PROGNOSTIC RISK STRATIFICATION OF ACUTE CORONARY SYNDROME ROLE OF HIGHLY SENSITIVE C - REACTIVE PROTEIN

A Dissertation Submitted to

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for the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

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Bonafide Certificate

This is to certify that **PROGNOSTIC RISK STRATIFICATION OF ACUTE CORONARY SYNDROME ROLE OF HIGHLY SENSITIVE C-REACTIVE PROTEIN** is a Bonafide work done by **Dr. M. DHANASEKAR**., Post Graduate Student, Department of Internal Medicine, Government Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamil Nadu Dr. M.G.R. Medical University** for the award of **M.D. Degree Branch I (General Medicine)** during the academic period from September 2011 and August 2012.

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DECLARATION

I **DR. M. DHANASEKAR** solemnly declare that this dissertation "**PROGNOSTIC RISK STRATIFICATION OF ACUTE CORONARY SYNDROME ROLE OF HIGHLY SENSITIVE C-REACTIVE PROTEIN"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Prof. Dr. D. SURENDRAN, M.D**. Professor of Internal Medicine, Govt. Kilpauk Medical College and Hospital, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine).**

Place : Chennai
Date : **(Dr. M. DHANASEKAR)**

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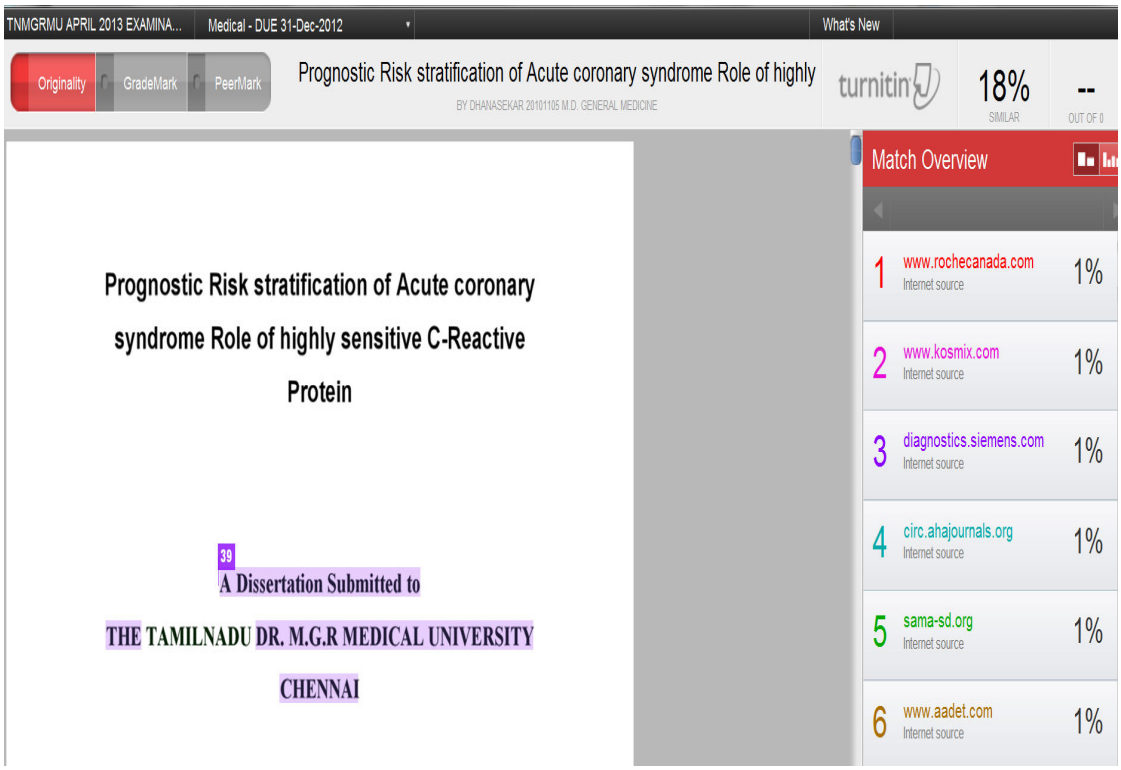
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INTRODUCTION

Acute coronary syndrome is an umbrella term which involves a varied spectrum of clinical manifestations suggesting myocardial ischemia. It varies from benign to potentially fatal illness.[1] Acute chest pain is one of the most common reasons for presentation to the emergency department. This presentation suggests acute coronary syndrome (ACS), but after diagnostic evaluation, only 15% to 25% of patients with such symptom actually have ACS.[2,3]

The usual clinical tools for risk stratification such as History, Physical Examination, ECG, Lipid Profile may be inadequate in diagnosis of MI in approximately 2% of patients, leading to short term mortality for patients with Acute MI, who are mistakenly discharged from Emergency department. These missed cases are about more than two-fold over the expected for patients who are admitted to the hospital.[3] This has led to the search for circulating markers that establish the diagnosis better.

Atherosclerosis, is a process which starts in the early childhood and progresses slowly with out manifesting any symptoms for decades. Atherosclerosis is not simply a disease of lipid deposition but it also inflammation.[4]

Histological picture from an atheromatous plaque showed the presence of inflammatory cells like macrophages, T- Lymphocytes and Monocytes. These inflammatory cells are most abundant in the shoulder region of the plaque. This region is the most common site of plaque rupture in ACS. [5-8]

As inflammation has a key role in the pathogenesis of coronary artery disease, CRP, a marker for inflammation, is a prognostic marker for stable angina pectoris, unstable angina and non-Q wave MI.[9,10] In addition to CRP, cardiac specific Troponin "T" (cTnT) a very sensitive and specific marker of myocardial necrosis has also been associated with better identification of patients having increased risk from cardiac events resulting in death and subsequent non fatal MI.[11]

cTnT has only one assay for its measurement and thus it demonstrates high degree of precision at the low end of measurement range and a relatively uniform cut off concentration. These biomarkers may be mutually complementary to each other and so multi marker testing would be helpful in better characterizing each case of ACS. (**Fig 1**)

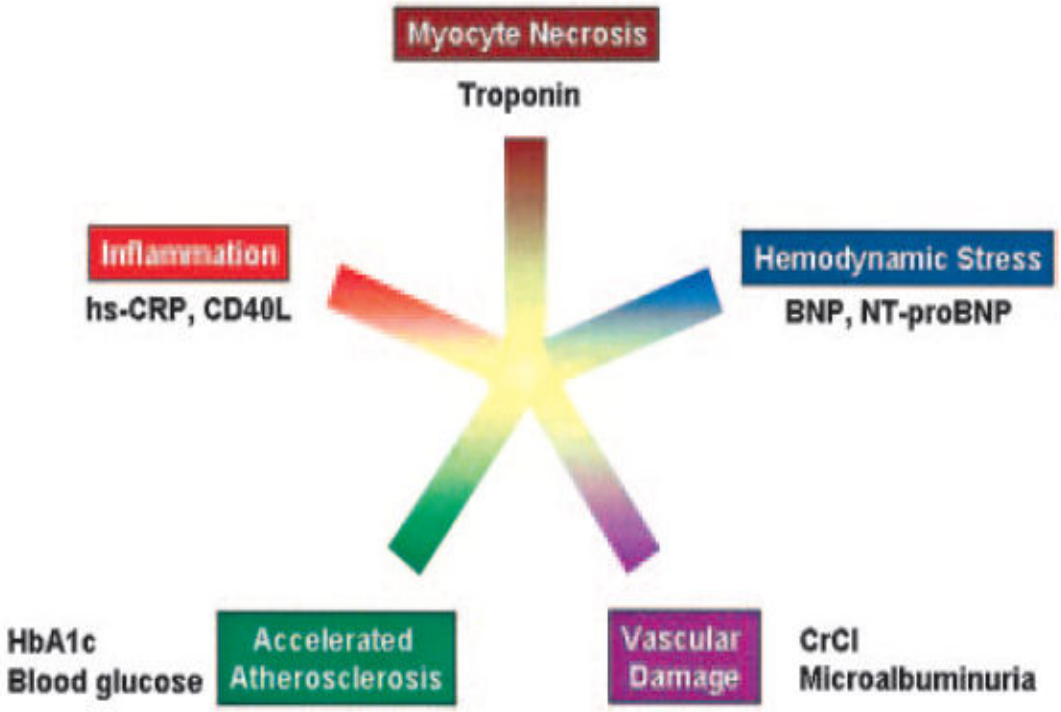


Figure 1. Biomarkers in acute coronary syndrome

In our prospective study, we decided to investigate the association of hs-CRP and cTnT obtained in patients with ACS and development of nonfatal MI and all cause mortality with in 14 days. Previous studies have little information regarding the association between highly sensitive CRP and cTnT in the adverse events of patient with ACS.

AIM AND OBJECTIVES

Aim

To access the association of hs- CRP and cTnT after 6 hours of admission in patients having ACS with nonfatal MI and Mortality with in 14 days.

Objectives

To evaluate highly sensitive CRP alone and in conjunction with cTnT as predictor of risk of individual end points of All cause Mortality and MI with in 14 days in patients admitted in the Emergency dept and ICCU of Cardiology Dept in Kilpauk Medical College Hospital.

REVIEW OF LITERATURE

UA/NSTEMI is commonly due to severe obstruction, but not total occlusion, of the culprit coronary artery. The incidence of NSTE-ACS, is increasing, probably due to demographic changes in the population, including progressively increasing numbers of older persons and higher rates of diabetes and hypertension.[12] According to OASIS registry, Indian patients are 7 to 8 years younger than western patients with mean age of 57 years as against 65 years in western population. According to CREATE registry in the year 2008, 20,000 patients admitted in multiple centres in india, 33 percent of this patients were less than 50 years of age. Smoking was the risk factor in 50% patients. The mortality rate of NSTEMI was 4% which is 1% more than in western population.[13]

Definition

Stable angina pectoris typically manifests as a deep, poorly localized chest or arm discomfort or pain, reproducibly precipitated by physical exertion or emotional stress, and relieved within 5 to 10 minutes by rest or sublingual nitroglycerin. In contrast, **unstable angina** is defined as "angina pectoris (or equivalent type of ischemic discomfort) with at least one of the three features: (1) occurring at rest (or minimal exertion) and usually lasting >20 minutes, (2) being severe and usually described as frank pain; or (3) occurring with a crescendo pattern (i.e., pain that awakens the patient from sleep or that is more severe, prolonged, or frequent than previously)".

Pathophysiology

Five patho physiologic processes contribute to the development of **UA/NSTEMI,[14] shown in Fig 2.**

1. Plaque rupture or erosion with superimposed non occlusive thrombus,
2. Dynamic obstruction due to
    a. Spasm of an epicardial coronary artery,
    b. Local vasoconstrictors, such as thromboxane A2, released from platelets;
    c. constriction of the small, intramural muscular coronary arteries, that is, the coronary resistance vessels,
    d. adrenergic stimuli including cocaine and cold and
    e. dysfunction of the coronary endothelium;
3. Inflammation and
4. Severe coronary luminal narrowing caused by progressive coronary atherosclerosis or post–percutaneous coronary intervention restenosis;
5. Secondary unstable angina, that is, severe myocardial ischemia due to increased myocardial oxygen demand or decreased oxygen supply (e.g., tachycardia, fever, hypotension, or anemia).

Individual patients may have several of these processes coexisting as the cause of UA/NSTEMI.

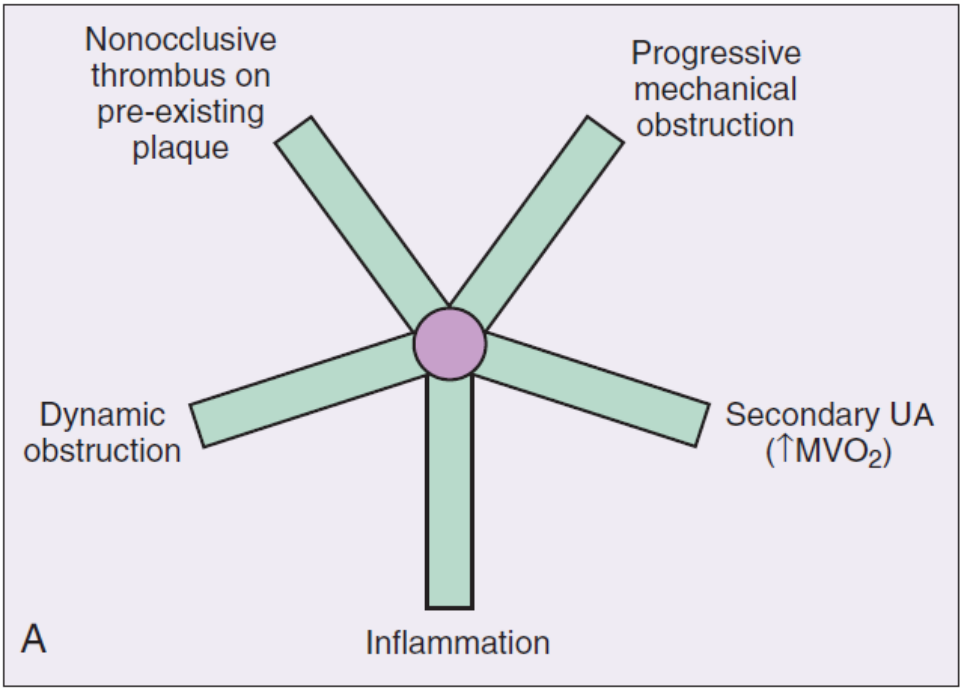


Figure 2. Causes of unstable angina (UA)

MVO2 = myocardial O2 consumption.

ACS is the manifestation of sudden plaque rupture with subsequent occlusive or subocclusive thrombus formation, leading to distal myocardial ischemia or myonecrosis (**Fig 3**).[15]

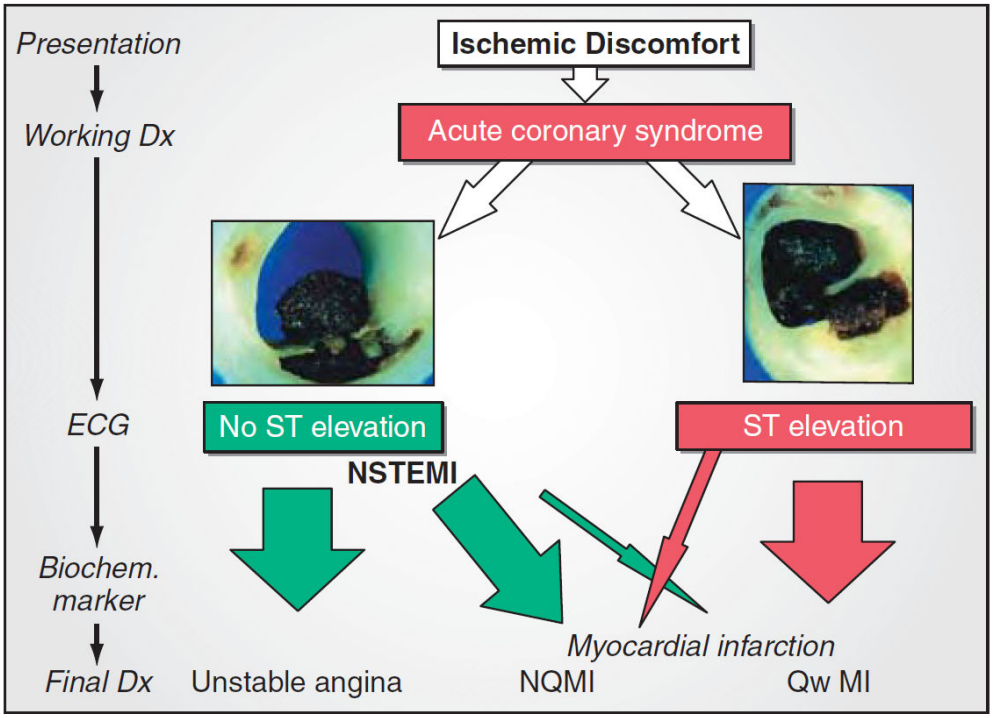


Figure - 3. Various presentations of ACS

Cardiac muscle Necrosis disrupts the structure of sarcolemmal membrane. Following the disruption intracellular macromolecules (cardiac enzymes) begins to diffuse in to the cardiac interstitium,vasculature and lymphatics surrounding the infarct. [16,17] The rate of appearance of these macromolecules in the peripheral circulation depends on several factors, including intracellular location, molecular weight, local blood and lymphatic flow, and rate of elimination from the blood.[18]**(Fig 4) .**

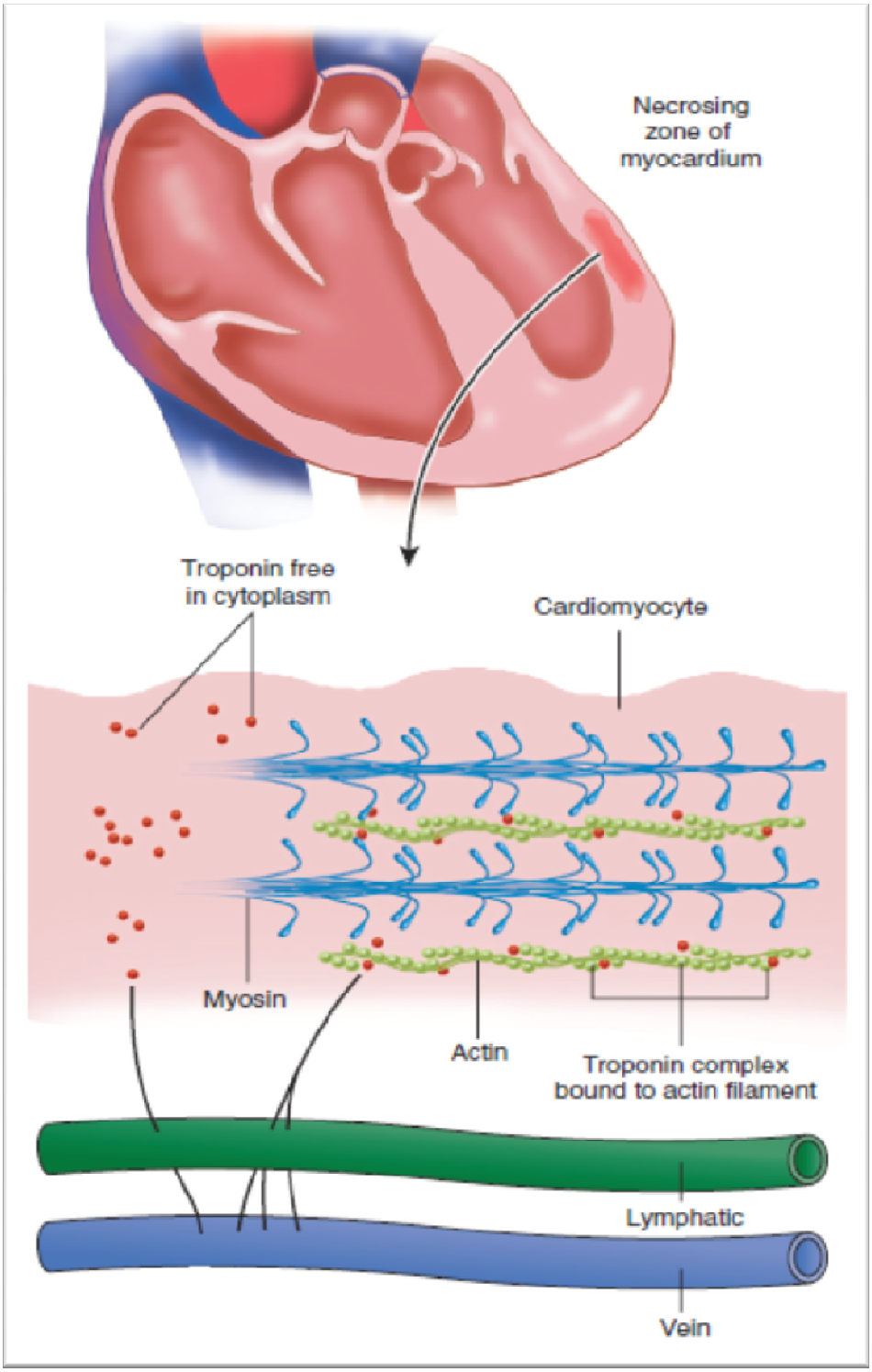

Necrosing
zone of
myocardium
Troponin free
in cytoplasm
Cardiomyocyte
Myosin
Actin
Troponin complex
bound to actin filament
Lymphatic
Vein

Figure 4

Cardiac Bio Markers Predicting Unstable Angina and NSTEMI are,

- **Increased troponin T** or **I** or creatine kinase–MB
- **Increased C-reactive protein** or white blood cell count
- Increased B-type natriuretic peptide
- Elevated creatinine
- Elevated glucose or hemoglobin A_{1c}

Cardiac bio markers predicting STEMI are shown in **(Table 1),**

Table 1 Biomarkers for Evaluation of Patients with STEMI

Biomarker	Molecular Weight (Da)	Time Of Elevation (Hr)	Time of Peak Elevations (Nonreper fused)	Time To Return To Normal
CK-MB	86,000	3-12	24 hr	48-72 hr
C TnI	23,500	3-12	24 hr	5-10 days
CtnT	33,000	3-12	12 hr-2 days	5-14 days
Myoglobin	17,800	1-4	6-7 hr	24 hr

These serum markers form the foundation of a "multimarker strategy" for evaluation and risk stratification of UA/NSTEMI patients. (**Fig. 5**)

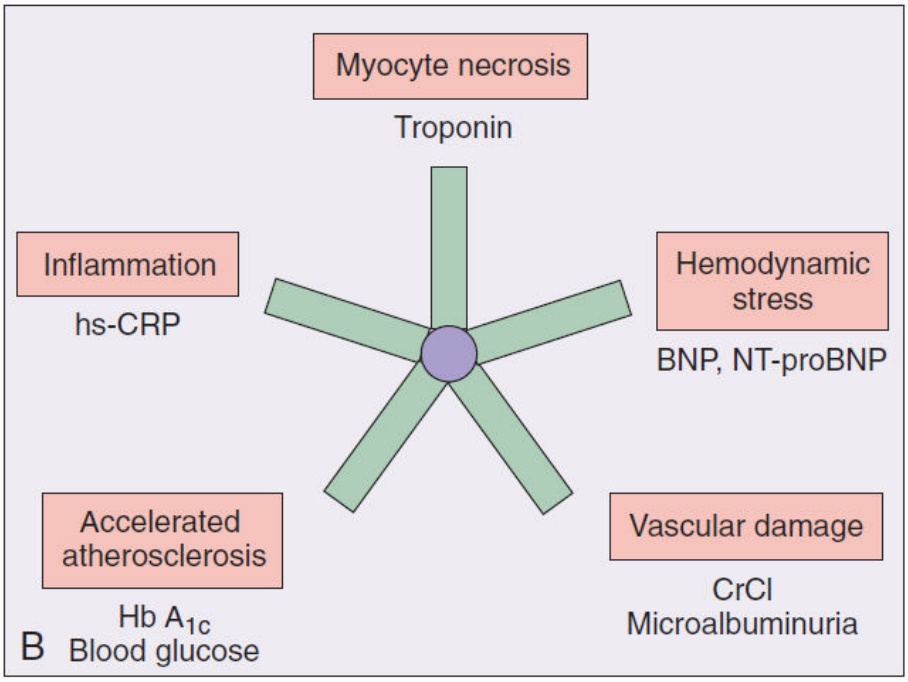


Fig 5. A multimarker strategy for evaluation of the etiology and prognosis of UA/NSTEMI. In addition, these now have been seen to be independent markers of an adverse prognosis. BNP = B-type natriuretic peptide; CrCl = creatinine clearance; Hb A1c = hemoglobin A1c; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-BNP; UA/NSTEMI = unstable angina or non–ST elevation myocardial infarction.

Clinical Classification

A clinical classification of UA/NSTEMI [19] (**Table 2**) provides a useful means to stratify risk. Patients fall into three groups according to the clinical circumstances of the acute ischemic episode: (1) primary unstable angina caused

by reductions of myocardial perfusion (2) secondary unstable angina (e.g., with ischemia related to precipitating factors such as anemia or an acute MI), and (3) post-MI unstable angina. Patients are classified simultaneously according to the severity of the ischemia. This classification provides valuable prognostic information (with postinfarction angina at rest having the worst prognosis).

Table 2 Braunwald Classification of Unstable Angina (UA)

Severity		**Clinical Circumstances**		
		A	**B**	**C**
		Develops in presence of extra cardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extra cardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (post infarction UA)
I	New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hr (angina at rest, sub acute)	IIA	IIB	IIC
III	Angina at rest within 48 hr (angina at rest, acute)	IIIA	IIIB Troponin negative IIIB Troponin positive	IIIC

hr, hours; IAM, myocardial infarction; UA, unstable angina.

INFLAMMATORY CELLULAR BASIS IN ATHEROGENESIS

Atherosclerosis is an inflammatory reaction which occurs due to lipid accumulation in the damaged arterial wall. The science of inflammation in atherosclerosis is due to localization of blood leucocytes mainly monocyte and T lymphocytes in the earliest lesion. Generally, when the arterial endothelium is normal the blood leucocytes do not bind to the endothelium. But when they are damaged by the atherogenic diet, the arterial endothelium expresses certain adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1) and (ICAM-1). **Fig 6**

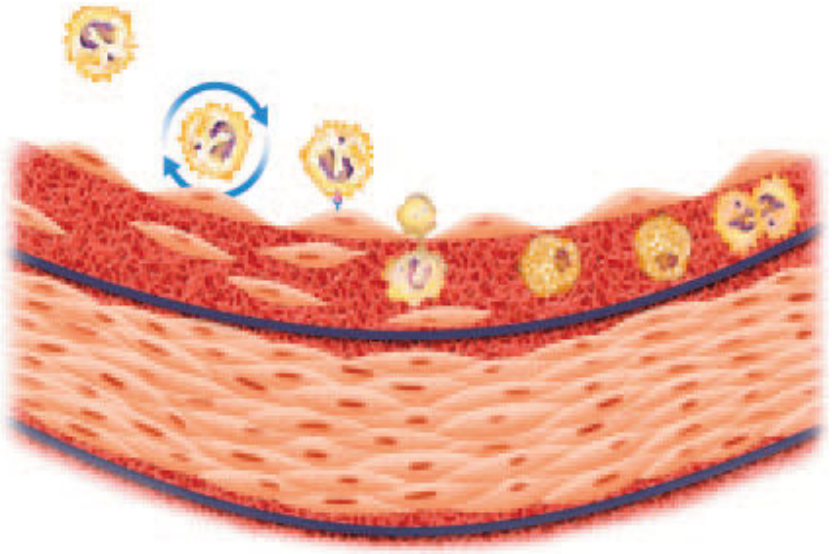


Fig. 6. Initiation of atherosclerosis

VCAM-1 binds mainly to monocyte and T-lymphocytes which are found in atheromatous plaque.[20,21]

In the arterial tree there exists a natural protective mechanism, produced by the anti-inflammatory property of NO, which are secreted by arterial trees. This decreases the expression of vascular cell adhesion molecules (VCAM-1).[22,23]

However, due to disturbed blood flow and increased stress on the arterial wall there increases the expression of selective adhesion molecule and proteoglycans that retain leucocytes and lipoprotein particles respectively at the site of lesion.[24]

The leucocytes after adhering to the endothelium at the site of lesion migrate to the intima with the help of monocyte chemoattractant protein-1 (MCP-1).[25,26] This is followed by local inflammatory response by blood derived inflammatory cells. **Fig 7**

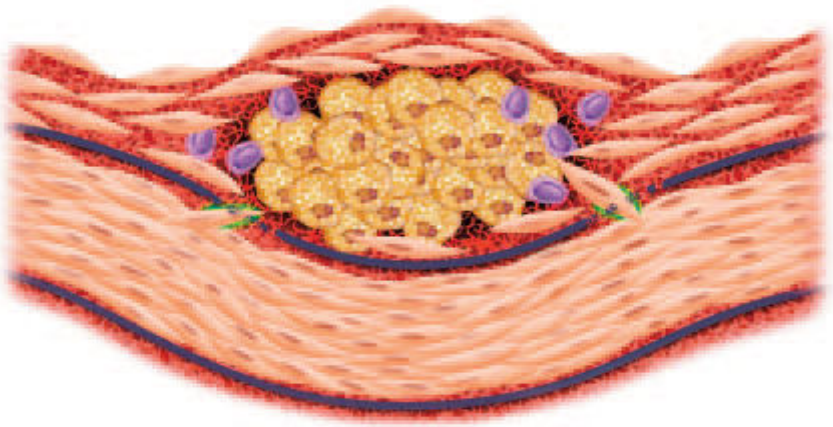


Fig 7. Atherosclerosis Progression

Monocyte chemoattractant protein-1 (MCP-1) and macrocyte colony stimulating factor are involved in the differentiation of monocytes to

macrophages. These macrophages express receptors for modified lipoproteins which engulf lipids and become foam cells. [27,28]

T Cells elaborate cytokines like lymphotoxin and γ-interferons which stimulates macrophage, smooth muscle cells and endothelial cells.[29] This process of inflammation continues and a dense extracellular matrix is laid, which is characteristic of advanced atherosclerosis. [30]

This inflammatory process which is involved in initiation and evaluation is also involved in acute thrombotic complication. **Fig 8**

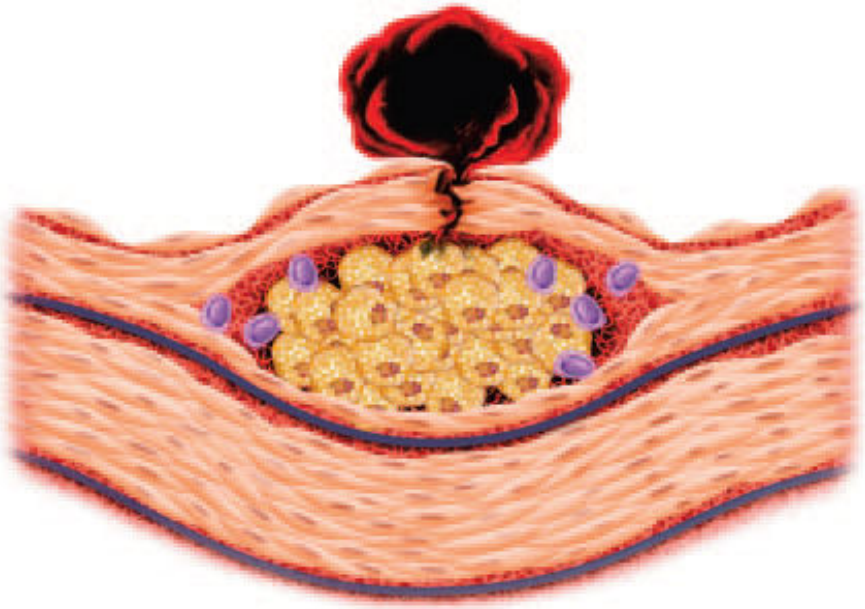
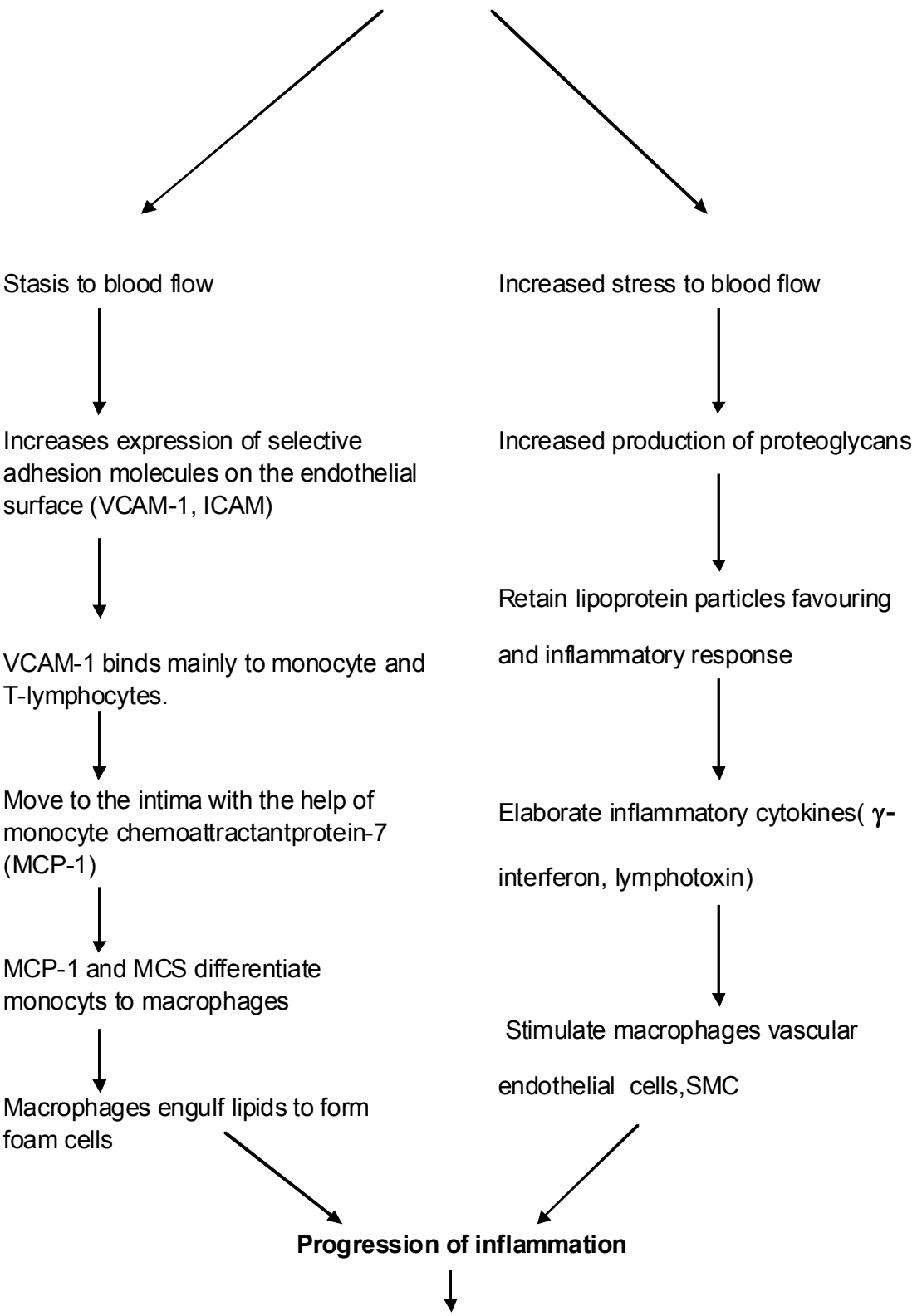


Fig 8. Formation of Thrombosis in atherosclerosis


Arterial tree endothelial injury(caused by atherogenic diet
Stasis to blood flow
Increases expression of selective adhesion molecules on the endothelial surface (VCAM-1, ICAM)
VCAM-1 binds mainly to monocyte and T-lymphocytes.
Move to the intima with the help of monocyte chemoattractantprotein-7 (MCP-1)
MCP-1 and MCS differentiate monocyts to macrophages
Macrophages engulf lipids to form foam cells
Increased stress to blood flow
Increased production of proteoglycans
Retain lipoprotein particles favouring and inflammatory response
Elaborate inflammatory cytokines(γ-interferon, lymphotoxin)
Stimulate macrophages vascular endothelial cells,SMC
Progression of inflammation

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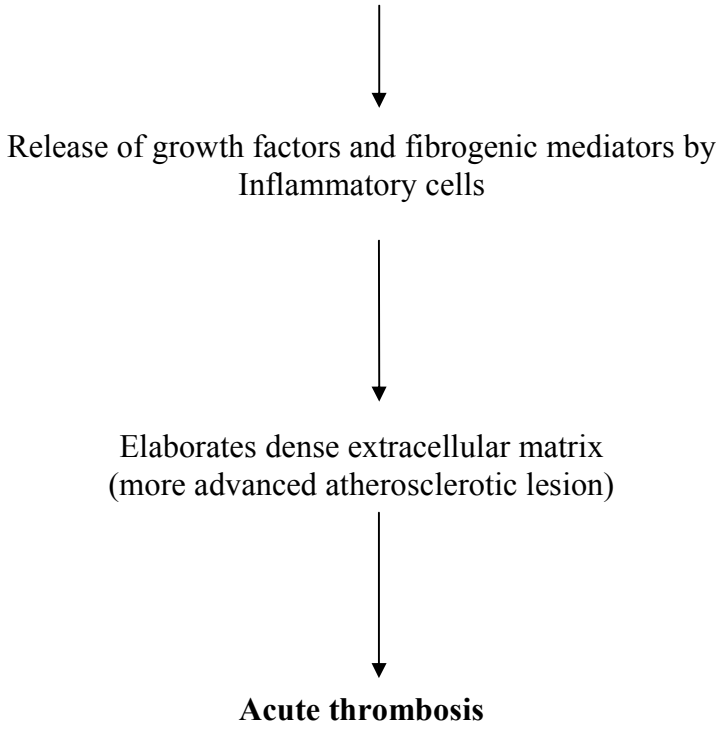


Normally collagen renders strength to the plaque and prevents rupture. T lymphocytes in the plaque produces **γ**-interferon which inhibits smooth muscle cells from synthesising collagen which in turn decreases plaque formation. Along with this the activated macrophages in the atheroma produces proteolytic enzymes which degrade the collagen and renders the cap thin, weak and susceptible to rupture. [31,32] Macrophages also triggers thrombus formation by producing a tissue factor, which is a major procoagulant. These ruptured atherosclerotic plaque causes most of the fatal acute M.I. [33] Several mediators or markers of inflammation and various sources have been described in **(Figure 9)**. **Table 3** shows the assay of inflammatory markers, which have potential for clinical use.

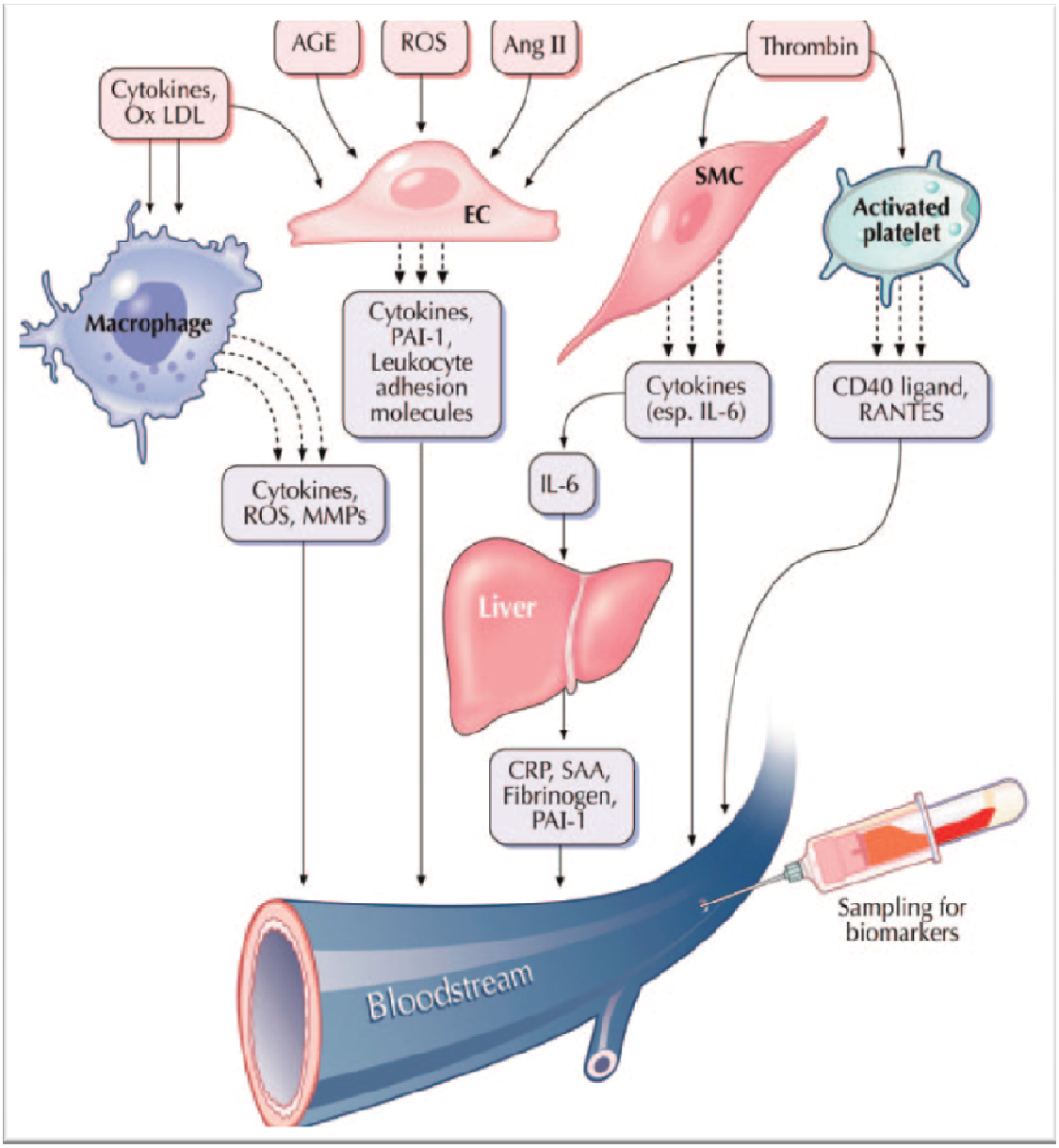


Fig 9. Various inflammatory markers release in the circulation during inflammation

Table 3. Assays of Inflammatory Markers their stability, standards available

Analyte	**Stability**	**Assay Availability**	**Standards Available**
Soluble adhesion molecules (E-selectin, P-selectin, ICAM1,VCAM-1)	Unstable (unless frozen)	Limited	No
Cytokines (interleukin-1,6 and TNF-α)	Unstable (unless frozen)	Few	Yes
Acute-phase reactants			
Fibrinogen	Unstable (unless frozen)	Many	Yes
SAA	Stable	One	Yes
hs-CRP	**Stable**	**Many**	**Yes**
WBC count	Stable	Many	Yes

PLATELET ACTIVATION AND AGGREGATION

Platelets play a key role in the transformation of a stable atherosclerotic plaque to an unstable lesion. Rupture or ulceration of an atherosclerotic plaque often exposes the subendothelial matrix (e.g., collagen and tissue factor) to circulating blood. The first step in thrombus formation is platelet adhesion via platelet glycoprotein (GP) Ib binding to von Willebrand factor and GP VI binding to collagen. The ensuing platelet activation leads to (1) a shape change in the platelet (from a smooth discoid shape to a spiculated form, which increases the surface area on which thrombin generation can occur); (2) degranulation of the platelet alpha and dense granules, releasing thromboxane A2, serotonin, and other platelet aggregatory and chemoattractant agents; (3) increased expression of the GP IIb/IIIa receptor on the platelet surface followed by a conformational change of the receptor that enhances its affinity for fibrinogen; and (4) platelet aggregation, in which fibrinogen binds to the activated platelet fibrinogen inhibitor GP IIb/IIIa, causing a growing platelet plug.

SECONDARY HEMOSTASIS

Simultaneous with the formation of the platelet plug, the plasma coagulation system is activated. Tissue factor triggers most coronary artery thrombosis. Ultimately, factor X is activated (to factor Xa), which leads to the generation of thrombin (factor IIa, which plays a central role in arterial thrombosis). Thrombin, which converts fibrinogen to fibrin, is also a powerful

stimulant of platelet aggregation and activates factor XIII, which leads to cross-linking of fibrin and stabilization of the clot. Thrombin molecules are incorporated into coronary thrombi and can form the nidus of rethrombosis.

C-REACTIVE PROTEIN

C-Reactive protein was discovered by Tillelt and Francis in 1930. It was first discovered as a substance present in the serum of individuals with acute inflammation which reacts with the capsular polysaccharide of pneumococcus.[34]

CRP belongs to pentraxin family of calcium dependent legand-binding plasma proteins. The human CRP molecule has five identical nonglyeosylated polypeptide subunits.[35] **Fig 10**

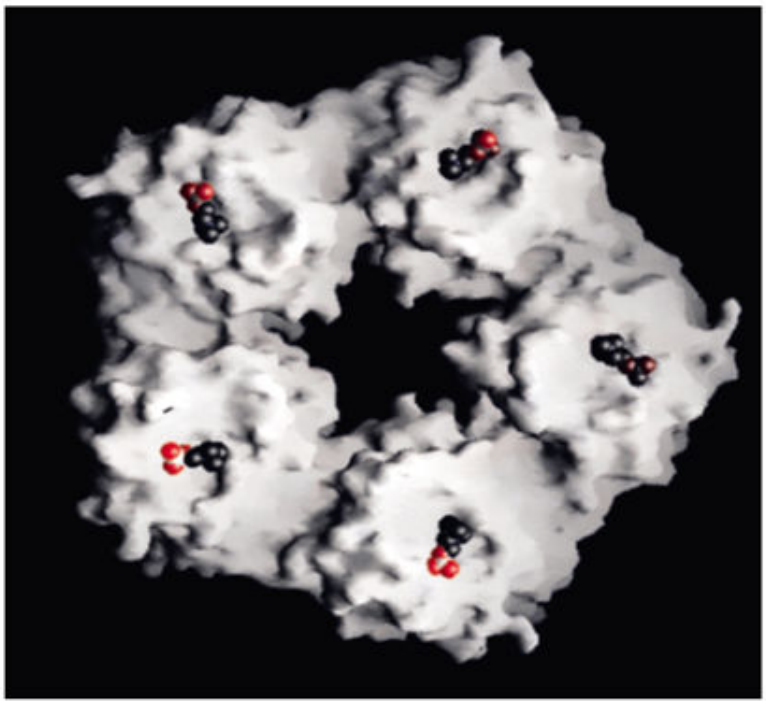


FIG - 1O. STRUCTURE OF C-REACTIVE PROTEIN

ACTION OF CRP

CRP of human beings binds with phosphocholine residues, autologus and extrinsic ligands. Auto logous ligands include plasma lipoprotein,[36] damaged cell membrane[37] etc. Extrinsic ligands include glycan, phospholipid, constituent of microorganisms such as capsular and somatic component of bacteria, fungi and parasites. When CRP binds with these ligands it is recognised by both classical and alternative complement pathway.[38,39] The CRP after binding to ligand behaves like an antibody and contributes to host defence against infection, acts as a proinflammatory mediator. Thus their levels are increased in acute inflammation.

CRP CONCENTRATION IN CIRCULATION

The median CRP concentration in healthy individuals is 0.8 mg/l, but following acute stimulus the value increases from 50μg/l to more than 500mg/l.[40] CRP value tends to slightly increase with age. It is a stable compound and shows little variation in repeated measurements. There is no significant diurnal variation and there is no difference between fasting and non-fasting values.

C reactive Protein is a Strong Predictive Biomarker Why?

Choosing CRP as a predominant biomarker of cardiovascular events, is due to some of its potential advantages over other biomarkers.

CRP has:

- Lack of age and sex dependence·
- Long half-life of (18 to 20 hours)
- Lack of its diurnal variation
- Long-term stability during storage (no special collection procedure)
- It is also a factor of proatherogenesis

CRPs are produced only by hepatocytes under the control of IL-6 are more sensitive and reliable indicator than others like leucocyte count and ESR.

CRP Genetics

The pentameric CRP must undergo structural modification,forming monomeric CRP before producing a proinflammatory reaction. Baseline levels of CRP show a clear heritability of approximately 40% in studies of families.[41] Currently, 3 poly- morphisms in the CRP gene that are associated with changes in CRP level.[42] By identifying genetic variations in the CRP gene, at-risk genotypes may be deciphered, providing additional information for overall risk assessment. Such genotype-specific risk categories may identify individuals who have relatively low serum CRP levels yet display an enhanced proinflammatory phenotype. Perhaps these higher-risk individuals will be found to have a polymorphism that decreases the stability of the pentameric structure, thereby promoting monomeric CRP formation, or alternatively, one that increases the stability of monomeric CRP binding to the cell membrane, thereby resulting in enhanced endothelial cell activation. **(figure11)**

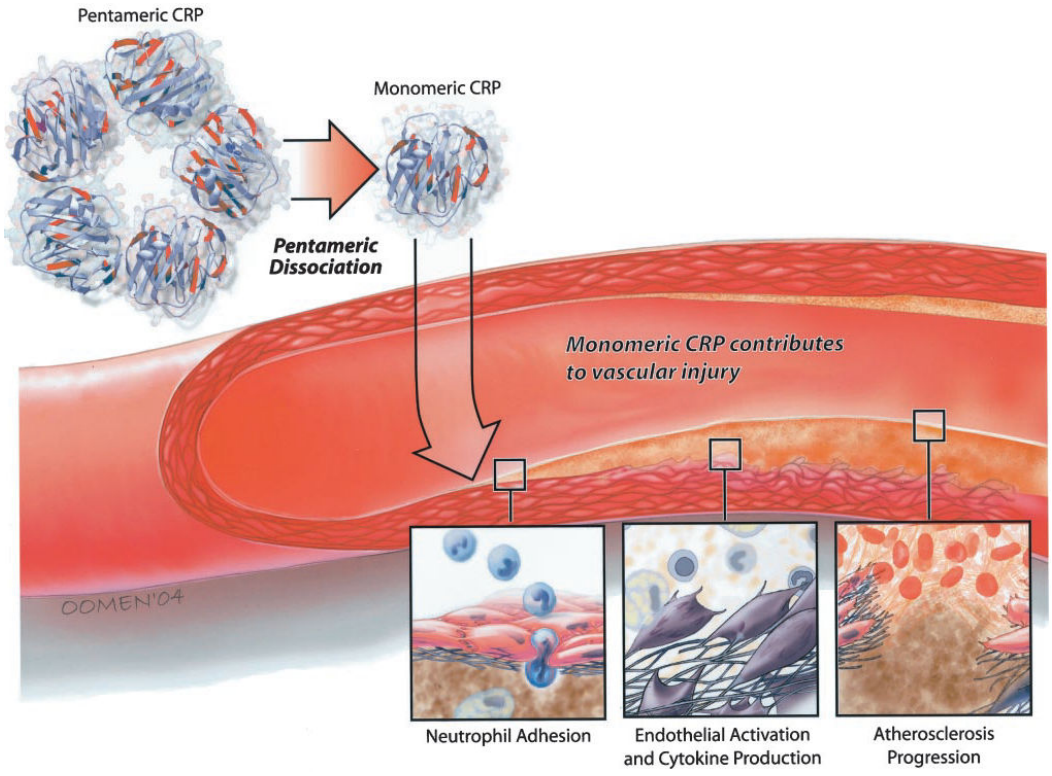


Figure 11. Changing of Pentameric CRP into Monomeric CRP and Producing Inflammatory Reaction

C - reactive protein (CRP) – A mediator in Atherogenesis and endothelial dysfunction

CRP levels correlate inversely with endothelial vasoreactivity.[43] The CRP acts by decreasing the stability of endothelial nitric oxide synthase (eNOS) m RNA. By inhibiting eNOS , CRP inhibits the release of NO which in turn blocks NO dependent angiogenesis. CRP not only inhibits eNOs but also decreases the release of prostacyclin F-1α[44] which is a stable metabolite of prostacyclin. It is a very potent vasodilator. It also prevents atherosclerosis by inhibiting platelet aggregation and by inhibiting the proliferation of smooth muscle cells. This C-

Reactive protein also stimulates superoxide anion ($O2^-$) release which inturn inhibits eNOS and PGIs activity.

It is said that PAI-1 synthesised in the liver, adipose tissue, EC, vascular smooth muscle cells and macrophages is a marker of impaired fibrinolysis and atherothrombosis and is increased in CAD patients. Increased expression of PAI-1 gene on atherosclerotic artery correlates with the increased incidence of atherosclerosis and vice versa. [45] The CRP induces PAI-1 mRNA activity in EC. **Fig12**.

Thus it strongly suggests that CRP functions as a procoagulant by a) inhibiting eNOS b) Prostacyclin c) Incresed PAI-1 gene expression

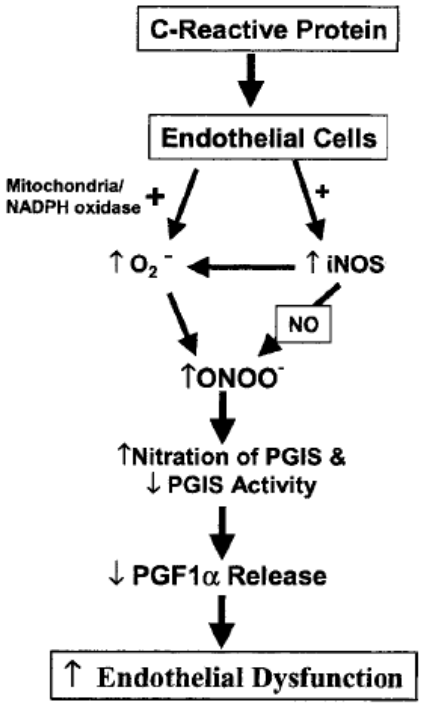


Figure12. Mechanism of CRP in atherosclerosis

CRP AND MONOCYTE-MACROPHAGES

CRP is proatherogenic in monocyte-macrophage by inducing tissue factor secretion,[46] increases cytokines (IL-1,TNFα,IL-6), increased uptake of oxidised LDL [47], etc. CRP has no effect on tissue inhibitor of metallo proteinase-1 and also that CRP is present in foam cells in the atherosclerotic lesion. **Fig 13,14**

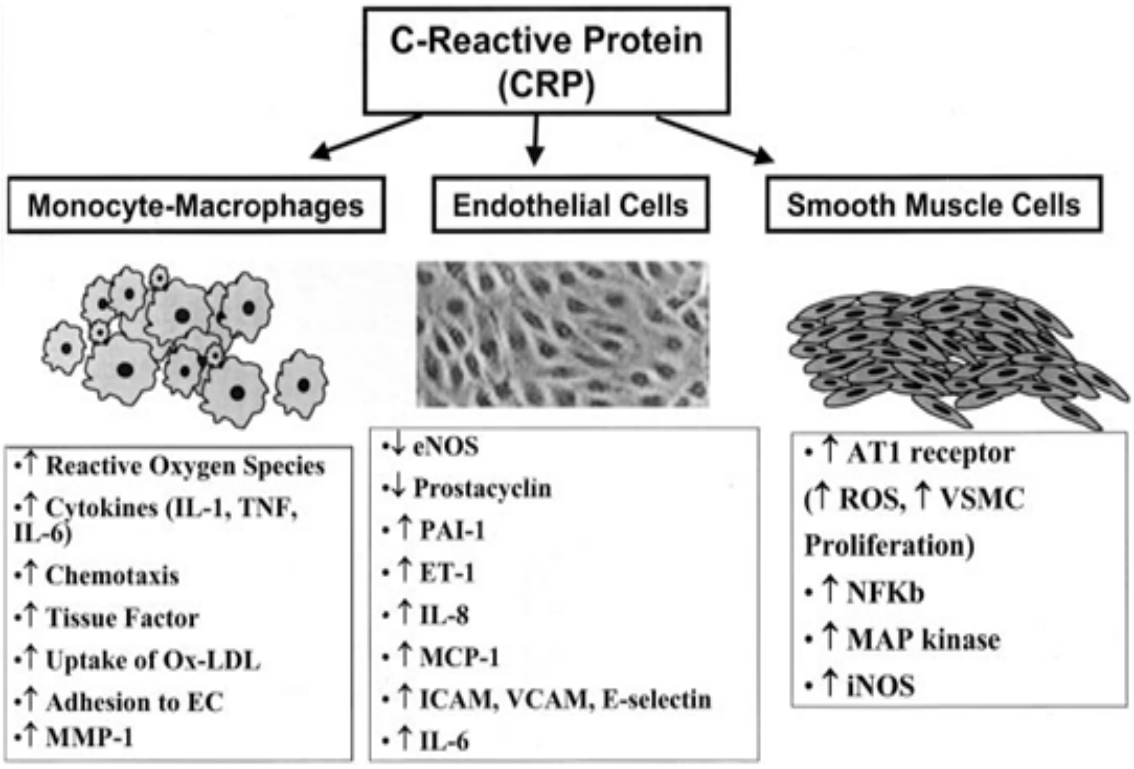


FIG - 13. EFFECTS OF CRP ON VARIOUS CELLS

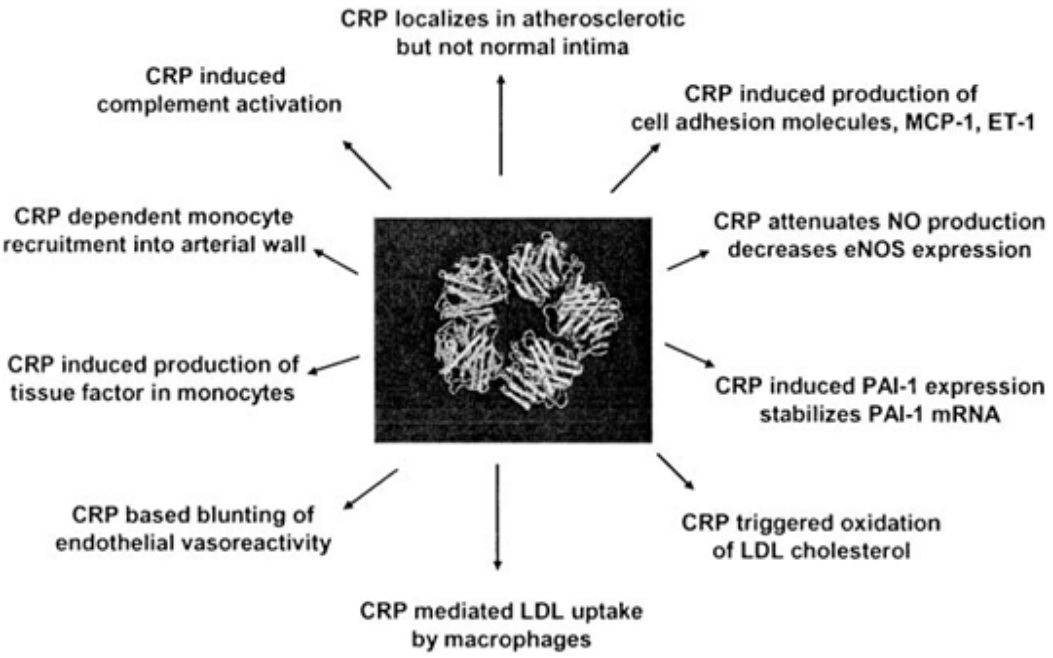


Figure 14. CRP and its association with development of atherothrombosis.

CRP IN ACUTE CORONARY SYNDROME AND STUDIES RELATING TO IT

MI is usually associated with increasing CRP level. CRP falls to normal in patients who recover uneventfully with in 3-5 days. The level of CRP remains elevated in patients with complications such as persistant cardiac dysfunction, aneurysm formation, further infarction,intercurrent infection, thromboembolism. European Concerted Action on Thrombolysis and Disabilities study showed that the elevation of CRP levels by 20% or more was found in survivors of MI and it increases further if other sites, such as peripheral vasculature are involved.[48]

In the study by Liuzzo et al [49], it was showed that patients with unstable angina and with increased CRP(≥3mg/l) and increased serum amyloidA had higher rate of death, acute MI and need for revascularisation surgery compared to patients with normal levels. In another study, TIMI showed that the risk increased when the CRP level was high and it presented very early i.e., within 14 days. [50]

In FRISC study they showed that the level of CRP measurement was associated with increase risk. The CRP level was measured at the time of study only. The risk of coronary events continues to increase throughout for many years.[9] **Table 4**

Table 4: Studies relating CRP and its association with risk of coronary events.

Study/Trial	Results
Liuzzo et al. (23)*	Increased rate of death, MI, and revascularization in patients with unstable angina and CRP ≥3 mg/l plus elevated serum amyloid A.
TIMI IIa substudy (24)*	Increased risk associated with higher CRP levels, evident as early as 14 days after ACS.
CAPTURE (25)*	CRP is an independent predictor of increased risk at 6 months.
FRISC (26)*	Increased risk associated with higher CRP levels at index event.
Mueller et al. (27)	CRP predictive of short- and long-term mortality among ACS patients treated with early revascularization.

*The predictive value of CRP was independent of, and additive to, that of troponin.
ACS = acute coronary syndromes; CAPTURE = Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment; CRP = C-reactive protein; FRISC = FRagmin during InStability in Coronary artery disease; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

In a study by R.J. de winter et al said that an abnormal CRP >0.5mg/l and an abnormal TnI (>0.4mg/l) was more in patients with major cardiac events.[51]

Suleiman et al reported that hs-CRP in patients admitted with acute MI is predictor of future heart failure and early death. The CRP also provides information about the prognosis in these patients.[52] **Fig 15**

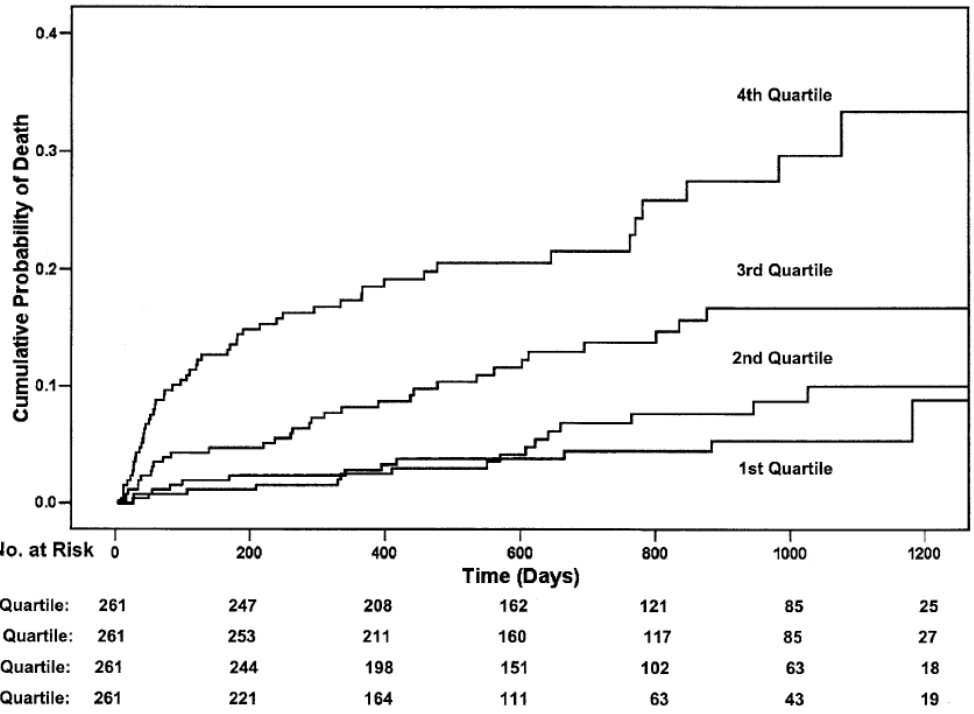


Figure 15. Incidence of death with respect to CRP

C.M.Nagesh & Ambuj Roy et al reported. In cases of AMI, CRP release is triggered as an acute phase reactant secondary to necrosis and levels of CRP are much higher and these have been correlated with infarct size.[1] **A.Dibra et al**. reported Myocardial salvage was measured by technetium (Tc)-99m sestamibi scintigraphy. Patients in the high CRP group had a significantly lower salvage index (0.35 ± 0.42 vs 0.48 ± 0.34, p=0.01) and higher 18-month mortality (11.7 vs 3.2%, p=0.03) compared to those in the low CRP group **Fig16** .[53]

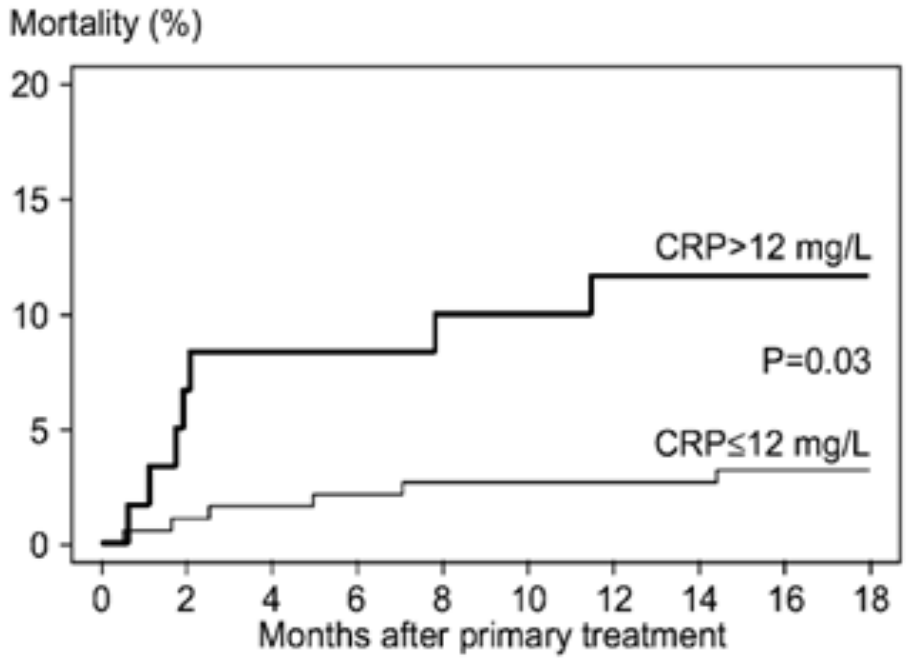


Fig 16 Percentage Of Mortality With Respective CRP Level During 18 Months Of Follow Up

TIMI 11A study reported that the mortality was high in patients having both an early positive rapid cTnT and CRP>1.55mg/dl followed by either of them but there is very low risk in patients with both CRP< 1.55mg/dl and a negative value of cTnT.[50]

Sano et al in their study they included only patients with AMI treated within 6 hours of the onset of symptoms. There were no differences in CK-MB or Troponin T at admission, which suggests their elevated CRP levels may reflect coronary lesions just before rupture but are unlikely to reflect myocardial necrosis.

It has also been suggested that CRP is elevated in the setting of "active" angina and that elevated CRP may be a predictor of a future risk of the onset of AMI.

[54,55]CRP not only plays an role in vascular inflammation but also in plaque rupture. So Serum CRP levels may reflect lesion characteristics in the setting of AMI.

De Servi et al, in his study evaluated the cTnT is a sensitive and specific marker of myocardial necrosis and is the best in the prediction of both death and myocardial infarction. In that study it was also told that the highest values of cTnT was associated with mortality only and not with Myocardial infarction. In the same study they reported various values of CRP in Acute Coronary Syndrome as CRP level depends on various stimulus. This explains that why high CRP level in ACS is good predictor of death and MI.[56]

RISK STRATIFICATION OF ACS AND hS-CRP

In individuals with ACS, CRP level has been showed to predict adverse and future cardiac events. In many prospective studies it has been reported that CRP is a strong predictor of future coronary events among apparently healthy women and men. CRP is an independent risk factor for the cardio vascular disease. CRP as hs-CRP is need for risk stratification.[4] In a substudy, GUSTO-IV, they reported that in patients with ACS both cTnT and CRP were independent risk factor for the predicton of mortality, but only cTn was associated with the

predicton of MI and that the combination of both CRP and cTnT provided a better risk stratification for mortality.[57] In physician's health study they measured baseline value of CRP, TC, HDL-C and found that individuals with both raised CRP and TC subsequently developed their first MI (RR 55.0, P50.0001) than with individuals with either increased CRP (RR 51.5) or TC (RR 52.3). [58] **Fig 17** shows various prospective studies relating baseline CRP levels to the risk of first cardiovascular events.

Albert and Ridker et al, made a study on hs-CRP and CVD risk prediction among women.

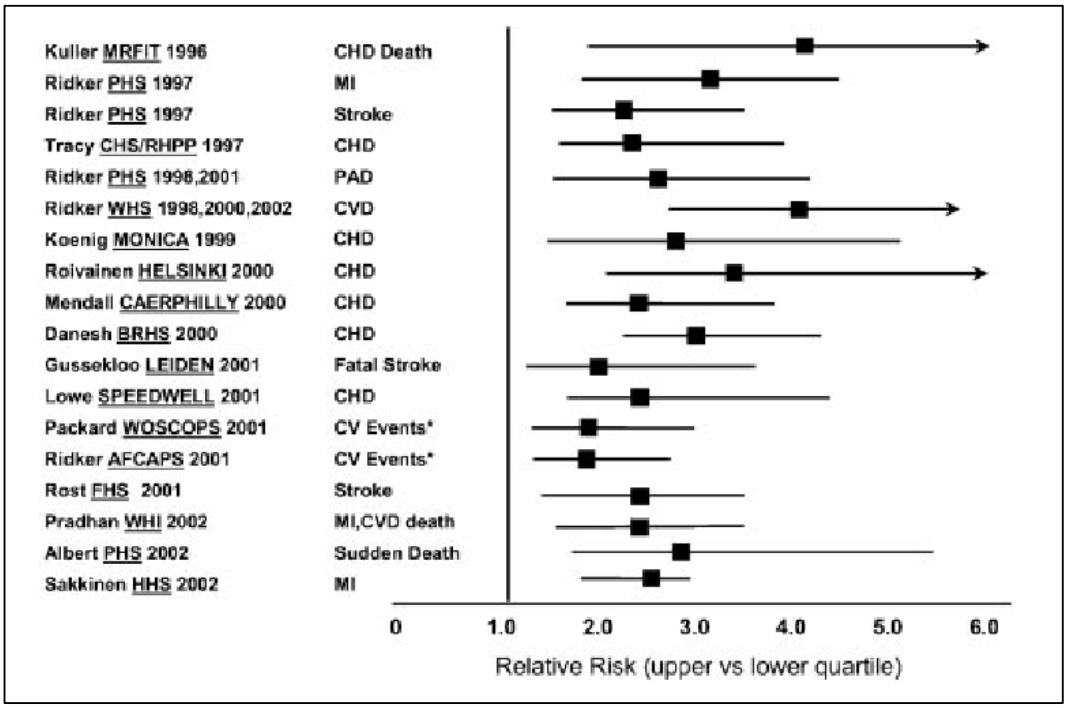


Figure 17. Levels of CRP to the cardiac vascular events in different studies

National health and nutrition examination survey 1999-2000 showed that hs-CRP level increases with age and also showed that the values of CRP was significantly high among women than men and aged>15 years. [59] In the same study they showed that hs-CRP level was higher in post menopausal women taking conventional oral HRT than those who do not. [60,61]

On admission in patients with unstable angina blood should be drawn for hs CRP while admission or at discharge. Higher level of CRP should be considered as high risk for future ischemic events and managed aggressively. These include appropriate medical therapy (Statins, Aspirin, ACE inhibitors) and also coronary revascularisation in needed.

IN PATIENTS WITH CORONARY REVASCULARISATION

It has been told that CRP levels > 0.3mg/dl before or > 0.5mg/dl at 72 to 96 hours after the procedure should be closely followed up for ischemic complications and late restenosis. [62]

Clearfield MB et al in their study reported that hs-CRP is an independent predictor of future risk of cardiovascular events among healthy individuals and among patients with ACS. Most of the cardiovascular events occured in patients with low to average level of LDL cholesterol. In these patients also hs-CRP aids as a predictor of first cardiovascular events which would be missed by lipid screening alone. Thus hs-CRP is a potential adjunct for global risk assessment in the primary prevention of cardiovascular disease.[63]

Rifai and Ridkar et al in their study reported hs-CRP is a strong and independent predictor of future coronary events in apparently normal individuals and also has a progonostic utility in patients with ACS. [4] **Fig 18**

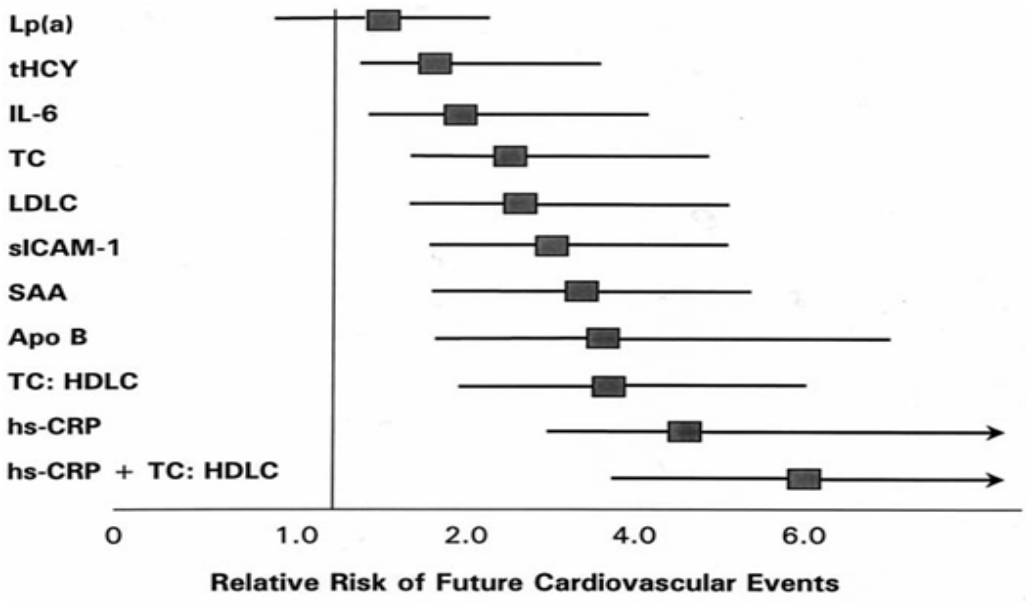


Fig. 18. RR Of Future Cardiovascular Events With Respect To Various Biochemical Markers.

Speidl WS, Graf S et al reported that CRP level > 1.6mg/l in individuals with < 50 years , who are clinically stable and have a positive history of acute coronary symptom, indicates future risk of coronary events. This also indicates an ongoing inflammatory process.[64]

Paul M Ridker et al reported that the baseline levels of CRP and LDL cholesterol each had a strong linear relation with the incidence of cardiovascular events.

In a separate analysis for each component of the end point among users and nonusers of HRT among women. 77% of all events occurred in patients with LDL < 160 mg/dl and 46% among LDL < 130 mg/dl. But, by screening, both CRP and LDL provides a better prognostic information than either alone. Independent effects were also observed for CRP. These suggest that CRP is a strong predictor of cardiovascular events.[65] **Fig 19**

C.M. Nagesh and Ambuj Roy et al, reported association of CRP and ACS. It is important to distinguish cases without (unstable angina) and with necrosis (acute MI). In cases of AMI, CRP release is triggered as an acute phase reactant secondary to necrosis and levels of CRP are much higher and these have been correlated with infarct size. Mortality has been shown to be related to CRP levels independent of left ventricular systolic function. In the absence of infarction, CRP levels correlate to the extent of atherosclerosis and shown that it predicts coronary events in patients of unstable angina independent of troponin levels.[1]

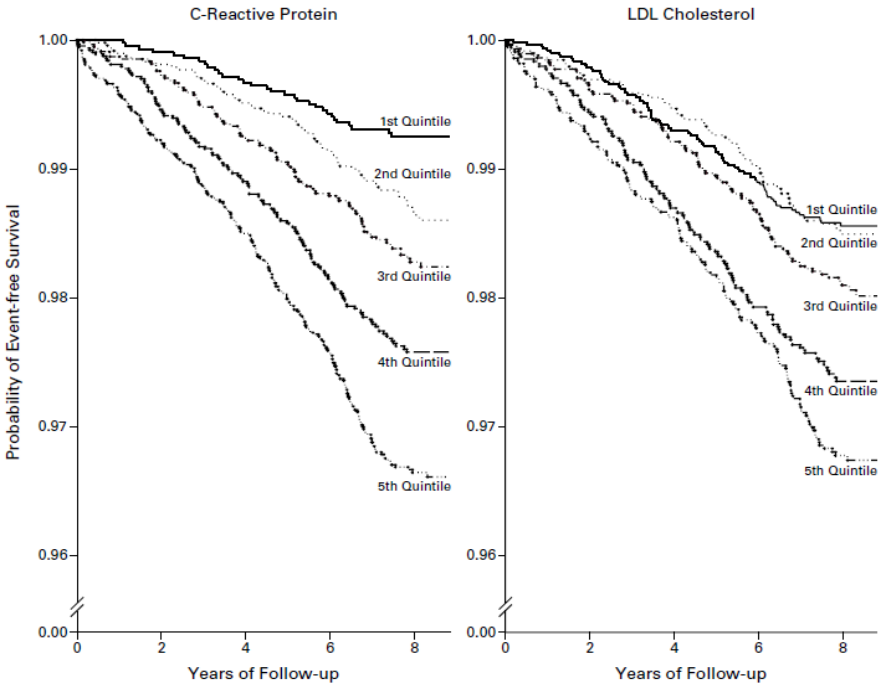


FIGURE 19. Comparison between CRP and LDL Cholesterol in Probability of Event Free Survival

STRUCTURE OF TROPONIN

Troponin is a complex of three regulatory proteins (troponin C, troponin I and troponin T) that is integral to muscle contraction in skeletal and cardiac muscle (**fig20**) but not smooth muscle. Troponin is attached to the protein tropomyosin and lies within the groove between actin filaments in muscle tissue. In a relaxed muscle, tropomyosin blocks the attachment site for the myosin crossbridge, thus preventing contraction (**fig21**). When the muscle cell is stimulated to contract by an action potential, calcium channels open in the

sarcoplasmic membrane and release calcium into the sarcoplasm. Some of this calcium attaches to troponin which causes it to change shape, exposing binding sites for myosin (active sites) on the actin filaments. Myosin binding to actin forms cross bridges and contraction (cross bridge cycling) of the muscle begins. Troponin is found in both skeletal muscle and cardiac muscle, but the specific versions of troponin differ between types of muscle. The main difference is that the TnC subunit of troponin in skeletal muscle has four calcium ion binding sites, whereas in cardiac muscle there are only three. Both cardiac and skeletal muscles are controlled by changes in the intracellular calcium concentration. When calcium rises, the muscles contract, and when calcium falls, the muscles relax. Troponin is a component of thin filaments (along with actin and tropomyosin), and is the protein to which calcium binds to accomplish this regulation. Troponin has three subunits, TnC, TnI, and TnT. When calcium is bound to specific sites on TnC, tropomyosin rolls out of the way of the actin filament active sites, so that myosin (a molecular motor organized in muscle thick filaments) can attach to the thin filament and produce force and/or movement. In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed.[66]

Individual subunits serve different functions:

1. Troponin C binds to calcium ions to produce a conformational change in TnI.

2. Troponin T binds to tropomyosin, interlocking them to form a troponin-tropomyosin complex.

3. Troponin I binds to actin in thin myofilaments to hold the troponin-tropomyosin complex in place.

Though troponin is found both in skeletal and cardiac muscles, the high specificity depends on the unique peptide sequence of cardiac troponin which is absent in skeletal muscle troponin.

TnI Is a 24 KD protein that maintains a 40% structural distinction from the skeletal Troponin I isoforms.[67,68,69] TnT is a 37 KD protein that is 10-30%dissimilar from skeletal troponin T isoforms. Following myocardial damage, TnT and TnI are released in different forms.

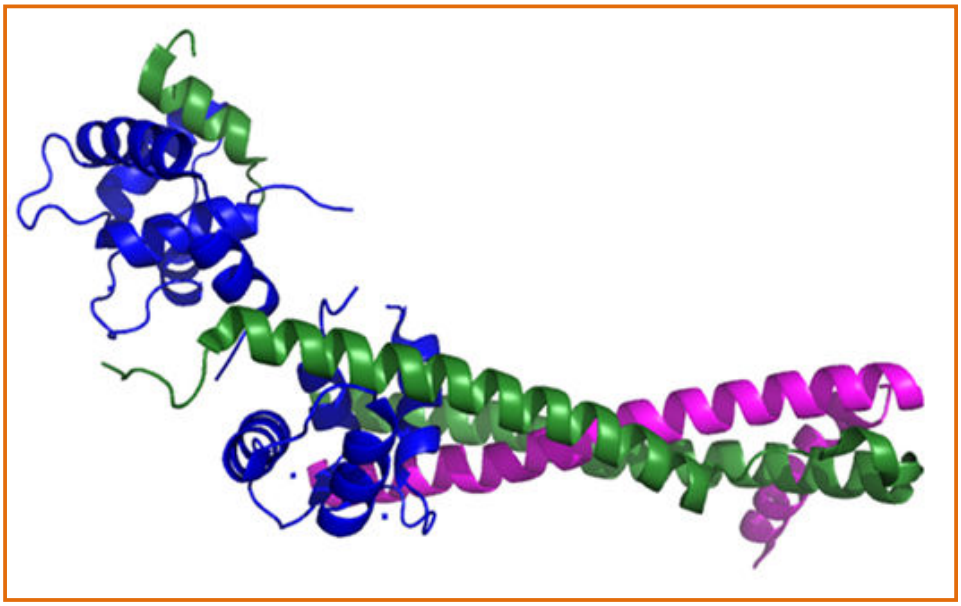


Fig 20. CTnT in calcium-saturated form.

Blue = troponin C green = troponin I magenta = troponin T

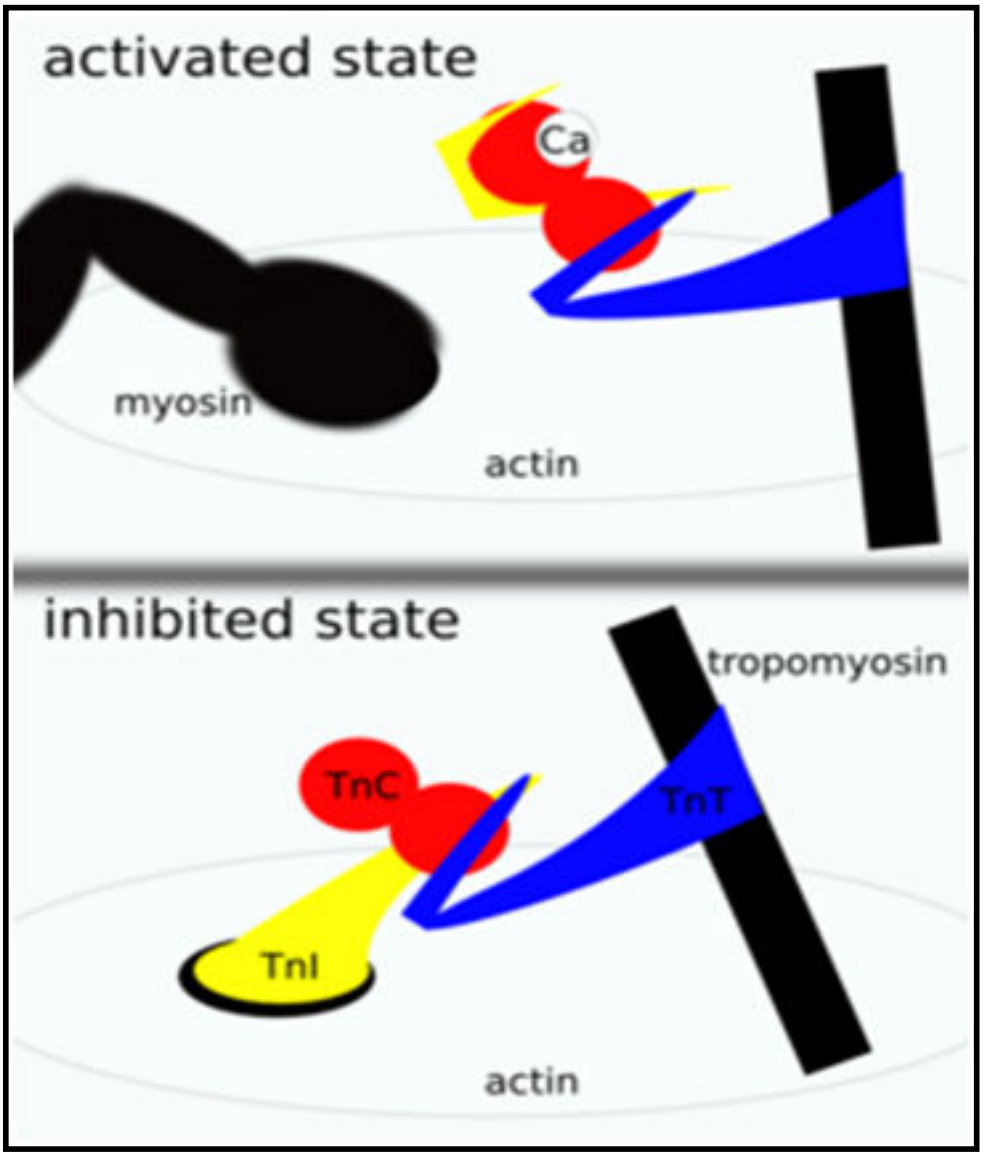


Fig 21 Troponin in activated and inhibited state

CARDIAC TROPONIN IN ACUTE CORONARY SYNDROME

Cardiac troponin which is structurally different from skeletal troponin has been very useful in the differentiation of MI from other causes of chest pain. Troponin T is a contractile protein that is normally not present in serum. It is released only when myocardial necrosis occurs. There are many cardiac biomarkers like CK-MB, myoglobin, cardiac troponin, but cardiac troponin are the more sensitive and specific for detection of even a minor amount of myocardial damage. (**Table 5)**

Enzyme Marker	Discription	Source	Cause Of Increase
Cardiac Troponins	Contractile Protein Complex Two Isoforms I And T	Heart	Injury To Heart
Ck-Mb	Isoenzymes Related To Myocardium	Primarily Heart,Skeletal Muscle Also	Injury To Heart And Skeletal Muscle
Myoglobin	Oxygen Storing Proteins	Heart And Skeletal Muscle	Injury To Heart And Skeletal Muscle

Table 5 Cardiac Biomarkers: description source and reason for increase

A large number of studies have shown that cardiac troponin are “the gold standard” for diagnosis of acute MI.

There are evidence based on studies supporting that cardiac troponin has a role both in the diagnosis of MI and for post infarct risk assessment. Current guidelines from the European Society of Cardiology (ESC), American College of Cardiology (ACC) and American Heart Association (AHA) state that Cardiac troponin is the preferred marker for MI diagnosis, particularly in the absence of clear ECG evidence. NSTEMI patients usually present with normal ECG or inconclusive ECG irregularities like T-wave inversion or ST depression. In myocardial necrosis (ischemia induced and others) there increases the release of cardiac troponin contained in the cell cytosol. Usually the cardiac troponin is detected in the serum 6 hours after infarction and the peak usually at 12-24 hours and then return to normal by 7-14 days of infarction. The persistence of cardiac troponin is due to secondary degradation of myofibrils. **Fig 22**

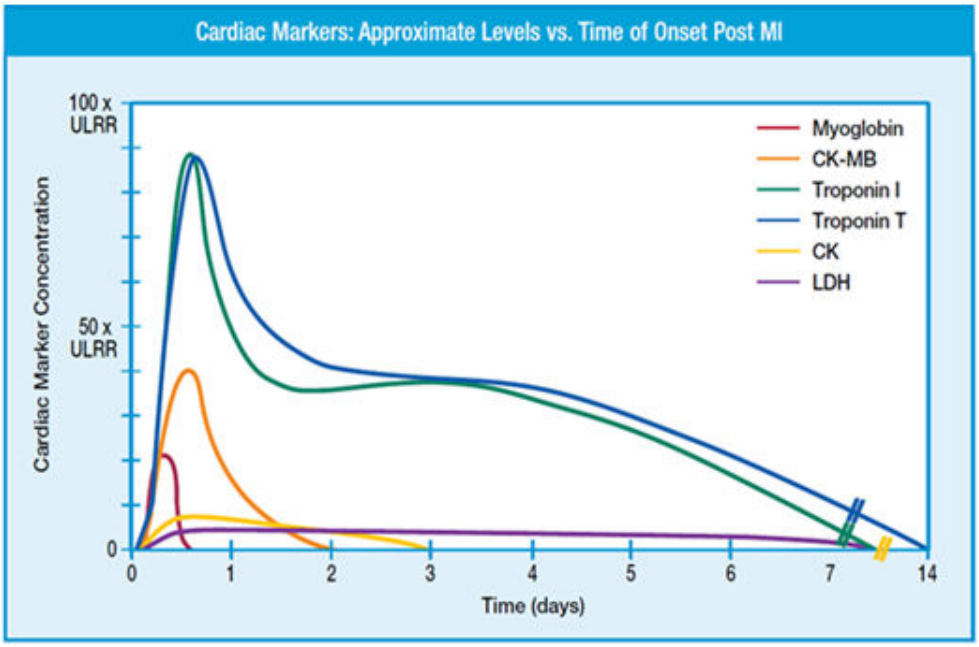


Fig 22

As the cardiac troponin rises only after 6 hours and when the patients are unable to say the time of onset of symptoms, it would be difficult to assess the single sample if taken before 6 hours of onset of MI (**Table 6).** A second sample should be collected 6-12 hours post presentation. [70,71]

Enzyme Marker	Time Of Increase	Remain Elevated Till	Sensitivity	Specificity	Assay
Cardiac Troponin	3-4 Hrs After Injury	7-14 Days	High	High	cTnT - **One** cTnI - **Many**
CK-Mb	4-6 Hrs After Injury	48-72 Hrs	Less Than Cardiac Troponin	Less Than Cardiac Troponin	-
Myoglobin	2-4 Hrs After Injury	24 Hrs	High	Poor	-

Table 6

Katus et al, reported that cTnT has high efficacy (94%) when compared to creatine kinase (63%) in detecting cardiac damage. [72]

C.M. Nagesh and Ambuj Roy et al, reported Cardiac troponin is a well established biomarker for diagnosis and prognosis of ACS .[1] The data for troponins in ACS is robust even at minimally elevated levels. Cardiac troponins are now very useful in the diagnosis of MI.[73] With current high quality analytic methods, cardiac troponin measurements are highly sensitive and specific for

myocardial injury .[74] In the appropriate clinical setting (high certainty that the troponin is due to acute coronary syndrome) even minor elevations of troponin identify high risk underlying coronary morphology like patients with plaque rupture, large thrombus burden and distal embolisation.[75] These patients clearly benefit from aggressive anti-platelet, antithrombotic and revascularization therapy . cTn typically increases more than 20 times above the upper limit of the reference range in myocardial infarction as compared to creatine kinase myocardial band (CK-MB) which usually increases 10 times above the reference range. The cTn begins to elevate 3 h from the onset of chest pain in MI. Because of the continuous release, cTn elevation persists for days (cTnI: 7-10 days, cTnT: 10-14 days). This prolonged course of release with troponin is very useful in the late diagnosis of MI, However, it limits the diagnosis of early reinfarction. However, the important advantage of cTnT is that due to international patent restrictions there is only one assay for its measurement.[76] Thus measuring cTnT is more advantageous than cTnI as troponin I has 18 different commercial assays and different cut off concentrations.

RISK STRATIFICATION OF TROPONIN-T IN ACS

Ischemic heart disease has a wide range which includes silent ischemia and progresses to acute MI. The gold standard for the diagnosis are the cardiac specific bio markers which include CKMB, Troponins. Initially CK-MB was used for the diagnosis of MI and was proposed as a component of diagnostic criteria by WHO.[77] This elevated CK-MB not always detects MI. Sometime death suddenly occurs in patients with silent MI. In these patients CKMB may be negative but at

atopsy micro necrosis may be revealed. This leads to the measurement of better cardiac marker like cTnT and cTnI, which has high specificity and sensitivity for myocardial damage.[78] Troponins are the biomarkers which identify myocardial micronecrosis which may not be diagnosed by conventional definition.[79,80] American College of Cardiology/American Heart Association guidelines for management of NSTE ACS, included measurement of Troponins as a basic investigation in the diagnosis of NSTEMI. Troponin was also involved in the risk identification.

The Troponins (T&I) have similar release mechanism. In the serum both are detected at about 4-12 hours and peaks around 12 to 48 hours and remains elevated for about 7-14 days. Thus they are useful even when the patient is delayed for presentation after symptom onset. [81]

CARDIAC SPECIFIC TROPONIN AS PROGNOSTIC INDICATOR IN NSTE-ACS

Patients who have chest pain with normal ECG are considered as important individuals, as there are more chances to miss them than those who have elevated ST changes in ECG.[82] As myocardial necrosis is an important prognostic indicator [83], early identification of patients with MI becomes essential for Initial triage decision and initiation of treatment.

In FRISC study they showed that there was a strong correlation between troponin elevation and 30-days mortality.[84]

Thrombolysis is myocardial infarction (TIMI) IIIB investigators reported that cTnI elevation was directly proportional to the risk of mortality in patients with UA. This result was found in 42 days study.[85]

(GUSTO)-IIB investigators in their study found that troponin T was a powerful marker of short term mortality risk. [86] This leads to the measurement of troponin in prediction of MI in non –ST elevation patients. [87]

SUMMARY

The pathogenesis of atherosclerotic heart disease is not simply due to lipid deposition but inflammation has a key role in endothelial damage. Acute phase reactants which are non-specific markers of inflammation and elevated in all stages of atherosclerotic heart disease. Among them hs-CRP measurement appears to be highly specific. It predicts long term risk of mortality in patients of ACS. HsCRP when combined with cTnT a cardiac specific biomarker gives a high predictive value of myocardial necrosis than when measured alone. Elevated serum cTnT in patients with ACS is associated with increased incidence of MI and death. Previous studies reported the increased CRP even with negative cTnT had worse clinical outcomes. These include mortality and prolonged hospitalisation.

MATERIALS & METHODS

Study population:

The study was conducted among patients admitted with ACS of UA/NSTEMI in the emergency Department and ICCU of Cardiology Department in Kilpauk Medical College Hospital, Chennai.

Study type

It is a Prospective study

Study period:

Data collection was done from September 2011 and August 2012.

Base line assessment:

A detailed medical history regarding risk factors like-diabetes mellitus, hypertension, smoking, obesity, dyslipidemia, H/O previous CABG or PTCA, H/O stroke, H/O peripheral vascular disease and family history of premature coronary artery disease; as well as previous symptoms such as pre infarction angina were obtained. Full physical examination was done in all patients. Blood sugar, urea, serum creatinine, lipid profile level were obtained. Serum level of hsCRP and cTnT was measured 6hrs after admission in all patients. Any evidence of the presence of an obvious source of infection, either by clinical assessment or laboratory investigations served as basis for exclusion from the study.

Definition:

Death was defined as all-cause mortality.

Unstable angina or NQMI defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features: (1) occurring at rest (or minimal exertion) and usually lasting >20 minutes (if not interrupted by the administration of a nitrate or an analgesic); (2) being severe and usually described as frank pain and of new onset (i.e., within the prior 4–6 weeks); and/or (3) occurring with a crescendo pattern (i.e., pain that awakens the patient from sleep or that is more severe, prolonged, or frequent than previously). The diagnosis of NSTEMI is established if a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated cardiac biomarkers. To support the presence of ischemic heart disease, patients must have met at least one of the following criteria: a history of typical myocardial ischemic-type discomfort; electrocardiographic changes (ST-segment depression of at least 0.5 mm ,persistent negative T wave over the involved area ,Deeply negative T waves across all the precardial leads) in association with ischemic discomfort; a history of previous myocardial infarction (MI); previous coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty.

New MI during current hospitalization was defined as a new episode of prolonged chest pain, resistant to nitrates, with new electrocardiographic changes of ST-T changes and an increase in the plasma cTnT level and CKMB level at least three times the upper limit of normal value.

Inclusion criteria:

All Patients admitted with unstable angina and NSTEMI in the Emergency department and ICCU of the cardiology department in Kilpauk Medical College hospital.

Exclusion criteria:

- Active infection
- Chronic inflammatory disease,
- hepatic dysfunction,
- Renal dysfunction,
- Malignancy,
- Major surgery in the previous 1 month,
- Peripheral arterial disease,
- Metabolic syndrome,
- Patients with ST elevation MI and Thrombolysed within 48 hours,
- Trauma,
- CABG within the previous 2 months.

Laboratory methods of measuring hs-CRP:

Quantitative determination of hsCRP is done by **COBAS-C** systems of Roche diagnostics USA. hsCRP is measured by particle enhanced immune-turbidimetry assay. Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbid metrically. Reagents used are R1-TRIS buffer with bovine serum albumin and

immunoglobulins (mouse), R2-Latex particles coated with anti-CRP (mouse) in glycine buffer.

Laboratory methods of measuring cTnT:

Quantitative determination of CTnT is done by **Cobas-e 602** analyser of Roche diagnostics USA, based on sandwich principle. Total duration of assay is 9 minutes. During a 9 minutes incubation, antigen in the sample,a biotinylated monoclonal troponin T- specific antibody, monoclonal troponin T- specific antibody labelled with a ruthenium complex and streptavidin- coated micro particles react to form a sandwich complex, which is bound to solid phase.

The reaction mixture is aspirated in to the measuring cell where the micro particles are magnetically captured on to the surface of the electrode. Unbound substances are then removed with Procell. Application of voltage to the electrode then induces chemiluminescent emission which is measured by a photo multiplier. Results are determined via a calibration curve which is instrument –specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Laboratory methods of measuring CKMB:

CKMB was measured by **Cobas-e** analyser by Roche diagnostics USA based on sandwich principle. During a 9 minutes incubation, antigen in the sample, a biotinylated monoclonal anti-CKMB antibody, monoclonal CKMB - specific antibody labelled with a ruthenium complex and streptavidin- coated microparticles react to form a sandwich complex, which is bound to solid phase.

The reaction mixture is aspirated in to the measuring cell where the micro particles are magnetically captured on to the surface of the electrode. Unbound substances are then removed with Procell. Application of voltage to the electrode then induces chemiluminescent emission which is measured by a photo multiplier. Results are determined via a calibration curve which is instrument –specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

STATISTICAL ANALYSIS

The data obtained were maintained in the master chart in Microsoft Office Excel format. The statistical analysis was done using SPSS 20th version. hs-CRP and cTnT were measured 6 hours after admission as cTnT raises only about 4-6 hours after the onset of symptoms.

The values of CRP were divided into quintiles, quartiles. cTnT was taken as positive (>0.01μg/l) and negative (<0.01μg/l). For continuous variables means were expressed with one standard deviation. For the outcome of death and subsequent MI at 14 days a 2X2 table was constructed and sensitivity, specificity and likelihood ratio for each test was determined. All statistical significance was defined as a p value < 0.05 using chi square test.

RESULTS

Initially we recruited 122 patients in our study. But 26 patients did not come for review. So finally 96 patients were taken for our study. Out of them 60(62%) were males and 36(38%) were female (**Chart1&2)**. Among them 55(57.3%) had HTN and 40(41.6%) patients had diabetes. 23(24%) patients had both HTN and diabetes. ECG changes in 85(88.5%) patients. 50(52.08%) patients had previous history of Angina. 3(3.1%) had past history of MI and 4(4.16%) had previous CABG done.

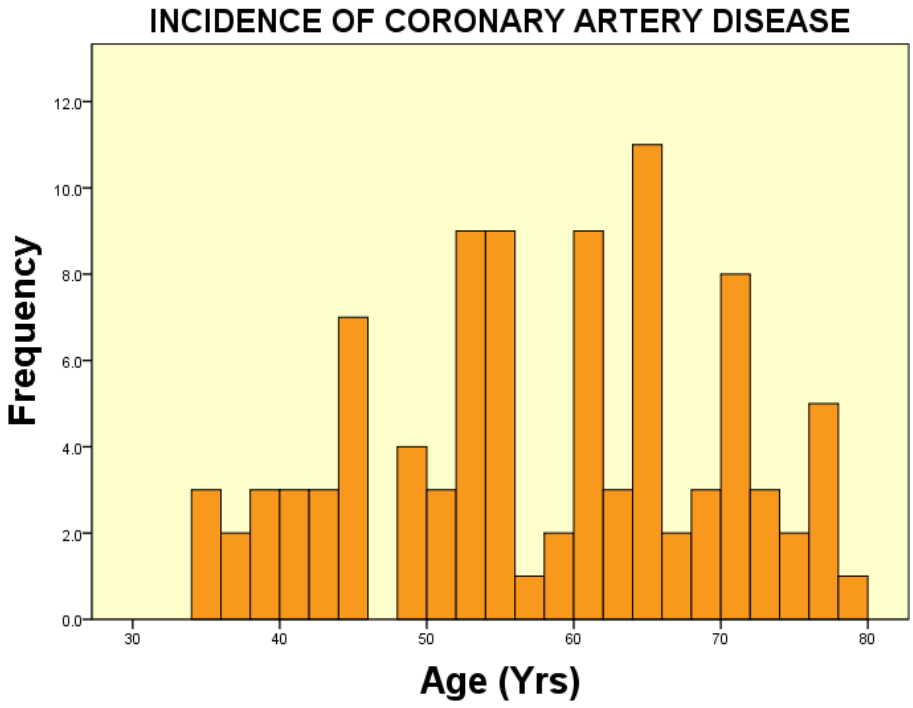


Chart1.Age distribution of coronary artery disease patients

Higher incidence of CAD was found in patients between 50-70 years

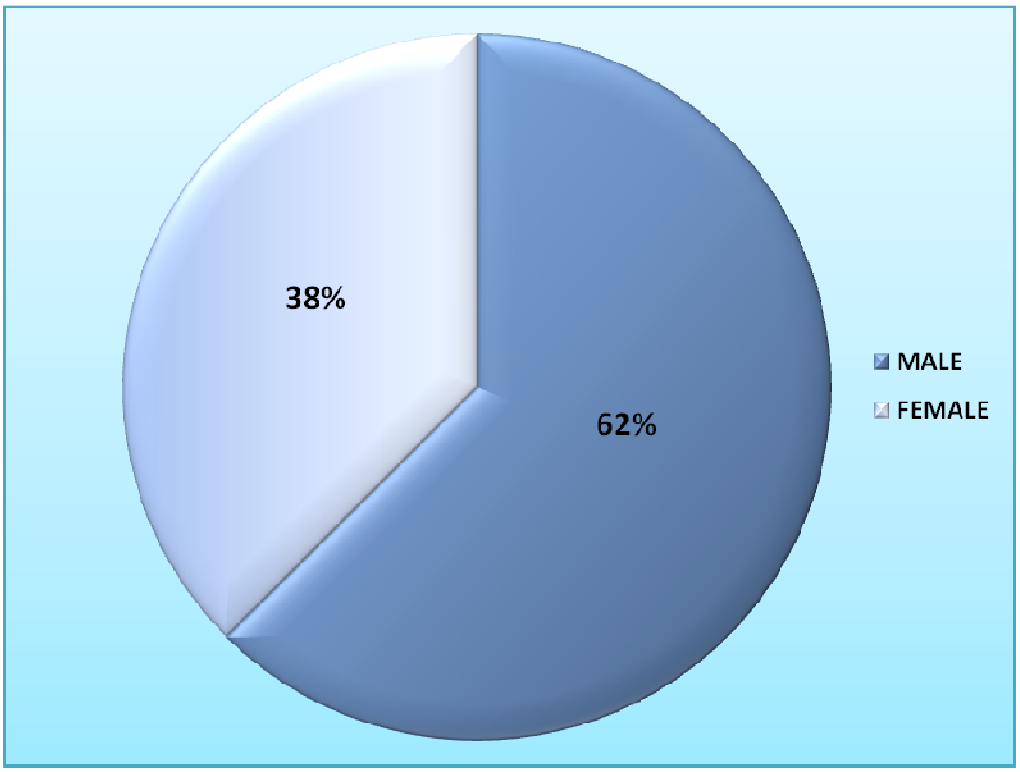


Chart - 2. Sex distribution

We measured hsCRP and cTnT 6 hours after admission for all patients. Range of hsCRP obtained was 0.1mg/lt to 17.11mg/lt (median 0.76mg/lt). Among them patients with hsCRP >3mg/lt were 30(31.25%). cTnT was positive in 16 patients (16.5%). These patients baseline characteristics are shown in **Table 7**.

Table - 7 (Base Line Characteristics)

Base line characteristics	CRP <3mg/l (N=66)	CRP >3mg/l (N=30)
Mean age (yr)	56.91	58.7
Male	42 (70%)	18 (30%)
Female	24 (66.6%)	12 (33.3%)
Mean Weight (KG)	67	67
Diabetes	24(60%)	16 (40%)
Current smoker	14(56%)	11(44%)
Hypertension	40(72.8%)	15(27.2%)
Previous Angina	34(68%)	16(32%)
MI	1	2
CABG	1	3
PTCA	1	0

In our study it showed that there is a positive correlation between

a) BMI and increasing quintiles of hsCRP,

b) DM and increasing quintiles of hsCRP,

c) LDL>130mg/dl and increasing quintiles of hsCRP. It also showed a negative correlation with HTN and no relationship was found between hsCRP and previous angina. **Charts 3,4,5,6,7**

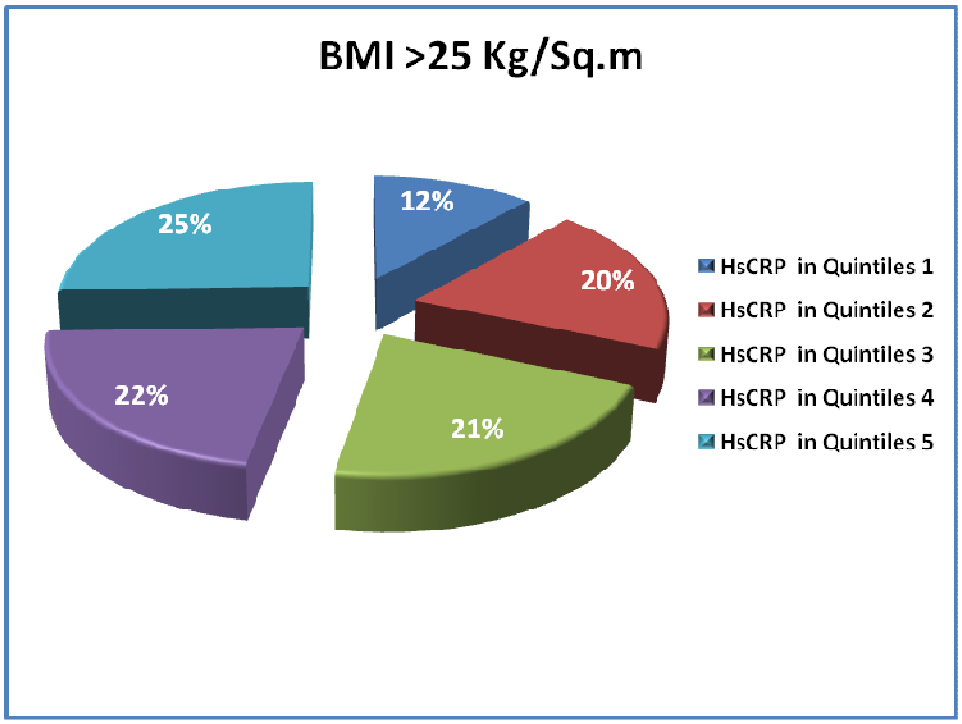


CHART 3.BMI WITH RESPECT TO INCREASING QUINTILES OF CRP

BMI>25kg/sq.m is considered as over weight and is supposed to be a risk factor for CAD.

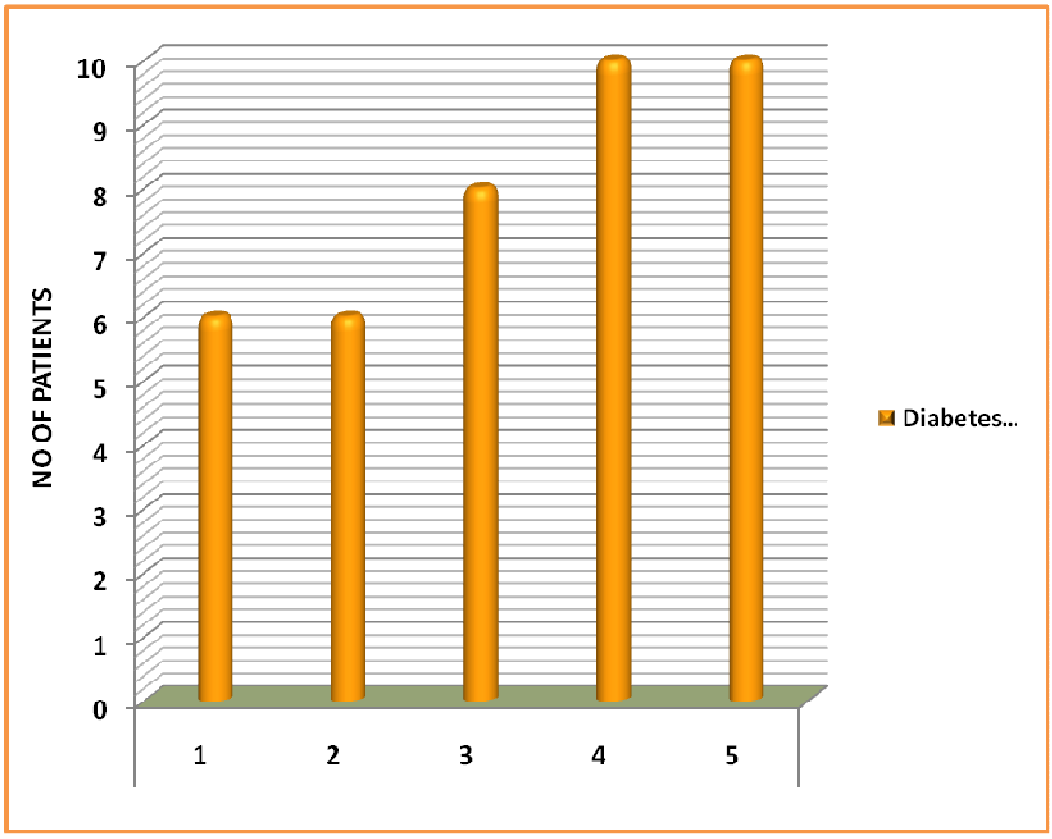


CHART 4.DIABETES MELLITUS WITH RESPECT TO INCREASING QUINTILES OF CRP

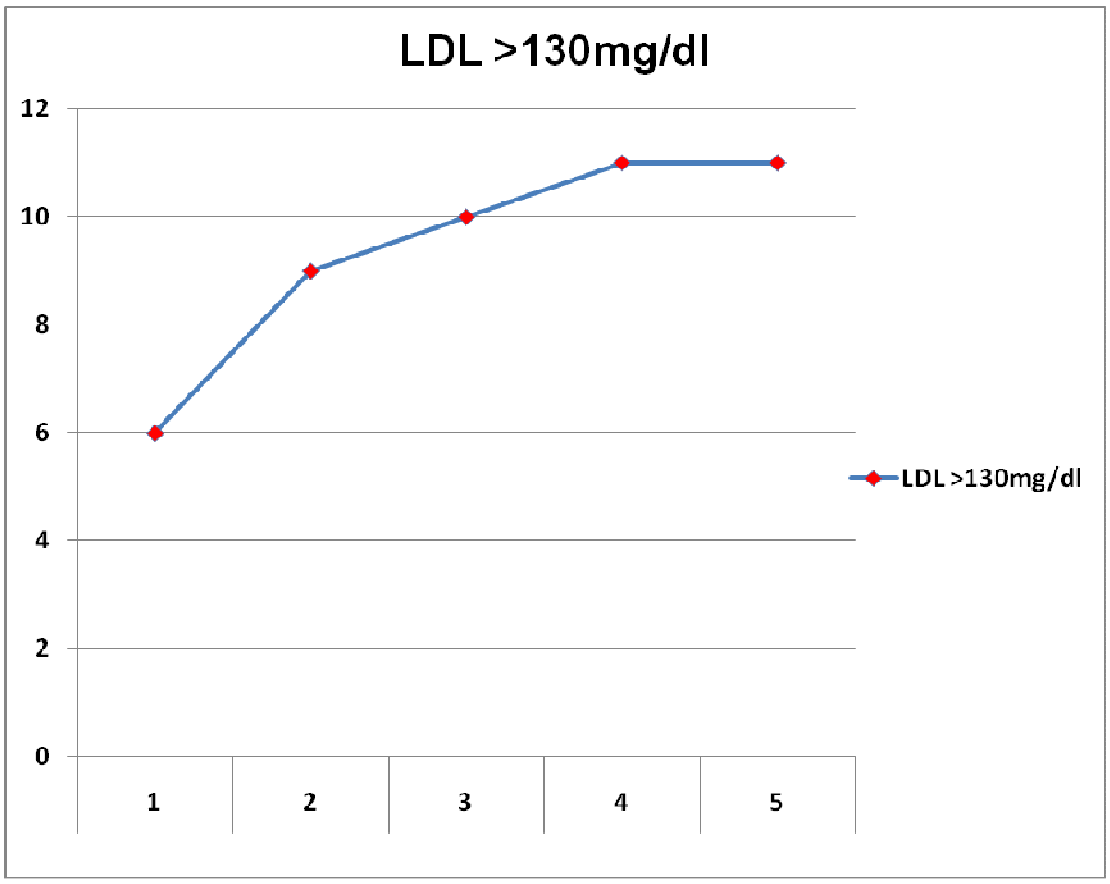


CHART 5. LDL >130 Mg/dl WITH RESPECT TO INCREASING QUINTILES OF hSCRP

There were 6,9,10,11,11 patients who had LDL>130 mg/dl in 1st, 2nd, 3rd, 4th, 5th quintiles respectively. This showed a positive correlation.

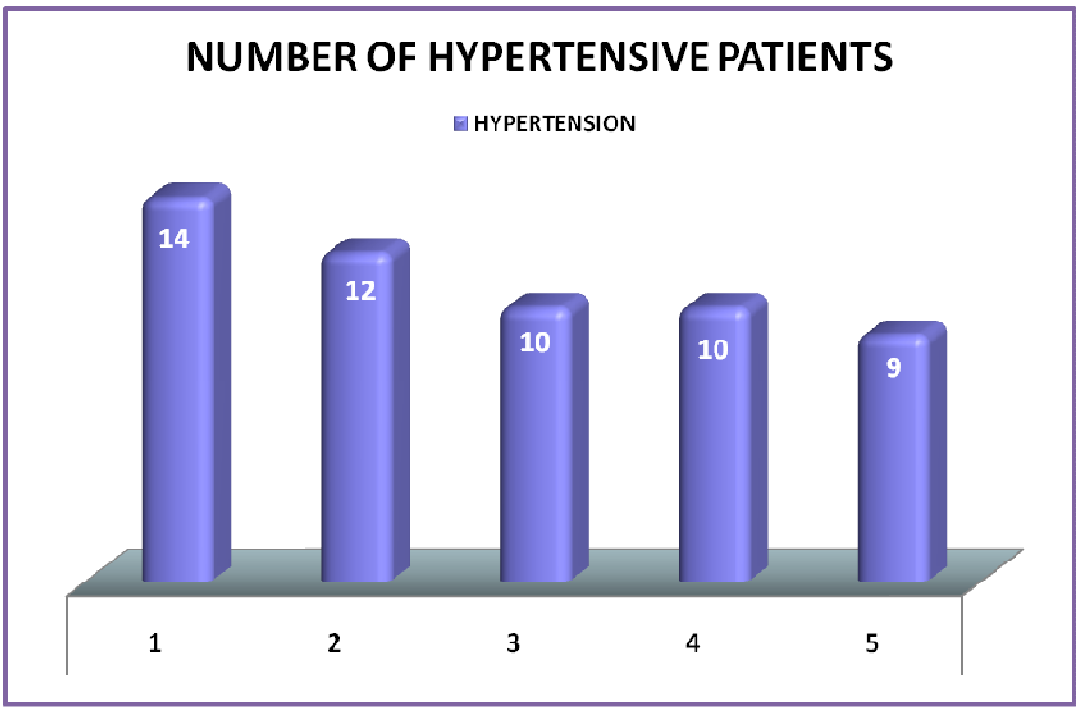


CHART 6. HYPERTENSION AND INCREASING QUINTILES OF hSCRP

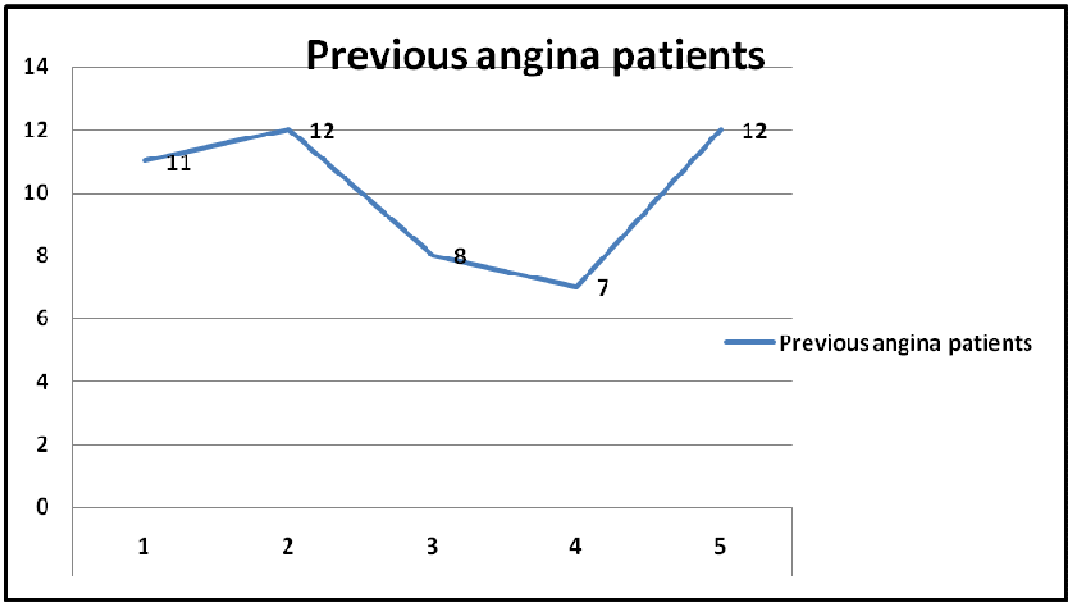


CHART 7.PREVIOUS ANGINA AND CRP

Previous angina showed no relation with hsCRP in our study.

All the patients included in the study received inj.Heparin, aspirin, clopidogrel, ACE inhibitor, Statins, nitrates and Beta blockers by ruling out their specific risk factors. 14 days follow up was made. While in the hospital stay 5 patients died. Among them 4 were males and 1 female patient. 1 death was due to Arrythmia, 3 deaths were due to cardiogenic shock, 1 death due to Non cardiac cause.

5 patients had subsequent ST elevation MI during hospitalisation. Among them 3 were males and 2 females. One male patient was readmitted for MI within 14 days of study.Thus totally 6 persons developed MI during the study period.

Association of cTnT with CRP

Out of 96 patients included in the study 80 patients had negative cTnT and 16 patients had positive cTnT. The positivity of cTnT was taken as cTnT value >0.01μg/l. The percentage of patients with positive cTnT increased with increasing concentration of hs-CRP.

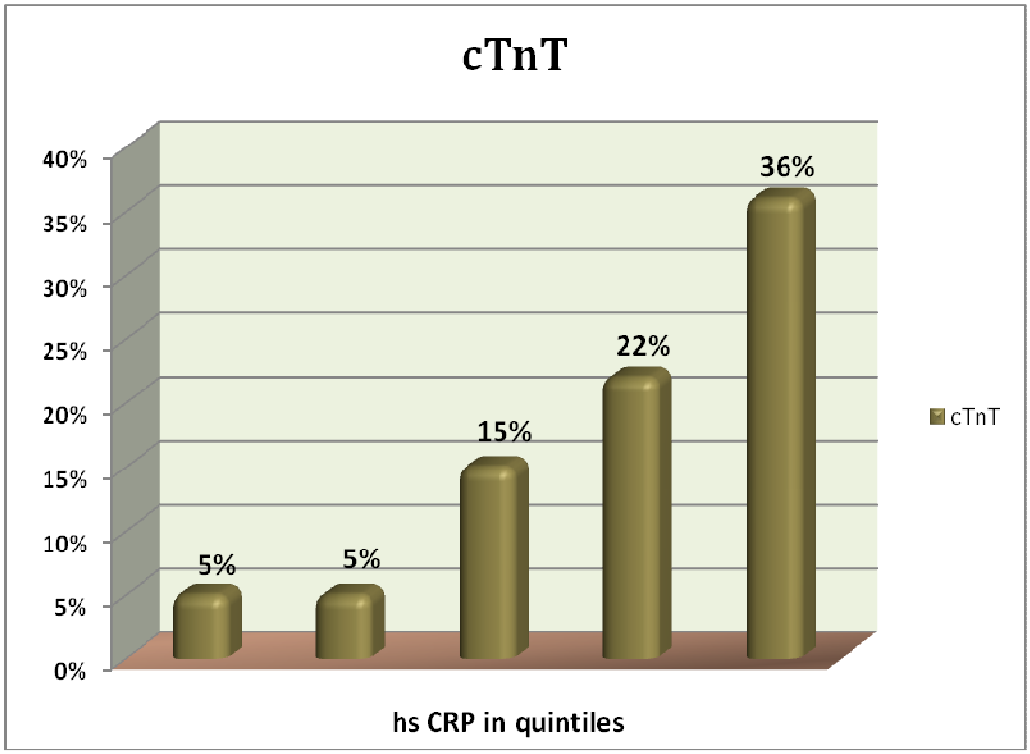


CHART - 8

N=96 Percentage of patients with positive cTnT in each quintile of CRP concentration

The median value of CRP was 0.76 mg/l. 5% of the patients with positive cTnT were in the Ist quintile, 5% in 2nd quintile, 15% in the 3rd quintile, 22% in the 4th quintile and 36% in the 5th quintile of CRP. **Chart 8**

Association of Serum Markers with Clinical Outcomes

CRP and Mortality

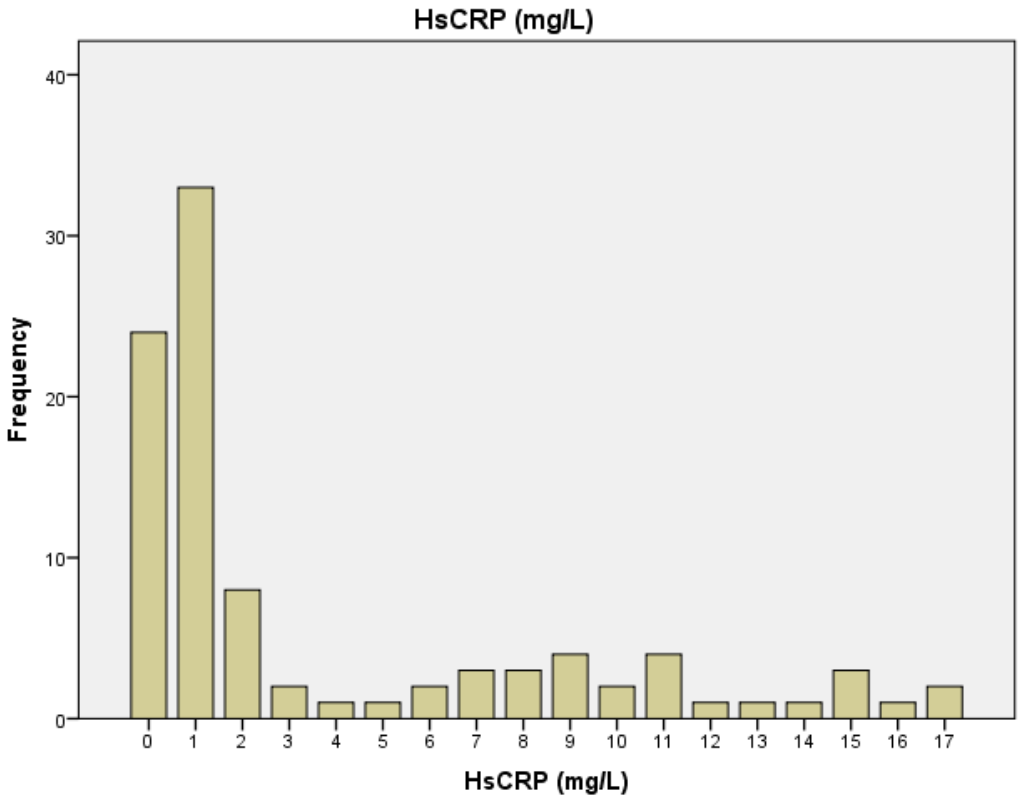


CHART 9.FREQUENCY OF HSCRP IN OUR STUDY GROUP

CRP values were divided into four quartiles. (<0.50mg/l, 0.51-0.76mg/l, 0.77-6.58mg/l and >6.58mg/l) The all cause mortality within 14 days among the patients (study group) was 5.2%. Mortality was higher among patients with CRP>3mg/l than others **(chart 9)**. In the study population of 96 patients, 5 patients died and among them 4 patients had hs-CRP > 3 mg/l.

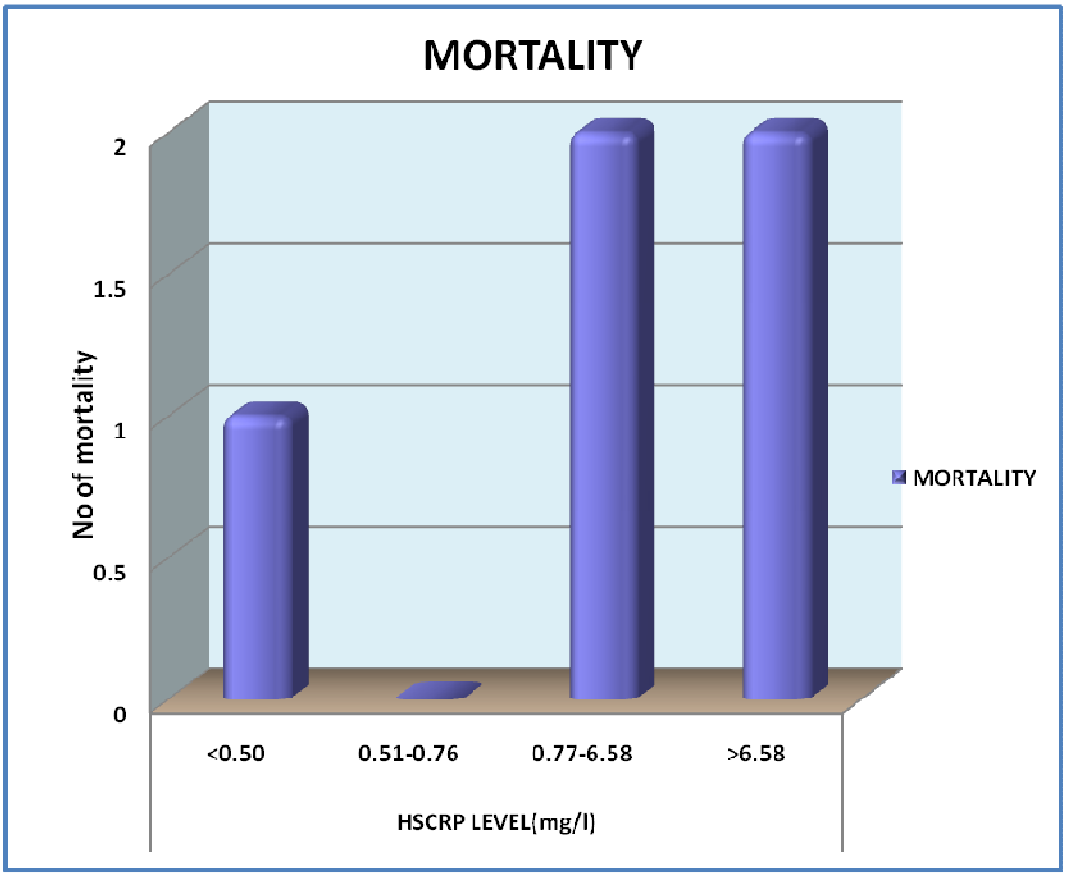


CHART 10. No OF DEATH IN EACH QUARTILE OF CRP

hsCRP	<0.50	0.51-0.76	0.77-6.58	>6.58	**P value**
Mortality	1	0	2	2	**.001**

Table 8. MORTALITY WITH RESPECT TO CRP AND ITS P VALUE.

HsCRP (mg/L) * Death during Hospitalisation

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	42.831[a]	17	**.001**
Likelihood Ratio	21.606	17	.200
No of Valid Cases	96		

TABLE - 9

Table 8 and 9 shows the mortality with respect to CRP values and its P value is calculated as 0.001.

CTnT and Mortality and comparison with CRP

Among the 5 patients, who died, 3 patients had positive cTnT(>0.01µg/l) 18% and 2 negative cTnT (<0.01µg/l), P value = 0.008 **(Chart 11)**

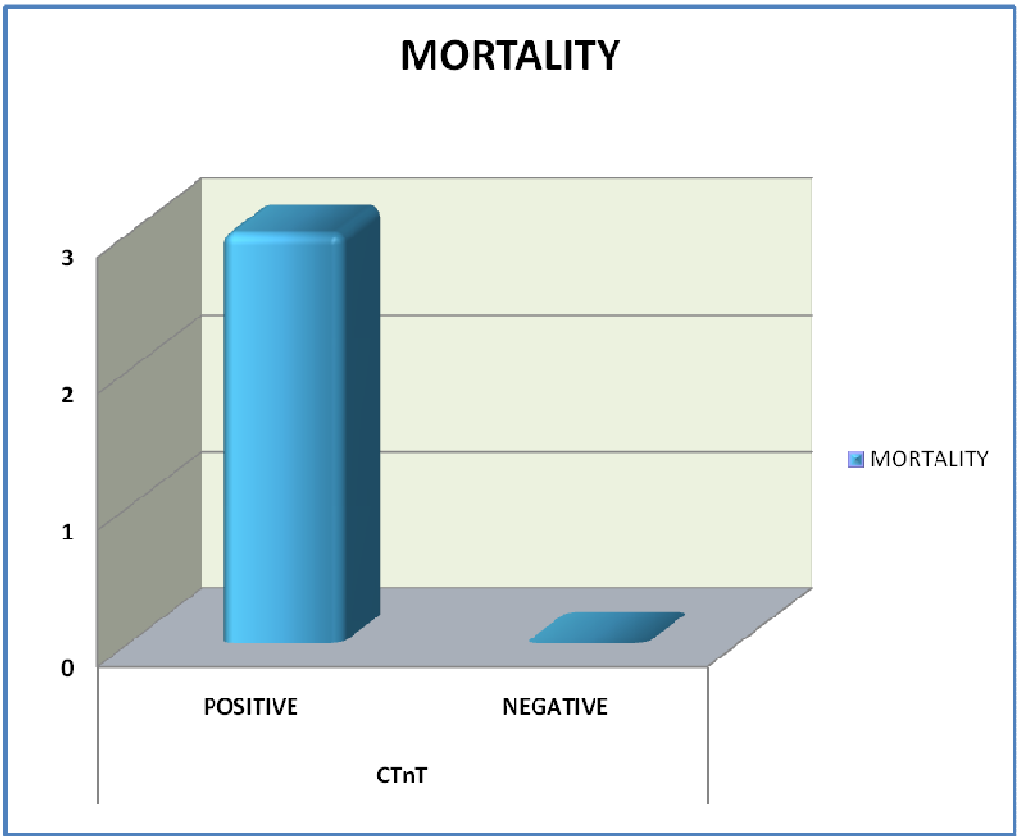


CHART 11. MORTALITY WITH RESPECT TO cTnT

CTnT	Positive >0.01µg/l	Negative <0.01µg/l
Mortality	3	2

TABLE 10. MORTALITY WITH RESPECT TO cTnT

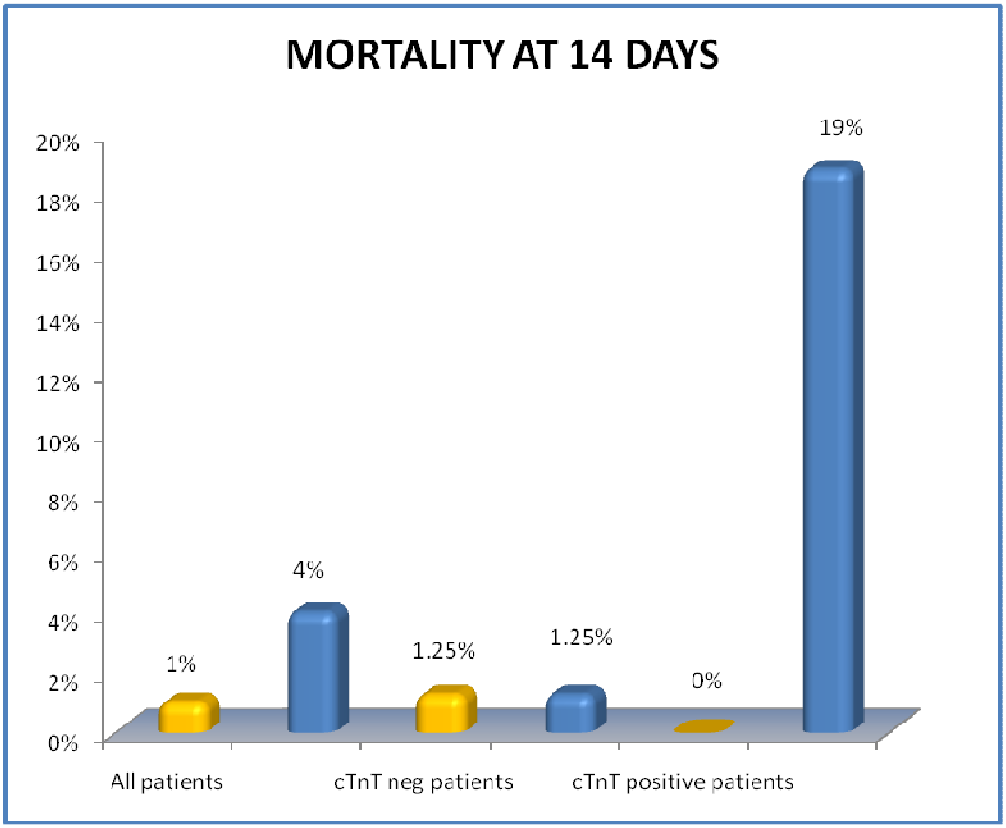
CTnT(mg/L) * Death during Hospitalisation

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.131[a]	1	**.008**		
Continuity Correction[b]	4.220	1	.040		
Likelihood Ratio	5.136	1	.023		
Fisher's Exact Test				.031	.031
No of Valid Cases	96				

TABLE 11

Table 10&11 Shows the Mortality with respect to CTnT and P value (0.008) is calculated using chi-square test.

3 patients, who died, had positive cTnT also had CRP>3mg/l. The mortality rate of cTnT positive group with CRP<3mg/l was 0% when compared with CRP>3mg/l was 19%. Stratifying by both hsCRP and cTnT, we found that a) Mortality was high among patients with both CRP >3 mg/l and cTnT positive b) Followed by either CRP> 3 mg/l or cTnT positive and c) Low risk was found in patients with negative cTnT and CRP< 3 mg/l. **Chart 12.**



Yellow bar- hsCRP<3mg/l

blue bar-hsCRP>3mg/l

CHART- 12. MORTALITY AT 14 DAYS BY COMPARING hsCRP AND cTnT

Cardiac Markers and MI

Among the 96 patients who were taken into the study **6** patients developed subsequent MI (6.25%) . **5** (5.20%) of them developed MI while in the hospital stay itself and **1** patient was discharged on the 10th day and was readmitted in the hospital on the 12th day from the date of first episode of MI. The subsequent MI in this patient was confirmed by ECG changes and also by CK-MB elevation.

hs-CRP and MI

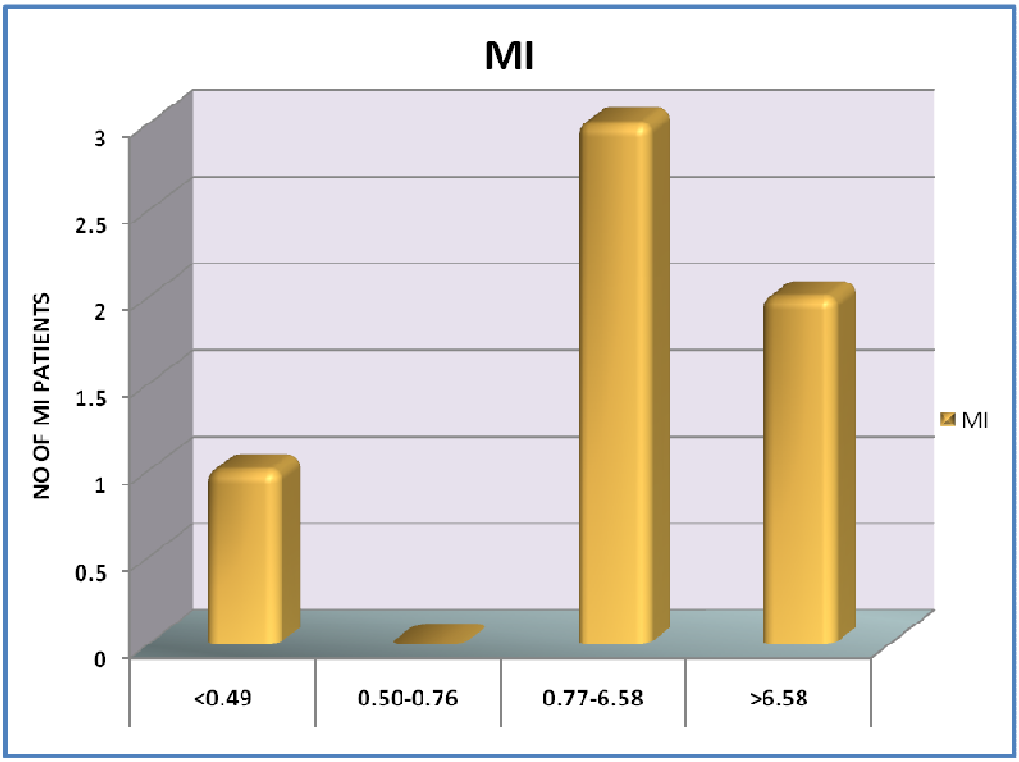


CHART -13. OCCURRENCE OF MI WITH RESPECT TO hSCRP

hsCRP	<0.49	0.50-0.76	0.77-6.58	>6.58	**P value**
MI	1	0	3	2	**0.061**

TABLE.-12 MI WITH RESPECT TO CRP AND P VALUE CALCULATED BY CHI-SQUARE TEST

Among the 6 patients who developed subsequent MI after admission for ACS, only 3 patients had hs-CRP > 3 mg/l. The CRP values were diveded into quartiles and the occurence of MI was plotted into the quartile and we found that 1 case occured in first quartile(1.04%), 0 in second quartile(0%), 3 in third quartile(3.12%) and 2 in the fourth quartile(2.08%).P value = 0.061, which is insignificant. **(Chart 13), TABLE 12.**

cTnT and MI

5 patients who developed subsequent MI while admission and one patient who was readmitted for MI diagnosed by elevated CKMB and ECG changes (6 patients) all had cTnT positive(>0.01µg/l) (100%). This showes that there is very strong association between MI and cTnT positivitiy. **(Chart 14), Table 13.**

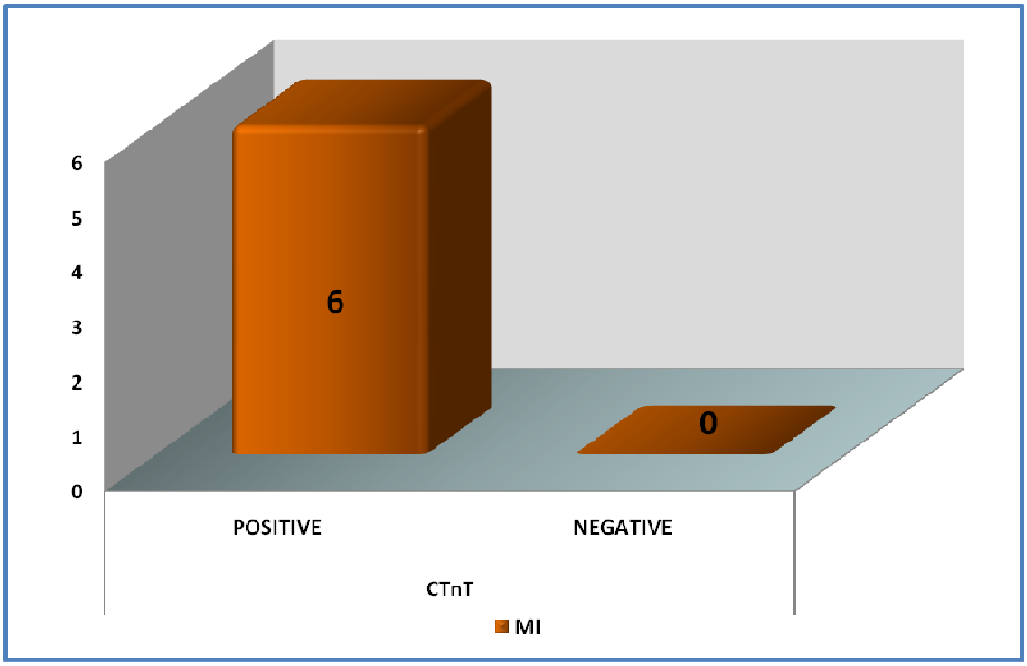


CHART 14. MI WITH RESPECT TO cTnT

cTnT	Positive	Negative	**P value**
MI	6	0	**0.0001**

TABLE 13. P VALUE CALCULATED BY CHI-SQUARE TEST

COMBINATION OF CTNT AND CRP

With respect to Mortality in ACS patients study group

During our study period of 14 days, the all cause mortality among 96 patients was 5 (5.21%). When mortality was taken into account the rate of its occurence in the study group increases with increase in the value of hs-CRP. We found that the rate of mortality was more among patients with hs-CRP > 3 mg/l (4.16%) when compared to CRP < 3 mg/l (1.04%). **Chart 15.**

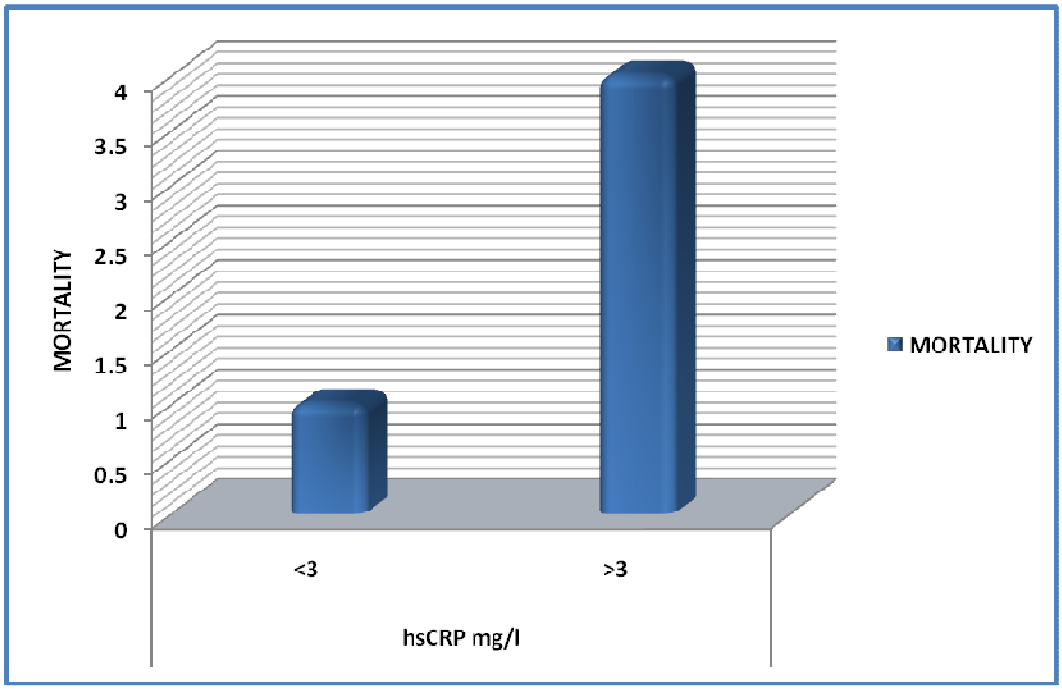


Chart 15. Mortality and hsCRP

Similarly, when cTnT is taken into account , 3 patients had positive cTnT > 0.01 µg/l i.e., 3.12% and 2 patients had cTnT(<0.01 µg/l) negative i.e., 2.08%. This showed that cTnT is also a good predictor of occurrence of mortality in patients with ACS. P value 0.008.

While comparing both markers with mortality, 3 patients had both CRP>3mg/l and also cTnT positive (3.15%), 1 patient had CRP alone > 3 mg/l but cTnT negative (1.04%) and 1 patient had CRP < 3 mg/l and cTnT negative (1.04%). This clearly shows that the rate of death among patients with acute coronary syndrome is low when both the markers are below the normal values (CRP < 3 mg/l and cTnT negative) (01.04%) and the rate of occurrence of death increases when both the markers are above the normal acceptable limits. (CRP >3 mg/l and cTnT positive) (3.12%) **Table 14.**

Bio marker	hsCRP>3mg/l & cTnT positive	hsCRP>3mg/l or cTnT positive	hsCRP<3mg/l or cTnT negative
Mortality	3	1	1

Table - 14. Biomarkers and mortality

Bio marker	cTnT positive	hsCRP>3mg/l	hsCRP>3mg/l & cTnT positive
Sensitivity	**60%**	**80%**	**30%**
Specificity	**97.5%**	**98%**	**97.5%**

Table 15. This table gives the Sensitivity and Specificity of the biomarkers with respect to mortality

With Respect to Subsequent MI after the Admission

During the study period, taking the occurrence of subsequent MI after admission into account, we found that among the 6 patients all the 6 patients had cTnT positive. (> 0.01 µg/l) but only 3 of them had CRP > 3 mg/l. We also found that there was a decline in the rate of occurrence of subsequent MI in the fourth quarter of hsCRP. These findings clearly show cTnT had a very strong association with occurrence of MI in acute coronary syndrome. However there was no relationship between the rate of occurrence of subsequent MI and increasing quartile of hs-CRP 1.01%, 0%, 3.12% and 2.1% respectively.

DISCUSSION

Acute Coronary Syndrome is a disease of inflammation which is associated with increase in serum biomarkers. Our study was designed to predict the association of hs-CRP and cTnT in Unstable/NSTEMI patients with the occurrence of subsequent MI and death in 14 days after admission in ICCU and Emergency ward. Of the total 96 patients, 5 (5.20%) died while in hospital and 6 (6.25%) patients developed subsequent MI during the study period.

In our study 60 were male patients and 36 female patients. The mean age of occurrence of ACS in male was 57.36 years and in female was 57.28 years. 18 (30%) males with ACS had hs-CRP> 3 mg/l and 12(33.3%) females with ACS had hs-CRP > 3 mg/l.

In our study, a high hs-CRP level > 3 mg/l was found to be significantly associated with mortality with in 14 days with sensitivity 80%, specificity 98% and p value .001 and the elevated CRP had no relation with the occurrence of MI with a p value of 0.061. Our study is in agreement with GUSTO IV and Scirica et al where the blood sample for hs-CRP was drawn at serial intervals 8,16,24 and 48 hours and on admission respectively. In **GUSTO IV**[65] in a 30 days study, with increasing quartiles of CRP there was increase in the rate of mortality p(0.001) but the rate of occurrence of subsequent MI had no relation with increasing CRP. In **Scirica et al** [88] reported the same that CRP > 15 mg/l on admission had increased rate of short term and long term mortality ($p<0.001$) and also that increased CRP

had no association with the occurrence of rate of short term and long term MI (p=0.09 and 0.54 respectively). Our study was in partial agreement with Liuzzo et al, TIMI 11A, Ernest.R. Ferriero et al. In **Liuzzo et al,**[49] blood sample was collected at the time of admission and they reported that hs-CRP > 0.3 mg/dl was associated with increased incidence of ischemic episodes, MI, death while hospital stay (p= 0.004). In **TIMI 11A,**[50] they reported CRP > 1.55 mg/dl had a strong association with the rate of occurrence of mortality within 14 days with a specificity of 76% and sensitivity 86%. **Ernest R. Ferriero et al**[89] collected sample for hs-CRP 3 times (on admission, after 48 hours and at discharge). They reported that the value of hs-CRP >1.5 mg/dl at discharge had a Strong correlation with the rate of occurrence of MI, angina, mortality at 90 days (P=0.0001).

STUDY	MEASUREMENT OF hsCRP	CONCLUSION
Liuzzo et al[49]	At the time of admission	>0.3 mg/dl associated with more ischemic episode, MI, death while in hospital stay(p=0.004)
TIMI 11A[50]	6 hours after admission.	>1.55 mg/dl was associated with increased mortality with sensitivity 86% and specificity 76% (p=0.001)
GUSTO IV[65]	Blood sample collected at 8,16,24,36 and 48 hours	a) Increasing quartile of CRP associated with increasing rate of mortality (p=0.001) at 30 days. b) not related to occurrence of MI at 30 days (p=0.4)

Ernest Ferriero et al[89]	Measured on admission, 48 hours and while discharged	CRP > 1.5 mg/dl at discharge was a strong independent marker of combined end point of MI or death on 90 days (p=0.0001).
Scirica et al[88]	Immediately on admission	Hs-CRP > 15mg/l associated with increased mortality at 30 and 90 days (p<0.001), not associated with recurrent MI (p=0.09 and 0.54 at 30 and 90 days respectively)
Our study	6 hours after admission	Hs-CRP >3mg/l was associated with increased mortality on 14 days study with sensitivity 80% and specificity 90% p=0.001and not associated with occurrence of subsequent MI (p=0.061)

We also found that cTnT positivity (>0.01 μg/l) is also an important predictor of occurrence of subsequent MI and death within 14 days of study period. P value < 0.0001, 0.008 respectively. Our results are in agreement with various studies. **TIMI 11A[50]**, in which blood for cTnT was collected 6 hours after admission and they reported that in their14 days study, a rapid positivity of cTnT i.e., appearance of red line in the test kit within 10 minutes was associated with increased mortality than with late cTnT positivity in patients with Acute Coronary Syndrome (sensitivity 29%, specificity 79%). In **GUSTO IV [65]** the blood sample was collected at serial intervals of 8,16,24,36 and 48 hours. They carried out the test for 30 days and reported that increasing quartiles of cTnT was

associated with increased mortality and subsequent MI in ACS ($p < 0.001$). In **FRISC II**[57] substudy blood was collected with a median time of 38.6 hours and reported that positive cTnT was associated with increased risk of reinfraction ($p < 0.001$) and increased risk of death ($p < 0.001$) in ACS. In **Robert H. Christenson**[90] blood sample for cTnT was collected 3.5 hours after admission and showed that there was a strong association between positive cTnT and death ($p < 0.001$) and with early MI ($p < 0.0001$) in ACS, than with late MI ($p=0.125$). In **Solymoss BC**[91] cTnT was measured within 6 hours after the onset of chest pain and reported that positive cTnT was associated with nonfatal MI and death within 48 hours ($p<0.001$).

STUDY	TIME OF MEASUREMENT cTnT	CONCLUSION
TIMI 11A[50]	6 hours after admission	Rapid cTnT positive individuals have increased mortality Sensitivity 29% Specificity 79%
GUSTO IV[65]	Blood sample collected at serial intervals	Associated with increased mortality and MI with increasing quartiles of cTnT ($p<0.001$)
FRISC II SUBSTUDY[57]	With median of 38.6 hours	Increased risk of reinfarction ($p<0.001$) Increased risk of death ($p<0.001$)

Rober H Christenson[90]	3.5 hours after admission	a)cTnT showed strong association with death (p<0.001) b)showed strong association with early MI than with late MI(p<0.0001)
Solymoss BC[91]	Within 6 hours after the onset of chest pain	Elevated cTnT was associated with nonfatal MI and death within 48 hours (p<0.001)
Our study	After 6 hours of admission	Positive cTnT was associated with increased mortality (sensitivity 60% and specificity 97.5%) (p=0.008) and with increased nonfatal MI (P=0.0001).

Our study has showed that **hs-CRP>3 mg/l** in ACS patients was associated with increased risk of mortality with the sensitivity of 80% and specificity 98% and p value of 0.001(significant). At the same time our study showed that the higher value of hs-CRP had no relationship with the occurrence of subsequent myocardial infarction P=0.061(not significant). **When cTnT** was taken as a marker it showed that the positive cTnT(>0.01µg/l) was associated with increased mortality (60% sensitivity and with a specificity of 97.5% and P value 0.008) and also with subsequent MI (p value0.0001) in ACS patients.

In our study when we combined both the markers (hsCRP and cTnT) there was a strong association with the occurrence of mortality than either alone. The correlations possibly reflect that coronary inflammation is an ongoing process during ACS. These cutoff values of hs-CRP (> 3 mg/l) and cTnT (>0.01 µg/l) could be useful in risk stratification. Thus the inflammatory marker hs-CRP and the biomarker cTnT can be used to predict short term prognosis in patients with ACS and could be used to triage the patients and treat them intensively.

CONCLUSION

1. In patients with Acute Coronary Syndrome (Unstable angina/NSTEMI) elevated hs-CRP was associated with increased mortality (Sensitivity=80%, Specificity=98% and p = 0.001).

2. The level of hs-CRP had no association with occurrence of subsequent non fatal MI in Unstable angina/NSTEMI patients (p = 0.06).

3. The positive cTnT in patients with Acute Coronary Syndrome (Unstable angina/NSTEMI) was associated with increased mortality (Sensitivity=60%, Specificity = 97.5% and p=0.008) and also with increased occurrence of subsequent non fatal MI.

4. Our results suggest that elevated hs-CRP level(>3mg/l) and positive cTnT(>0.01 μg/l) obtained 6 hours after admission in patients with Acute Coronary Syndrome can be used as markers for identification of patients who are likely to develop subsequent non fatal MI and mortality.

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ANNEXURE: A - PROFORMA

Name: Age: Sex:

Address: Phone No:

Occupation: Income:

Date of Admission: Date of Discharge:

HISTORY

Chest Pain	Y	N
Referred Pain	Y	N
Sweating	Y	N
Vomiting	Y	N
Palpitation	Y	N
Syncope	Y	N
Breathlessness NYHA Class	Y / Class	N
Cough	Y	N
H/O Orthopnoea	Y	N
H/O Paroxysmal Nocturnal Dyspnoea	Y	N
H/O Swelling Of The Legs	Y	N
H/O Previous Ischemic Heart Disease	Y	N
H/O Previous Myocardial Infarction	Y	N
Dyslipidemia	Y	N
Peripheral Arterial Disease	Y	N
H/O CABG	Y	N
H/O PTCA	Y	N

H/O Stroke	Y	N
H/O Surgery In Previous Month	Y	N
H/O Diabetes Mellitus	Y	N
H/O Hypertension	Y	N
History & Features Of SLE	Y	N
History & Features Of Rheumatoid Arthritis	Y	N
History & Features Of Scleroderma	Y	N
History & Features Of Hepatic Dysfunction	Y	N
History & Features Of Renal Dysfunction	Y	N
History & Features Of Malignancy	Y	N
Other Rheumatological Disease	Y	N

Personal history

Smoking Type Pk.Yrs

Alcohol Type Qty/d Duration

Tobacco Life style

Ht(cm): Wt(Kg): BMI:

BP: mmHg PR : /min Regular/Irregular

Peripheral Pulses: RR: /min JVP:

General Examination:

P Cl Cy Ln E J

System Examination:

CVS: S1 S2 S3 S4 Additional Sounds:

RS: Added Sounds:

Abdomen:

CNS:

Investigations

HEMOGRAM	
Hb	
Tc	
Dc	P L M E
Plt.C	
ESR	

URINALYSIS	
Sugar	
Alb	
RBS	
Pus Cells	
Epithelial Cells	
Casts	

RFT	
Bd.Sugar	
Bd.Urea	
Sr.Creatinine	
Na	
K	

Total Cholesterol	
LDL	
HDL	
TGL	

Hs CRP:

CTnT :

CK-MB:

ECG:

X- RAY chest:

ECHO Cardiogram:

ST Elevation MI during hospitalisation:

Death during hospitalisation:

Readmission as MI:

Annexure B - Master Charts

S.No	Pt Name	Age (Yrs)	Sex	Height in (CM)	Wt in kgs	BMI	current Smoker	HTN	H/O DM	H/O Previous Angina	H/O stroke	peripheral arterial disease	H/O Previous MI	CABG	PTCA	blood sugar (mg/dl)	urea (mg/dl)	serum creatinine (ng/ml)
1	KUMAR	55	M	160	75	29.3	Y	Y	Y	Y	N	N	Y	N	N	202	22	0.8
2	KATHAVARAYAN	60	M	162	60	22.9	Y	Y	Y	Y	N	N	Y	N	N	302	36	1.2
3	KANNAN	65	M	157	63	25.6	N	Y	N	Y	N	N	N	N	N	132	18	0.76
4	CHANDRAMOULI	41	M	165	86	31.2	N	N	N	N	N	N	N	N	N	112	21	0.89
5	RANGAMANI	55	F	156	72	29.62	N	N	N	Y	N	N	N	N	N	113	23	0.7
6	MAHALAKSHMI	35	F	160	66	25.8	N	N	Y	N	N	N	N	Y	N	278	30	1
7	JOTHIPRAKASH	53	M	165	76	28.9	N	Y	N	N	N	N	N	N	N	143	29	0.91
8	RAMAN	76	M	166	61	22.18	Y	Y	N	Y	N	N	N	N	N	132	29	1.1
9	ANWAR HUSSAIN	52	M	169	77	27.01	Y	N	N	Y	N	N	N	N	N	121	30	0.9
10	DHANALAKSHMI	40	F	159	59	23.41	N	N	N	N	N	N	N	N	N	127	31	1
11	MANOHARAN	52	M	171	69	23.63	N	Y	Y	N	N	N	N	N	N	321	33	1.5
12	KILIYAMMAL	58	F	154	66	27.84	N	N	N	Y	N	N	N	N	N	154	28	0.78
13	JAYAKUMAR	76	M	164	76	28.35	Y	Y	Y	Y	N	N	N	N	N	278	31	0.9
14	SAROJA	55	F	158	58	23.29	N	Y	N	N	N	N	N	N	N	142	30	1.02
15	ADIMOOLAM	60	M	169	74	26	N	Y	N	N	N	N	N	N	N	162	22	0.79
16	VIJAYA	52	F	159	81	32.14	N	Y	Y	Y	N	N	N	N	N	223	32	1.1
17	GNANAMANI	70	F	160	57	22.26	N	N	N	Y	N	N	N	N	N	109	21	0.93
18	RAMANI	55	F	162	56	21.37	N	Y	N	Y	N	N	N	N	N	152	24	0.91
19	CHINNAPPAN	52	M	163	67	25.28	N	Y	Y	N	N	N	N	N	N	245	32	0.9
20	NEELA	77	F	168	72	25.53	N	N	Y	Y	N	N	N	N	N	256	34	1.3
21	GOWRI	65	F	171	73	25	N	N	N	Y	N	N	N	N	N	141	31	0.67
22	VENGAIYA	49	M	172	68	23.05	Y	Y	N	N	N	N	N	N	N	117	24	0.91
23	MUNIYAMMAL	60	F	161	57	22	N	N	Y	Y	N	N	N	N	N	343	35	1.1
24	JOICE	66	F	164	68	25.37	N	N	N	N	N	N	N	N	N	101	26	1

S.No	Pt Name	Age (Yrs)	Sex	ECG changes	Total Cholesterol mg/dl	LDL mg/dl	HDL mg/dl	TGL (mg/dl)	CKMB (ng/mL)	HsCRP (mg/L)	CTnT(□g/L)	ST elevation MI during hospitalisation	Death during Hospitalisation	Re admission as MI
1	KUMAR	55	M	Y	246	170	34	145	_	9.8	N	N	N	N
2	KATHAVARAYAN	60	M	Y	198	122	41	156	_	0.23	P	N	N	N
3	KANNAN	65	M	Y	178	131	45	106	_	0.75	N	N	N	N
4	CHANDRAMOULI	41	M	Y	112	132	32	166	_	1.82	N	N	N	N
5	RANGAMANI	55	F	Y	232	177	37	177	_	1.23	N	N	N	N
6	MAHALAKSHMI	35	F	Y	192	110	43	235	23	11.2	P	N	N	N
7	JOTHIPRAKASH	53	M	Y	187	121	29	198	_	0.32	N	N	N	N
8	RAMAN	76	M	Y	176	123	34	154	_	0.11	N	N	N	N
9	ANWAR HUSSAIN	52	M	Y	201	110	42	156	_	9.6	P	N	Y	N
10	DHANALAKSHMI	40	F	Y	345	207	31	145	_	17.1	N	N	N	N
11	MANOHARAN	52	M	N	189	246	27	244	_	0.54	N	N	N	N
12	KILIYAMMAL	58	F	Y	171	129	38	160	_	0.66	N	N	N	N
13	JAYAKUMAR	76	M	Y	224	173	23	154	_	1.03	N	N	N	N
14	SAROJA	55	F	Y	201	129	37	167	_	0.71	N	N	N	N
15	ADIMOOLAM	60	M	Y	191	162	40	155	_	6.16	P	Y	N	N
16	VIJAYA	52	F	N	234	139	41	144	_	8.2	N	N	N	N
17	GNANAMANI	70	F	Y	97	98	38	164	_	0.54	N	N	N	N
18	RAMANI	55	F	Y	108	124	36	154	_	0.13	N	N	N	N
19	CHINNAPPAN	52	M	Y	179	114	39	167	_	0.21	N	N	N	N
20	NEELA	77	F	Y	336	202	24	167	_	0.51	N	N	N	N
21	GOWRI	65	F	Y	103	124	33	143	_	0.26	N	N	N	N
22	VENGAIYA	49	M	Y	198	181	28	154	_	1.72	N	N	N	N
23	MUNIYAMMAL	60	F	Y	277	158	33	167	_	11.72	N	N	N	N
24	JOICE	66	F	Y	197	175	30	153	_	10.99	N	N	N	N

S.No	Pt Name	Age (Yrs)	Sex	Height in (CM)	Wt in kgs	BMI	current Smoker	HTN	H/O DM	H/O Previous Angina	H/O stroke	peripheral arterial disease	H/O Previous MI	CABG	PTCA	blood sugar (mg/dl)	urea (mg/dl)	Serum creatinine (ng/ml)
25	PADMAVATHY	70	F	165	70	25.73	N	Y	Y	Y	N	N	N	Y	N	258	31	0.8
26	DEVAKI	55	F	159	59	23.41	N	Y	N	Y	N	N	N	N	N	116	31	1
27	RAMAMOORTHY	64	M	158	67	26.9	Y	N	N	Y	N	N	N	N	N	107	22	0.88
28	SELVARAJ	49	M	162	61	23.28	N	Y	N	N	N	N	N	N	N	86	21	0.78
29	POONKAVANAM	43	F	160	62	24.21	N	Y	N	Y	N	N	N	N	N	98	27	0.91
30	GOPAL	51	M	160	72	28.12	Y	Y	N	Y	N	N	N	N	N	188	21	1
31	SAKUNTHALA	35	F	157	59	23.98	N	N	Y	N	N	N	N	N	N	223	27	0.83
32	KOTHANDAM	73	M	174	83	27.48	N	Y	Y	Y	N	N	N	N	N	114	29	1
33	SUDAMANI	43	M	171	75	25.68	Y	Y	Y	N	N	N	N	N	N	277	38	1.3
34	RAMAN	76	M	170	71	24.43	N	Y	N	Y	N	N	N	N	N	132	32	1
35	SELVARAJ	39	M	165	67	24.63	Y	N	Y	N	N	N	N	N	N	128	25	0.76
36	ARAVINDKUMAR	49	M	161	60	23.16	Y	N	Y	N	N	N	N	N	N	198	30	1.1
37	THANGAMANI	67	F	156	66	29.21	N	Y	Y	Y	N	N	N	Y	N	223	34	1.3
38	SANKAR	45	M	159	71	28.17	N	N	Y	N	N	N	N	N	N	107	23	1
39	CHANADRA	65	F	160	55	21.48	N	Y	Y	Y	N	N	N	N	N	244	34	1.1
40	STELLA	45	F	159	61	24.2	N	Y	N	N	N	N	N	N	N	118	29	0.92
41	PETER	52	M	158	54	21.68	Y	Y	Y	Y	N	N	N	N	N	102	25	0.91
42	MAHALINGAM	48	M	157	62	25.2	Y	Y	N	Y	N	N	N	N	N	131	21	1.01
43	PANDIYAN	61	M	161	67	25.86	Y	Y	Y	Y	N	N	Y	N	N	211	29	0.9
44	SAHUL HAMEED	39	M	174	68	22.51	N	N	N	N	N	N	N	N	N	105	27	1.02
45	ARUL JYOTHI	45	M	161	69	26.64	Y	Y	Y	N	N	N	N	N	N	123	31	1.1
46	RANI	70	F	160	62	24.21	N	Y	Y	Y	N	N	N	N	N	376	42	1.7
47	SAKTHIVEL	50	M	158	59	23.69	N	Y	N	Y	N	N	N	N	N	111	29	0.96
48	KUMARI	45	F	159	66	26.19	N	N	N	N	N	N	N	N	N	131	28	1.06

S.No	Pt Name	Age (Yrs)	Sex	ECG changes	Total Cholesterol mg/dl	LDL mg/dl	HDL mg/dl	TGL (mg/dl)	CKMB (ng/mL)	HsCRP (mg/L)	CTnT(□g/L)	ST elevation MI during hospitalisation	Death during Hospitalisation	Re admission as MI
25	PADMAVATHY	70	F	Y	278	156	30	164	_	0.73	N	N	N	N
26	DEVAKI	55	F	N	167	130	38	164	_	1.8	N	N	N	N
27	RAMAMOORTHY	64	M	Y	145	109	27	165	_	8.87	N	N	N	N
28	SELVARAJ	49	M	Y	208	143	35	207	_	0.13	N	N	N	N
29	POONKAVANAM	43	F	Y	249	143	37	209	_	0.51	N	N	N	N
30	GOPAL	51	M	Y	188	134	39	228	25.1	13.1	P	Y	N	N
31	SAKUNTHALA	35	F	Y	197	167	40	239	_	1.8	N	N	N	N
32	KOTHANDAM	73	M	Y	200	127	39	156	_	0.62	N	N	N	N
33	SUDAMANI	43	M	Y	191	117	34	123	_	0.14	N	N	N	N
34	RAMAN	76	M	Y	176	123	34	145	_	0.3	N	N	N	N
35	SELVARAJ	39	M	N	78	105	32	163	_	14.57	P	N	N	N
36	ARAVINDKUMAR	49	M	Y	187	211	31	276	_	0.49	N	N	N	N
37	THANGAMANI	67	F	Y	378	256	21	156	_	16.15	N	N	N	N
38	SANKAR	45	M	Y	75	121	31	151	_	0.61	N	N	N	N
39	CHANADRA	65	F	Y	102	124	35	126	_	8.11	N	N	N	N
40	STELLA	45	F	Y	351	206	27	189	_	0.42	N	N	N	N
41	PETER	52	M	N	177	126	34	134	_	0.75	N	N	N	N
42	MAHALINGAM	48	M	Y	197	111	30	152	_	0.11	N	N	N	N
43	PANDIYAN	61	M	N	166	109	32	106	_	14.28	P	N	N	N
44	SAHUL HAMEED	39	M	Y	145	119	31	149	_	0.13	N	N	N	N
45	ARUL JYOTHI	45	M	Y	168	132	39	157	_	7.2	P	N	Y	N
46	RANI	70	F	Y	154	101	30	164	_	17.11	N	N	N	N
47	SAKTHIVEL	50	M	Y	176	121	21	163	_	0.22	N	N	N	N
48	KUMARI	45	F	Y	178	176	33	189	_	0.61	N	N	N	N

S.No	Pt Name	Age (Yrs)	Sex	Height in (CM)	Wt in kgs	BMI	current Smoker	HTN	H/O DM	H/O Previous Angina	H/O stroke	peripheral arterial disease	H/O Previous MI	CABG	PTCA	blood sugar (mg/dl)	urea (mg/dl)	serum creatinine (ng/ml)
49	KUMARESAN	35	M	164	69	25.74	Y	N	N	N	N	N	N	N	N	122	32	1.01
50	PANDIYAN	61	M	166	70	25.5	N	Y	Y	Y	N	N	N	N	N	261	29	1.4
51	ANNAMALAI	40	M	172	66	22.37	N	N	N	N	N	N	N	N	N	166	25	0.9
52	SOKKU	62	M	164	71	26.49	N	N	Y	N	N	N	N	N	N	132	27	0.99
53	SAROJA	65	F	165	75	27.57	N	Y	N	Y	N	N	N	N	N	118	31	1.04
54	VIJAYAN	65	M	164	73	27.23	Y	Y	N	Y	N	N	N	N	N	104	24	1
55	DHANALAKSHMI	45	F	157	58	23.6	N	N	Y	N	N	N	N	N	N	354	34	1.1
56	KUPPU	55	F	158	55	22.08	N	N	N	N	N	N	N	N	N	97	24	0.76
57	MANI	72	M	160	68	26.56	N	N	Y	Y	N	N	N	N	N	106	22	0.75
58	SAJAHAN	60	M	163	65	24.5	N	Y	N	N	N	N	N	N	N	129	27	1.12
59	MAHARANI	70	F	160	59	23.04	N	Y	Y	N	N	N	N	N	N	271	30	1
60	RAJENDRAN	58	M	163	73	27.54	N	N	N	N	N	N	N	N	N	114	23	1.19
61	CHOKKALINGAM	72	M	164	69	25.74	N	Y	N	Y	N	N	N	N	N	111	28	0.91
62	NILAVAN	64	M	169	80	28.1	N	N	Y	N	N	N	N	N	N	308	31	0.9
63	SAKUNTHALA	69	F	167	70	25.17	N	Y	Y	Y	N	N	N	N	N	134	31	0.96
64	SIVAKALAI	60	F	161	71	27.41	Y	Y	Y	N	N	N	N	N	N	256	28.1	1.1
65	SOWDABEE	54	F	170	65	22.5	N	N	N	N	N	N	N	N	N	137	30	1.08
66	MARIMUTHU	65	M	164	64	23.88	Y	N	N	Y	N	N	N	N	N	101	27	1
67	MAJITH	45	M	165	66	24.26	Y	N	Y	N	N	N	N	N	N	139	29	1.21
68	PANDURANGAN	76	M	171	67	22.94	N	Y	Y	Y	N	N	N	N	N	249	27	1
69	VADIVAMMAL	68	F	170	67	23.18	N	Y	N	N	N	N	N	N	N	132	29	1.3
70	CHINNADURAI	50	M	163	68	25.66	N	N	N	Y	N	N	N	N	N	125	21	0.8
71	JAMALYA	64	F	165	69	25.36	N	Y	N	Y	N	N	N	N	N	113	27	0.9
72	KRISHNAN	65	M	164	68	25.37	N	N	Y	N	N	N	N	N	N	135	20	0.7

S.No	Pt Name	Age (Yrs)	Sex	ECG changes	Total Cholesterol mg/dl	LDL mg/dl	HDL mg/dl	TGL (mg/dl)	CKMB (ng/mL)	HsCRP (mg/L)	CTnT(□g/L)	ST elevation MI during hospital isation	Death during Hospital isation	Re admission as MI
49	KUMARESAN	35	M	Y	324	189	26	231	_	0.92	N	N	N	N
50	PANDIYAN	61	M	Y	201	152	29	170	_	7.67	N	N	N	N
51	ANNAMALAI	40	M	N	199	145	32	302	28	7.2	N	N	N	N
52	SOKKU	62	M	Y	199	126	39	163	_	0.69	P	N	N	N
53	SAROJA	65	F	N	165	145	31	143	_	9.2	P	Y	N	N
54	VIJAYAN	65	M	Y	184	166	37	367	_	0.1	N	N	N	N
55	DHANALAKSHMI	45	F	Y	225	178	29	185	_	0.24	N	N	N	N
56	KUPPU	55	F	Y	109	142	30	165	_	0.76	N	N	N	N
57	MANI	72	M	Y	134	144	31	154	_	10.93	N	N	N	N
58	SAJAHAN	60	M	N	187	122	34	149	_	0.93	P	N	N	N
59	MAHARANI	70	F	Y	203	123	39	153	_	0.71	N	N	N	N
60	RAJENDRAN	58	M	Y	89	145	21	134	_	0.51	N	N	N	N
61	CHOKKALINGAM	72	M	Y	178	129	32	158	_	0.49	N	N	N	N
62	NILAVAN	64	M	Y	167	190	32	154	_	3.01	N	N	Y	N
63	SAKUNTHALA	69	F	Y	106	112	36	132	_	0.56	N	N	N	N
64	SIVAKALAI	60	F	Y	199	158	31	164	21	1.7	P	Y	N	N
65	SOWDABEE	54	F	Y	163	178	34	172	_	4.52	N	N	N	N
66	MARIMUTHU	65	M	Y	179	111	40	160	_	0.41	N	N	N	N
67	MAJITH	45	M	Y	81	128	28	162	_	15.09	P	N	N	N
68	PANDURANGAN	76	M	Y	172	101	33	143	32.1	0.39	P	N	N	Y
69	VADIVAMMAL	68	F	Y	152	100	37	114	_	0.71	N	N	N	N
70	CHINNADURAI	50	M	Y	166	108	21	167	_	1.53	N	N	N	N
71	JAMALYA	64	F	Y	178	99	34	123	_	0.65	N	N	N	N
72	KRISHNAN	65	M	Y	182	105	31	160	_	2.92	N	N	N	N

S.No	Pt Name	Age (Yrs)	Sex	Height in (CM)	Wt in kgs	BMI	current Smoker	HTN	H/O DM	H/O Previous Angina	H/O stroke	peripheral arterial disease	H/O Previous MI	CABG	PTCA	blood sugar (mg/dl)	urea (mg/dl)	serum creatinine (ng/ml)
73	KONDAIYA	55	M	169	73	25.61	Y	N	Y	Y	N	N	N	N	N	231	33	1.1
74	VEERARAGAVAN	68	M	158	70	28.1	N	Y	N	Y	N	N	N	N	N	139	30	1
75	LAKSHMIPATHY	63	M	159	75	29.76	Y	Y	N	N	N	N	N	N	N	122	32	1.12
76	GUNAMANI	70	F	171	71	24.31	N	Y	Y	Y	N	N	N	N	N	342	36	1.2
77	ABDUL JALIL	55	M	159	68	26.98	N	N	N	N	N	N	N	N	N	132	34	0.74
78	RAJAMMAL	70	F	158	59	23.69	N	Y	Y	Y	N	N	N	N	N	235	30	1
79	SELVARAJ	52	M	157	59	23.98	N	N	Y	N	N	N	N	N	N	136	23	1
80	SAMPATH	45	M	163	65	24.52	Y	N	Y	N	N	N	N	N	N	246	31	1
81	MAHESH	37	M	160	62	24.21	Y	N	N	N	N	N	N	N	N	114	21	0.68
82	GOVINDAMMAL	70	F	159	66	26.2	N	Y	N	Y	N	N	N	N	N	112	23	0.91
83	KOWSALYA	75	F	164	63	23.5	N	Y	N	Y	N	N	N	N	N	131	25	1.01
84	PERUMAL	62	M	165	64	23.52	N	N	Y	N	N	N	N	N	N	118	21	1.09
85	BEER MOHAMAD	75	M	165	68	25	N	Y	N	Y	N	N	N	N	N	105	24	0.82
86	MALLIGA	65	F	160	60	23.4	N	Y	N	Y	N	N	N	N	N	141	29	0.75
87	SHANKAR	56	M	161	60	23.2	N	N	N	N	N	N	N	N	N	132	31	1.02
88	PARVATHY	70	F	173	75	25.08	N	Y	Y	Y	N	N	N	Y	N	78	27	1.1
89	GUNASEKARAN	53	M	157	69	19.91	N	Y	N	N	N	N	N	N	N	106	32	1
90	MUTHU	38	M	159	68	27	N	N	N	N	N	N	N	N	N	176	32	1.12
91	MOHAN	43	M	160	67	26.2	N	N	N	Y	N	N	N	N	N	143	25	1
92	DEIVASIGAMANI	36	M	163	69	26	N	N	N	N	N	N	N	N	N	122	22	0.91
93	BALAN	61	M	167	70	25.2	Y	Y	N	Y	N	N	N	N	N	95	22	1.11
94	RAJENDRAN	60	M	164	69	25.3	N	Y	N	N	N	N	N	N	N	165	25	0.9
95	WILLIAM MOSES	78	M	174	72	23.84	N	Y	N	Y	N	N	N	N	Y	115	22	1
96	ABUBAKKER	52	M	157	66	26.8	N	Y	N	N	N	N	N	N	N	131	19	0.97

S.No	Pt Name	Age (Yrs)	Sex	ECG changes	Total Cholesterol mg/dl	LDL mg/dl	HDL mg/dl	TGL (mg/dl)	CKMB (ng/mL)	HsCRP (mg/L)	CTnT (µg/L)	ST elevation MI during hospital isation	Death during Hospital isation	Re admission as MI
73	KONDAIYA	55	M	Y	198	112	40	161	_	1.2	N	N	N	N
74	VEERARAGAVAN	68	M	Y	199	112	34	132	_	1.81	N	N	N	N
75	LAKSHMIPATHY	63	M	Y	156	78	23	167	_	9.08	N	N	N	N
76	GUNAMANI	70	F	N	309	204	27	212	_	0.19	N	N	N	N
77	ABDUL JALIL	55	M	Y	200	101	41	165	_	1.41	N	N	N	N
78	RAJAMMAL	70	F	Y	89	78	34	158	_	0.7	N	N	N	N
79	SELVARAJ	52	M	Y	276	183	36	176	_	3.76	N	N	N	N
80	SAMPATH	45	M	Y	210	154	37	289	_	0.8	N	N	N	N
81	MAHESH	37	M	Y	312	199	31	224	_	11.43	N	N	N	N
82	GOVINDAMMAL	70	F	Y	87	110	29	98	_	15.06	N	N	N	N
83	KOWSALYA	75	F	Y	144	89	34	122	_	0.57	N	N	N	N
84	PERUMAL	62	M	Y	178	112	34	101	_	1.73	N	N	N	N
85	BEER MOHAMAD	75	M	Y	167	134	31	152	_	0.52	N	N	N	N
86	MALLIGA	65	F	Y	199	129	39	166	_	0.42	N	N	N	N
87	SHANKAR	56	M	Y	175	163	32	343	_	8.7	N	N	N	N
88	PARVATHY	70	F	Y	144	76	30	90	_	6.58	P	N	Y	N
89	GUNASEKARAN	53	M	Y	243	168	34	143	_	0.24	N	N	N	N
90	MUTHU	38	M	Y	179	188	32	167	_	0.32	N	N	N	N
91	MOHAN	43	M	Y	278	134	35	165	_	0.68	N	N	N	N
92	DEIVASIGAMANI	36	M	N	302	176	38	134	_	1.02	N	N	N	N
93	BALAN	61	M	Y	77	87	31	166	_	6.23	N	N	N	N
94	RAJENDRAN	60	M	Y	164	132	41	163	41	0.9	P	Y	N	N
95	WILLIAM MOSES	78	M	Y	103	110	33	99	_	0.48	N	N	Y	N
96	ABUBAKKER	52	M	Y	225	174	37	134	_	0.59	N	N	N	N

Annexure C – Abbreviation

ABBREVIATION	EXPANSION
ACS	Acute corornary syndrome
AMI	acute myocardial infarction
Ang II	angiotensin II
CAD	coronary artery disease
CKMB	cratine kinase myocardial band
cTn	cardiac troponin
EC	endothelial cell
ECG	electrocardiography
eNOS	endothelial nitric oxide synthase
ET-1	endothelin 1
GP	glycoprotein
HsCRP	highly sensitive C- Reactive protein
IL	interleukin
ICAM-1	inter cellular adhesion molecule
iNOS	inducible nitric oxide synthase
LDL	low density lipoprotein
MCP-1	monocyte chemoattractant protein - 1
MI	myocardial infarction
NF	tumor necrosis factor
NO	nitric oxide

NSTEMI	non ST elevation myocardial infarction
0_2^-	superoxide anion
$ONOO^-$	peroxide
PAI- 1	plasminogen activator inhibitor
PGIS	prostacyclin synthase
SMCs	smooth muscle cells
STEMI	ST elevation myocardial infarction
TIMI	thrombolysis in myocardial infarction
TNF	tumor necrosis factor
UA	unstable angina
VCAM-1	vascular cell adhesion molecule
VSMC	vascular smooth muscle cell

ANNEXURE D - ETHICAL COMMITTEE CERTIFICATE

ETHICAL COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE, KILPAUK,
CHENNAI- 10.
Venue: PANAGAL HALL, KMC
Dt: 01.02.2011

CHAIRPERSON
Prof. Dr.V.KANAGASABAI, MD.,
Dean
Govt. Kilpauk Medical College, Chennai-10
Sub: Ethical Committee project work - approved – regarding.
Ref: Lr.No.3944/Audit/E1/09 Dt. 30.11.2010

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With above reference, the Institutional Ethical committee meeting for the following students was conducted at our Institution on 01.02.2011.

S.NO.	Name	Topic
1.	Dr.Navin Kumar, MS(Ortho), PG., Govt. Royapettah Hospital, Chennai.	1.To Identify a Safe Zone to approach proximal Humerus 2.To study Anatomical relations of Axillary nerve, its course & its Variations
2.	Dr.T.Satheesh Kumar, D.Ortho., PG., Govt. Royapettah Hospital, Chennai	Heriditary Multiple Exostosis
3.	Dr.J. Jeya Shambavi, MD(Pathology), PG., Govt. Kilpauk Medical College, Chennai-10	Clinicopathological Histomorphological and Immunohistochemical Study of Neuroendocrine Tumors of GIT
4.	Dr.L. R. Saranya. MD., (Paed.)PG., Govt. Kilpauk Medical College, Chennai-10	Cord Blood Zinc Level in Term-Small for Gestational Age Neonates
5.	Dr. A.Satheesh Kumar, MS(ENT). PG., Kilpauk Medical College, Chennai	Study on Cases of Chronic Suppurative Otitis Media in Tubo Tympanic Type Due to Sinusitis as Focal Sepsis
6.	R.Prathiban,(Msc.,Physiology), PG., Student, The TN. Dr.MGR Medical University,Chennai-32	Prevalence of Cardiac Dysautonomia in Type I Diabetes mellitus
7.	B. Manikandan, (Msc., Physiology), PG., Student, The TN Dr.M.G.R. Medical University, Chennai-32.	A Comparative Study of Left Ventricular Structure and Function in Obese and Non Obese Subjects
8.	G. Selvakumar, (MSc., Physiology), PG., Student, The TN Dr.M.G.R. Medical University, Chennai-32.	A Study of the Intraocular Pressure In Patients with Diabetic Normotensive, Diabetic Hypertensive and Normal Subjects

9.	R. Ragulji, (Msc.,Physiology), PG., The TN Dr.MGR Medical University, Chennai-32.	A Study of Pulmonary function in insulin dependent diabetes mellitus
10.	V.M. Jenila Veny,(MscPhysiology), PG. The TN Dr.MGR Medical University, Chennai-32	Cardiovascular Autonomic Dysfunction in Chronic Kidney Disease
11.	Dr.G. Lakshmi, MD(O&G), PG., Govt. Kilpauk Medical College,Chennai-10	A Study of Association of Thyroid Disorders in Abnormal Uterine Bleeding
12.	Dr.R. Harini, MD(O&G), PG., Kilpauk Medical College, Chennai	Single Dose Antibacterial treatment for Asymptomatic Bacteriuria in Pregnancy
13.	Dr.E.Geetha, MD(O&G), PG., Govt. Kilpauk Medical College, Chennai-10	A Study of the incidence course of Pregnancy and Pregnancy outcome in Obstetric Cholestasis and to evaluate the efficiency of UDCA in relieving the Symptoms and Improving the Perinatal outcome in these Patients
14.	Dr.S. Nithya, MD(O&G), PG., Govt. Kilpauk Medical College, Chennai-10	Prospective Study of Prevalence of diabetes Mellitus, Thyroid Dysfunction and Hyperprolactinemia in Recurrent Pregnancy loss
15.	Dr.Mohideen Fathima, MD(O&G), PG., Govt. Kilpauk Medical College, Chennai-10	A Study of evaluation of multi system changes in Gestational hypertension / severe pre-eclamptic/eclampasia patients
16.	Dr.M.Padma Priya, MD(O&G), PG., Kilpauk Medical College, Chennai	Dyslipidemia as a Predictor of PIH
17.	Mrs.G. Savitha, (Msc.,Medical Bio Chemistry), TN Dr.M.G.R.Medical University, Chennai-32.	Association of subclinical hypothyroidism in metabolic syndrome patients
18.	Dr.K. Bharadhwaj, MD(G.M.), PG., Kilpauk Medical College, Ch-10	A Study on Peripheral Vascular Disease in Type 2 Diabetes Mellitus
19.	Dr.B.Priya, MD(G.M.), PG	Study of Serum Bilirubin Concentration in Established Coronary Artery Disease
20.	Dr.R.Hema, MD(G.M.), PG.,	Study of Troponin I level in Supraventricular Tachycardia in Non Cad Patients
21.	Dr.P.Manoj Kumar, MD(G.M.), PG., Kilpauk Medical College, Ch-10	A Study on Pulmonary Functions in Type 2 Diabetes Mellitus
22.	Dr.M.Dhanasekar, MD(G.M.), PG.,	Prognostic Risk Stratification of Acute Coronary Syndrome – Role of Highly Sencitive – Reactive Protien
23.	Dr.N. Karthik, MD(G.M.), PG., Govt.Kilpauk Medical College, Chennai-10	A Study of Comparison of QT Dispersion in Acute Myocardial Infraction Between Early Reperfusion and Late Reperfusion Therapy

24.	Dr.H. Anuradha, MD(G.M.), PG., Kilpauk Medical College, Ch-10	A Study of Stress Hyperglycemia in Moderate Degree Burns
25	Dr. V. Nandakumar, MD(G.M.), PG.,	A Prospective Study of Clinical Profile of Emphysematous Pyelonephritis in Type Two Diabetes Mellitus
26.	Dr.S.Sasikumar, MS(G.S.), PG., Govt. Royapettah Hospital, Chennai	A Study of Unusual Presentations of Appendicitis.
27.	Dr.S.R.Padmanabhan, MS(GS), PG., Govt. Royapettah Hospital, Chennai	A Comparative Study Between Autologous Platelet Rich Plasma and Saline Dressing for Diabetic Ulcer
28.	Dr.C.Rose, Scientist-G and Head, Biotechnology, Central Leather Institute, Chennai.	Wound healing efficacy of the chitosan – containing collagenous biomaterial, on burn wound
29.	E.K. Lavanya,B.Tech, Biotechnology, PG., Prathyusha Institute of Technology and Management, Tiruvallur.	Isolation and Characterization of Bacterial Pathogens from Eye Infection

We are glad to inform you that at the Ethical Committee meeting, the documents were discussed and the above short term projects are Ethically approved.

4/2/11
CHAIRPERSON
. DEAN
Govt. Kilpauk Medical College,
Chennai-10.

To: The Individuals