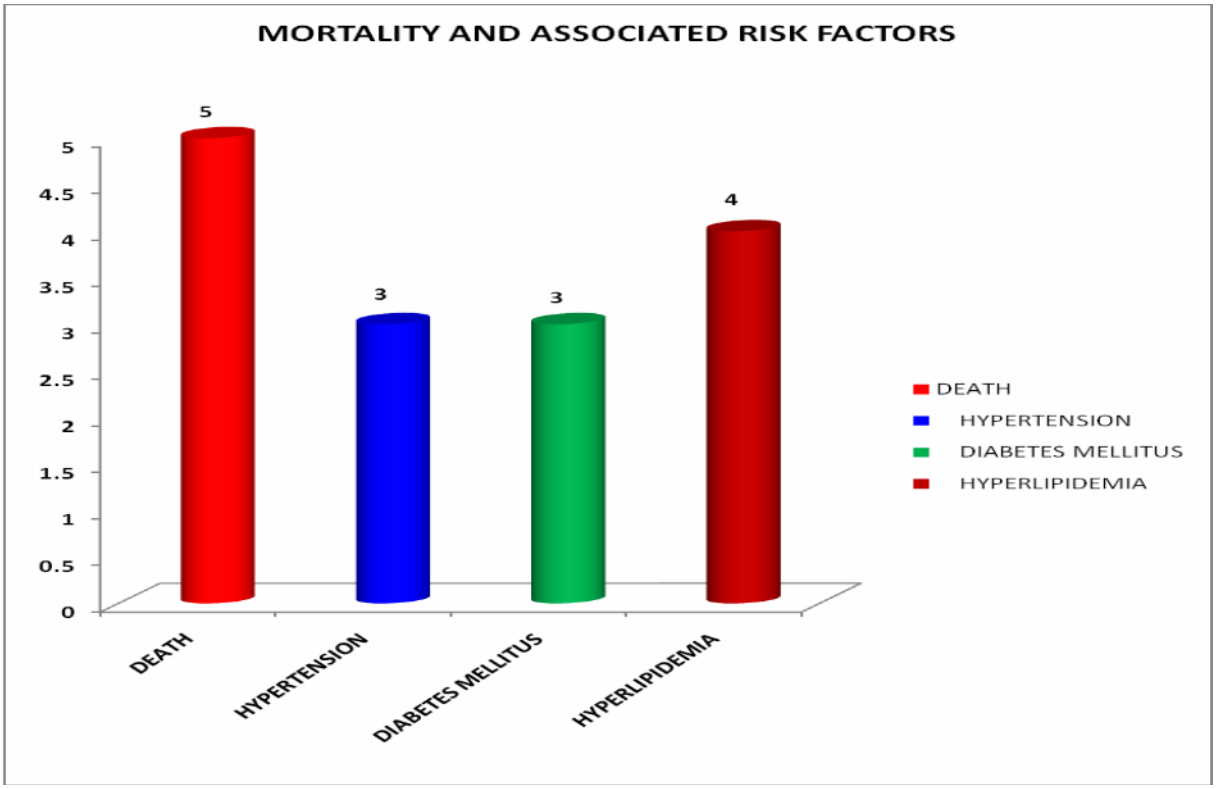
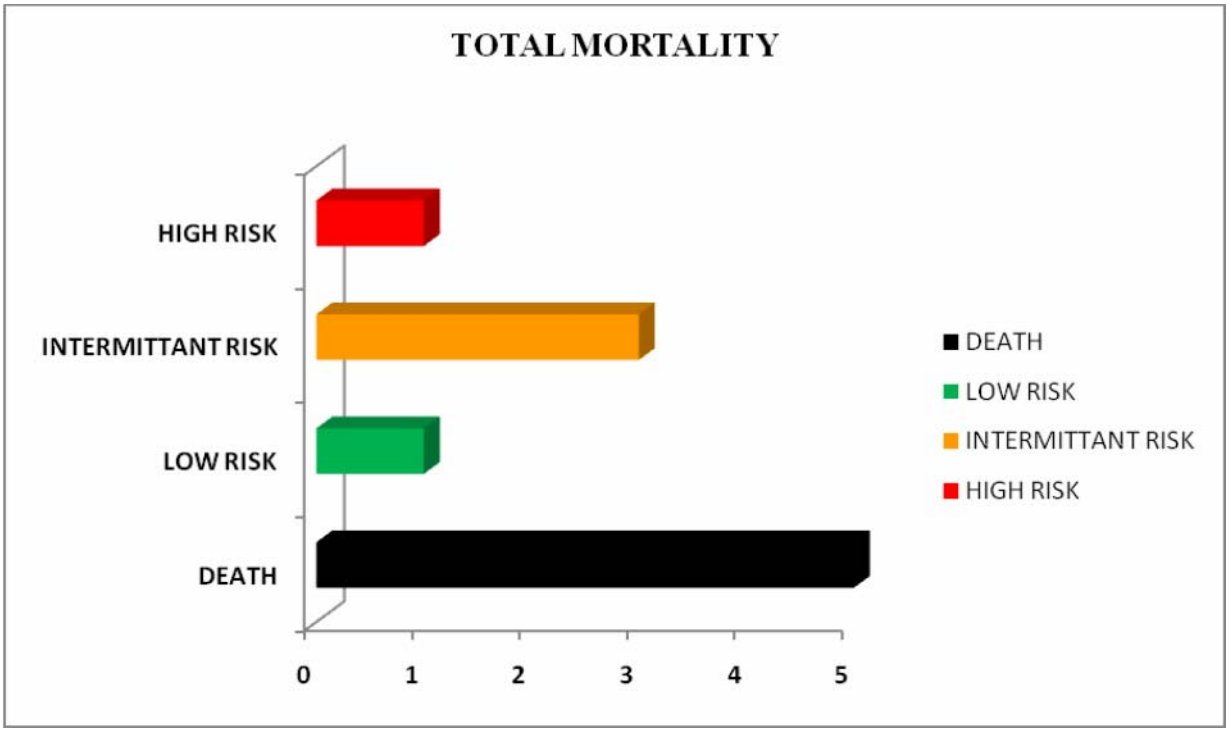


TABLE –10

TOTAL MORTALITY

	No. of patients
DEATH	**5**
LOW RISK	**1**
INTERMITTANT RISK	**3**
HIGH RISK	**1**



RESULTS

In my study, I found that:

The prevalence of elevated Hs CRP in selected cases

>0.3mg/dL - 46/50 92%

Prevalence of elevated Hs CRP in control

>0.3mg/dL - 43/50 86%

In considering the statistical significance, we had used Chi-square test and the result was obtained as follows:

Cases	**46**	**4**
Control	**43**	**7**

So, on cumulating the results, I found that:

The observed percentage of elevated Hs CRP in these patients (both Control and Cases) is = 89/100 = **0.89**.

The observed percentage of normal levels of Hs CRP in these patients (both Control and Cases) is = 11/100 = **0.11.**

INDEX	ELEVATED CRP LEVEL	NORMAL CRP LEVEL
No. of cases observed	**46**	**4**
No. of cases expected	**40.94**	**5.06**
No. of controls observed	**43.00**	**7.00**
No. of controls expected	**37.87**	**7.70**

According to Chi-square formula,

$X^2 = \Sigma$ (observed – expected)^2 / expected value

$$\Sigma (46 - 40.94)^2 / 40.94 + (43 - 37.87)^2 / 37.87 + (4 - 5.06)^2 / 5.06 + (7.00 - 7.70)^2 / 7.70$$

$$= \frac{25.6036}{40.94} + \frac{11.236}{5.06} + \frac{47.1969}{37.87} + \frac{4.9}{7.7}$$

$$= \mathbf{4.726}$$

Degree of freedom = 1

According to the above results, the **P.value is <0.05.** So, this signifies that HsCPR has a definitive role in the cardiovascular pathology.

While comparing for patients with risk factor and without risk factors, we have used chi-square test and the results are obtained as follows.

INDEX	NO. OF CASES	NO. OF CONTROLS
Mean observed in cases with risk factors	**32**	**3**
Expected mean in cases with risk factors	**29.44**	**2.4**
Mean observed in controls without risk factors	**14**	**1**
Expected mean in controls without risk factors	**11.88**	**0.8**

According to Chi-square formula:

$X^2 = \Sigma$ (observed – expected)^2 / expected value

$$\mathbf{\Sigma\ (32 - 29.44)^2 / 29.44 + (14 - 11.88)^2 / 11.88 + (3 - 2.4)^2 / 2.4 +}$$

$$\mathbf{(1 - 0.8)^2 / 0.8}$$

$$= \mathbf{1.3706}$$

Degree of freedom = 1

According to the above results, the P.value is >0.05. So, this shows that there is no statistical difference between prevalence of elevated HsCRP in cases with and without risk factors.

DISCUSSION

DISCUSSION

When evaluating any novel risk factor as a potential new screening tool, clinicians need to consider whether (1) there is a standardized and reproducible assay for the marker of interest; (2) there is a consistent series of prospective studies demonstrating that a given parameter predicts future risk; (3) the novel marker adds to the predictive value of lipid screening; and (4) there is evidence that the novel marker adds to global risk prediction scores, such as that in the Framingham heart study.

In AFCAPS and TESCAPS study which shown the role of HsCRP in cardiovascular events, has failed to include women in equal number. In Jupiter trial, one third of women was included with large sample size. But all the three studies have failed to include minority ethnics.

In our study, we have selected 16 females, one third of study population which was not done in most of the previous studies. Moreover, we had included 10% of minority ethnics in our study and the study shows there is no significant variation with community. In our study there is no significant difference in morbidity and mortality between males and females.

	AFCAPS	WOSCOPS	JUPITER
SAMPLE SIZE	6605	6595	17802
WOMEN	997	0	6801
MINORITY	350	0	5118
DURATION	5.2	4.9	1.9
DIABETES	6	1	0
LDL	150	192	108
HDL	36-40	44	49
TGL	158	164	118
CRP	-----	------	>2
INTERVENTION	LOVAS 10-40mg	PROVAS40mg	ROSUVA20mg

In our study, we had found that 35 persons have underlying cardiovascular risk factors. 35% of patients have family history of cardiovascular events. 15 patients have no risk factors, but have elevated CRP.

The average elevated level of CRP in cases with risk factors and without risk factors are significantly above level of controls we have selected.

Regarding the distribution of cases without risk factors, sevens cases are with intermediate risk value i.e., CRP between1 and 3. Six cases are with low risk value.

Regarding the distribution of cases, thirty two cases are in intermediate risk value, fifteen cases are with low risk value and three patients are in high risk group.

Regarding the total mortality, most of the patients who were died i.e. three in number belong to intermediate risk category, one person with low risk and one person with high risk.

On comparing the mortality in patients with various risk factors, hyperlipidemia plays a major role i.e. nearly four of the five deaths. Hypertension and diabetes are second most leading comorbid condition.

The study clearly shows HsCRP has a definite role in cardiovascular morbidity and mortality.

CONCLUSION

CONCLUSION

In this study it is clearly shown that most of patient selected had:

- Very high prevalence of elevated HsCRP patients with acute vascular events.
- There is definite association of HsCRP in acute vascular events than other non vascular conditions.
- The analysis in patient without any specific cardiovascular risk factors shows definite relative correlations
- Probably HsCRP may play a role in pathogenesis as mentioned in the literature above which needs further studies.
- Level of HsCRP has a definite role in determining the mortality in patients with acute vascular events.

SCOPE FOR FUTURE STUDY

SCOPE FOR FUTURE STUDIES

Although hsCRP is by far the best-characterized and most reliable inflammatory biomarker for clinical use, several other markers of inflammation have shown promise in terms of predicting vascular risk. These include cytokines such as interleukin-6, soluble forms of certain cell adhesion molecules such as intercellular adhesion molecule (sICAM-1), P-selectin, or the mediator CD40 ligand, as well as markers of leukocyte activation such as myeloperoxidase.

Other inflammatory markers associated with lipid oxidation such as lipoprotein-associated phospholipase A_2 and pregnancy-associated plasma protein A have also shown promise. However, each of these biomarkers has analytical issues that need careful evaluation before routine clinical use. For example, some have too short a half-life for clinical diagnostic testing, whereas the ability of others to predict risk in settings of broad populations has proved marginal thus far.

Nonetheless, several of these inflammatory biomarkers can shed critical pathophysiological light on the atherothrombotic process, particularly at the time of plaque rupture. For example, soluble CD40 ligand (probably released from activated platelets) may provide insight into the efficacy of specific antithrombotic agents independently of CRP.

Similarly, myeloperoxidase may provide prognostic information in cases of acute ischemia over and above that associated with troponin or CRP.Thus, continued evaluation of other inflammatory biomarkers may well provide targets for or monitors of therapy, particularly in the setting of acute coronary ischemia

DIRECT PLAQUE IMAGING

In addition to the use of inflammatory markers such as hsCRP, strategies to detect vascular disease will likely take several forms. One approach eschews risk factor measurement, but identifies preclinical disease through the noninvasive detection of atherosclerotic plaque. Such an approach can never truly prevent disease, only lead to early detection. However, because many therapies can delay clinical expression of disease once existing lesions are diagnosed, this approach merits consideration.

At this time, a number of studies have indicated that coronary calcification as detected by computed tomography (CT) can detect preclinical atherosclerosis. It remains highly controversial, however, as to whether this approach is cost-effective or has an acceptable false-negative rate. Enrollment in these studies may be biased by referral patterns or self-selection by patients. Part of the difficulty with coronary calcification as a clinical surrogate is that CT imaging probably detects the plaques least likely to rupture and does not detect the noncalcified thin-capped lesions

that appear to cause most clinical events. Thus, although coronary calcium provides a noninvasive measure of atherosclerotic burden, patients with low calcium scores cannot be dismissed as being at low risk.

Furthermore, the clinical determinants of calcification are largely unknown and may not reflect propensity to plaque rupture. Studies indicating that hsCRP elevation corresponds to an approximate doubling of risk of plaque rupture at all levels of coronary calcium have demonstrated the complexity of this approach.Although advocates of CT imaging have noted that sensitivity for the presence of angiographic coronary disease is comparable with that of noninvasive stress testing such as perfusion scintigraphy or dobutamine echocardiography, the specificity of CT imaging in this setting is low.

Relative to simple blood-based biomarkers, imaging tests currently incur considerable expense and thus may be cost-ineffective. One study has shown that provision of calcium scores does not effectively motivate patients' adherence to risk reduction regimens. In other cases, whole-body scans obtained for vascular screening have led to expensive and unnecessary work-ups and biopsies of incidental findings, often requiring repeat imaging at substantial radiation doses. Even when the costs of these false-positive findings are ignored, the quality-adjusted life-year cost estimates for CT screening have been found unfavorable. Several other

modalities for the noninvasive assessment of atherosclerosis exist, ranging from those that are well documented and inexpensive (e.g., ankle-brachial index) to those that are exploratory (e.g., thermography and magnetic resonance scanning).

Perhaps the best studied noninvasive approach is the ultrasonic measurement of carotid intimal medial thickness. This technique has proved to have strong predictive value in general population studies and minimal additional expense is required, because most centers already have the required sonographic tools in place. Whether any imaging technique will prove cost-effective as a screening tool is currently under study in the Multiethnic Study of Atherosclerosis (MESA) being funded by the National Heart, Lung, and Blood Institute. In the Rotterdam Heart Study, in which simultaneous measures of atherosclerotic burden were obtained, the ankle-brachial index performed as well as carotid intimal medial thickness (IMT) and x-ray evidence of abdominal aortic calcification, but can be performed at no cost at the bedside.

Genetic Determinants of Atherothrombosis

Venous thromboembolism has a major genetic component, and advances in genetic diagnosis (factor V Leiden and the G20210A prothrombin mutation), as well as pharmacogenetic management of

warfarin, have already been implemented in many clinical practices By contrast, although clinicians understand that myocardial infarction, stroke, and other forms of arterial disease also have a major heritable component, no genetic screening test for atherothrombosis has yet found a substantive role in routine clinical practice.

Nonetheless, with heritability estimates approaching 50 percent in several studies, this situation may well change in the future and has stimulated intensive ongoing investigation.

Deciphering the genetic underpinnings of atherothrombosis presents considerable challenges because of major gene environment interactions. Also, atherothrombosis represents a prototypic complex disease in which multiple small effects accumulate and have a substantial population attributable risk. Some genetic determinants of atherothrombotic cardiovascular disease are well established and have been replicated in multiple cohorts. Perhaps the best known of these is the relationship between polymorphism in the apolipoprotein E (apo E) gene that codes for three common isoforms (E2, E3, and E4), which in turn are associated with differential risks of coronary heart disease.

In a meta-analysis of 48 studies incorporating information from over 15,000 affected patients and 33,000 controls, carriers of the apo E e4 allele had a 42 percent higher risk for coronary heart disease (OR, 1.42; 95 percent CI, 1.26 to 1.61) compared with those with the more common e3/3 genotype, whereas carriers of the e4 allele had no significant increase in risk.Polymorphisms in the arachidonate 5-lipooxygenase–activating protein gene and its related pathways, gene, offspring Study, when compared with those with no parental history of cardiovascular disease, men with at least one parent with premature atherothrombosis (onset younger than age 55 for fathers and younger than age 65 for mothers) had an age-adjusted odds ratio of 2.6 (95 percent CI, 1.7 to 4.1) whereas the similar odds ratio for women was 2.3 (95 percent CI, 1.2 to 3.1).

These effects compare in magnitude with those of smoking, hypertension, and hyperlipidemia in the Framingham cohort itself. As noted subsequently, analysis of data from the Women's Health Study has also recently found that a parental history of myocardial infarction before age 60, along with knowledge of CRP levels, can reclassify large numbers of patients as being at higher or lower risk than would have been anticipated on the basis of traditional risk factors alone.

The ultimate promise of an improved genetic understanding of cardiovascular risk is the concept of “personalized medicine,” in which targeted interventions can get the right drug to the right patient at the right time.

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ANNEXURE

- **PROFORMA**
- **MASTER CHART**
- **ETHICAL COMMITTEE APPROVAL ORDER**
- **ABBREVIATIONS**
-

PROFORMA

Name: **Age:**

Sex: **Education:**

Occupation: **Community:**

H/O cardiovascular events

Comorbidities:

Diabetes: **Hypertension:**

Congestive Heart Failure: **Hepatitis B/C:**

H/O Smoking: **Alcoholism:**

Family h/o cardiovascular events:

Now admitted for:

EXAMINATION:

Height **weight** **BMI**

Pulse **BP (upper limb)**

CVS **RS** **Abd** **CNS**

INVESTIGATIONS:

CBC: **Hb:** **TC:** **DC:** **ESR:** **PCV:**

PLTS:

Renal Function Test: **sugar:** **urea:** **creatinine:** **Na, K**

Liver function tests:

CXR: if indicated

ECG

ECHO

CPK MB

CT BRAIN

FBS

FLP

HsCRP

Final diagnosis

MATER CHART

Sl.No.	Name	Age	Sex	Community	Family History	HT	DM	LDL > 100	HDL < 40/50	TGL > 150	CKMB elevated	FBS > 110	CT Brain	echo wall motion abnormalrmalities	HsCRP	DiagNosis	HsCRP > 0.3	Category	OUTCOME AFFTER 3O DAYS
1	Anjan	44	M	Hindu	No	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Yes	i.7	MI	Yes	II	
2	Elumalai	52	M	Hindu	No	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Yes	2.4		Yes	II	
3	Alagesan	50	M	Hindu	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	1.4		Yes	II	
4	Thirumathi	45	F	Hindu	Yes	Yes	No	No	No	No	Yes	Yes	Not applicable	Yes	1.3		Yes	II	
5	Selvi	47	F	Hindu	No	No	No	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	3		Yes	II	
6	Thiruvatharia	46	M	Hindu	Yes	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Normal	4		Yes	III	
7	Angel	39	F	Christian	Yes	Yes	No	Yes	No	No	Yes	Yes	Not applicable	Normal	0.94		Yes	I	
8	Eswar	41	M	Hindu	No	No	No	No	No	No	Yes	Yes	Not applicable	Yes	1.3		Yes	II	
9	Ebinezar	47	M	Christian	No	No	No	No	No	No	Yes	Yes	Not applicable	Yes	1.4		Yes	II	
10	Selvam	55	M	Hindu	No	No	Yes	Yes	No	No	Yes	Yes	Not applicable	Normal	1.7		Yes	II	
11	Senbagam	62	F	Hindu	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	1.9		Yes	II	
12	Rajalaxmi	59	F	Hindu	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	4		Yes	III	
13	Devi	41	F	Hindu	Yes	No	No	Yes	No	No	Yes	Yes	Not applicable	Normal	3		Yes	II	
14	Christoper	50	M	Christian	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	3		Yes	II	
15	Habeeb	41	M	Muslim	No	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Normal	1		Yes	II	
16	Saravanan	47	M	Hindu	No	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Normal	1.5		Yes	II	
17	Shanmugam	47	M	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	2	UNSTABLE ANGINA	Yes	II	
18	Anbu	54	M	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	1.5		Yes	II	
19	Anburajan	47	M	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	3		Yes	II	

20	Mathil	50	F	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	1.11		Yes	II	
21	Thulisai	41	F	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	1.5		Yes	II	
22	Arijagam	59	F	Hindu	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Not applicable	Normal	2.9		Yes	II	
23	Mani	62	M	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	2.7		Yes	II	
24	shanmugam	39	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	1.5		Yes	II	
25	Arunagiri	46	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	2.7		Yes	II	
26	Aseem	71	M	Muslim	No	No	No	No	No	No	Yes	No	Not applicable	Normal	2		Yes	II	
27	Fakurudin	64	M	Christian	No	No	No	No	No	No	Yes	No	Not applicable	Normal	3		Yes	I	
28	John	63	M	Christian	No	No	No	No	No	No	Yes	No	Not applicable	Normal	0.8		Yes	I	
29	Moorthi	60	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Yes	0.9		Yes	I	
30	Balaji	47	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	0.03		No	II	
31	Rajalaxmi	48	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	3		Yes	I	
32	Natarajan	52	M	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	0.7		Yes	I	
33	Nagaraj	51	M	Hindu	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Not applicable	Normal	0.02		No	II	
34	Govind	41	M	Hindu	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Not applicable	Normal	1.2		Yes	II	
35	Pichumani	35	M	Hindu	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	2.4		Yes	II	
36	Chellam	65	F	Hindu	No	Yes	No	No	No	Yes	Yes	No	Not	Normal	3	STROKE	Yes	II	

													applicable					
37	Raji	55	F	Hindu	No	Yes	Yes	No	No	Yes	Yes	Yes	Not applicable	Normal	4		Yes	III	
38	Devi	60	F	Hindu	Yes	No	No	Yes	Yes	Yes	Yes	No	Not applicable	Normal	3		Yes	II	
39	Dhanalaxmi	61	F	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	2.5		Yes	II	
40	Priya	49	F	Hindu	No	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Normal	2.6		Yes	II	
41	Danapriya	67	F	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	1		Yes	II	
42	Laxmi	81	F	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	0.67		Yes	I	
43	Psuedamani	47	M	Hindu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	0.2		No	I	
44	Kanna	52	M	Hindu	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not applicable	Normal	0.9		Yes	I	
45	Kandasamy	47	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	0.19		No	I	
46	Kasirajan	63	M	Hindu	Yes	Yes	Yes	No	No	No	Yes	Yes	Not applicable	Normal	0.79		Yes	I	
47	Veerapan	58	M	Hindu	No	No	No	No	No	No	Yes	No	Not applicable	Normal	0.2		No	I	
48	kumar	51	M	Hindu	No	No	No	Yes	Yes	Yes	Yes	No	Not applicable	Normal	0.19		No	I	
49	Pichai	60	M	Hindu	No	No	No	Yes	Yes	Yes	Yes	No	Not applicable	Normal	0.7		Yes	I	
50	siva	71	M	Hindu	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Normal	0.8		Yes	I	
															1.745714286				

MASTER CHART

Sl.No	Name	Age	Sex	Community	diagnosis	HsCRP
1	Rani	30	F	Hindu	fever	
2	Selvi	25	F	Hindu	LRI	1.2
3	Reeta	45	F	Christian	LRI	1.3
4	Prema	28	F	Hindu	FEVER	0.4
5	Kannamma	40	F	Hindu	TRAUMA	0.2
6	Rajeswari	35	F	Hindu	POST OP	1.3
7	Najma	28	F	Muslim	TRAUMA	1
8	Thawamani	40	F	Hindu	DKA	1.4
9	Nansi	35	F	Christian	TRAUMA	0.3
10	Mala	28	F	Hindu	AC.ABDOMEN	2
11	Usha	32	F	Hindu	DKA	1.2
12	Sarooja	40	F	Hindu	HAEMORHAGIC STROKE	1.4
13	Madhavi	29	F	Hindu	SLE	2.1
14	Kanmani	31	F	Hindu	FEVER	1
15	Mari	28	F	Hindu	FEVER	2
16	Kanjana	48	F	Hindu	FEVER	0.24
17	Muniyamman	50	F	Hindu	DKA	0.24
18	Revathi	42	F	Hindu	LRI	0.9
19	Amutha	50	F	Hindu	UTI	0.8
20	Indira	30	F	Hindu	AC.ABDOMEN	1.6
21	Rani	40	F	Hindu	DENGUE	1.4
22	Priya	32	F	Hindu	ARF	1
23	Rajeetha	40	F	Muslim	MYOACARDITIS	2
24	Patima	35	F	Muslim	DKA	1.8
25	Antony	40	M	Christian	FEVER	1
26	Raja	42	M	Hindu	FEVER	0.9
27	Rajendran	40	M	Hindu	TRAUMA	1.2
28	Abdulla	35	M	Muslim	POST OP	1
29	govindan	48	M	Hindu	TRAUMA	1.3
30	Kumaran	32	M	Hindu	DKA	1.2
31	Sekar	35	M	Hindu	TRAUMA	0.34
32	Senthil	28	M	Hindu	LRI	0.2
33	James	18	M	Christian	DKA	0.45
34	Santhanam	22	M	Hindu	LRI	0.35
35	Dharmaraj	30	M	Hindu	fever	0.6
36	Manoharan	40	M	Hindu	fever	0.7
37	Arockiam	38	M	Christian	UTI	0.8
38	Munian	28	M	Hindu	UTI	1.6
39	Mariappan	32	M	Hindu	DKA	1.25
40	Vellu	30	M	Hindu	FEVER	1.3
41	Amalraj	30	M	Christian	FEVER	0.4
42	venkatesh	28	M	Hindu	TRAUMA	0.46
43	Sridhar	40	M	Hindu	POST OP	0.34
44	Ganesh	41	M	Hindu	TRAUMA	1.2
45	Mayilswamy	23	M	Hindu	DKA	1.4
46	Durai	26	M	Hindu	TRAUMA	1.8
47	Mrugeasan	28	M	Hindu	fever	2
48	Dhanam	41	F	Hindu	FEVER	2
49	Velan	45	M	Hindu	FEVER	0.25
50						

ABBREVIATIONS

HsCRP	**:**	**High-sensitivity C-reactive protein**
IL	**:**	**Interleukin**
LDL	**:**	**Low-density lipoprotein**
PAI-1	**:**	**Plasminogen activator inhibitor-1**
sICAM-1	**:**	**Intercellular adhesion molecule-1**
SAA	**:**	**Serum amyloid A**
sCD40L	**:**	**Soluble CD40 ligand**
t-PA	**:**	**Tissue plasminogen activator**
ECG	**:**	**Electrocardiogram**
ECHO	**:**	**Echocardiogram**
CPKMB	**:**	**Creatinine Posphokinase (Miocardiam)**