DISSERTATION ON

ROLE OF NT- PRO BNP LEVELS IN PREDICTING THE PROGNOSIS IN ACUTE CORONARY SYNDROMES

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CERTIFICATE

This is to certify that the dissertation entitled "ROLE OF NT - PRO BNP LEVELS IN PREDICTING THE PROGNOSIS IN ACUTE CORONARY SYNDROMES" is a bonafide work done by **DR ANOOP C HARIDAS**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic period from April 2008 to April 2011.

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DECLARATION

I solemnly declare that the dissertation entitled "**ROLE OF NT - PRO BNP LEVELS IN PREDICTING THE PROGNOSIS IN ACUTE CORONARY SYNDROMES**" is done by me at Madras Medical College, Chennai-3 during May 2010 to November 2010 under the guidance and supervision of Associate Prof. S. TITO, M.D., to be submitted to The Tamilnadu Dr M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINE BRANCH-I.

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ABBREVIATIONS

BNP	- Brain Natriuretic Peptide
NT ProBNP	- N-Terminal Pro Brain Natriuretic Peptide
ACS	- Acute Coronary Syndrome
CAD	- Coronary Artery Disease
HF	- Heart Failure
UA	- Unstable Angina
MI	- Myocardial Infarction
NSTEMI	- Non ST Elevation Myocardial Infarction
STEMI	- ST Segment Elevation Myocardial Infarction
AF	- Atrial Fibrillation
ANP	- Atrial Natriuretic Peptide
LV EF	- Left Ventricular Ejection Fraction
TIMI	- Thrombolysis in Myocardial Infarction
SK	- Streptokinase
PCI	- Percutaneous coronary intervention
TIMI	- Thrombolysis in Myocardial Infarction
INC	- Including
SOB	- Shortness of breath
LV EF	- Left Ventricular Ejection Fraction
MILD LV DYS	- Mild Left ventricular dysfunction.
MOD LV DYS	- Moderate Left Ventricular Dysfunction.
SEVERE LV DYS	- Severe Left ventricular Dysfunction
INC	- Including
REC	- Recurrent
pg/ml	- Pico Gram per milli litres
ng/ml	- Nano gram per milli litres

CONTENTS

INTRODUCTION

INTRODUCTION

Cardiovascular diseases contribute 29.3 % of all deaths worldwide according to WHO statistics. Out of these around half of the deaths are due to ischemic heart diseases. In India it is the leading cause of death (15%) followed by respiratory infections (11 %) and cerebrovascular diseases (7 %).

Cardiovascular disease continues to be the major cause of death despite the use of new pharmacological strategies to lower blood lipids, more aggressive therapy of hypertension, and changes in lifestyle. Acute coronary syndromes include acute myocardial infarction (MI) with ST-segment elevation, non ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). This syndrome is a serious health problem because it is responsible for 20% of all medical emergency department admissions with the highest risk for adverse events and death.

In recent times lot of advances have been made in the field of biomarkers for the diagnosis of acute myocardial infarction like Ischemia-Modified Albumin, Myeloperoxidase, Phosphorylase Isoenzyme BB, IL- 6 , PAPP-A and many more are under trial.

But in the field of prognostic biomarkers only very few are available which includes high sensitivity CRP and initial Troponin I levels.

In an ideal scenario patients with acute myocardial infarction brought immediately to a specialist care center with good expertise in primary percutaneous coronary intervention (PCI) as well as in thrombolysis, often achieve good initial results with a fully reperfused heart, asymptomatic patient, fully normalized ECG, early resolution of enzymes and a good left ventricular function in echocardiography. Even in such ideally treated patients on regular follow up, quality of living is often guaranteed but the risk for another coronary event is still many fold higher than the general population.

Often the questions from patients are, will I be symptom free ?, will I get chest pain again even if I take the medicines regularly, is my heart working well ? Will there be any other complications?

Here in this study use of N- Terminal pro Brain Natriuretic Peptide (NT-proBNP) which is an inactive remnant of a hormonally active Brain Natriuretic peptide (BNP) is evaluated in predicting the prognosis after an acute coronary syndrome. This study intends to see whether its initial level of NT-proBNP taken during the first episode of an ACS, correlates with the risk of recurrent symptoms like angina, dyspnea, palpitations, recurrent hospital admissions for ACS including unstable angina, NSTEMI, STEMI or death in a period of 6 months after the first coronary event.

Measurement of NT proBNP is indeed an indirect measurement of Brain Natriuretic Peptide itself. The former is measured as it has a longer half-life than hormonally active BNP. [1][2][3]

BNP is a natriuretic peptide that is mainly released from the cardiac myocytes in the left ventricular wall in reaction to stretch and tension of the myocardial wall. The pro hormone proBNP splits into BNP and the hormonally inactive remnant N-terminal proBNP by proteolytic cleavage and both peptides will be secreted in equimolar amounts into the circulation. It protects the body from plasma overload by inducing diuresis, natriuresis, vascular dilatation and inhibition of the sympathetic nervous system.

The half-life of BNP is around 20 minutes and the half-life of NT-proBNP is around 120 minutes. [1]

At present for predicting the prognosis in an acute coronary syndrome we rely on scoring systems like Thrombolysis in Myocardial Infarction (TIMI) score and initial Troponin I levels. Few studies have come up with use of BNP in predicting the occurrence of cardiac failure in ACS patients in western population.[13][14][15]

As Brain Natriuretic Peptide is one of the most sensitive biomarker for cardiac muscle strain, this study intends to evaluate its use as a prognostic biomarker in patients admitted with Acute Coronary Syndromes in South Indian Population.

AIMS & OBJECTIVES

Aims & Objectives

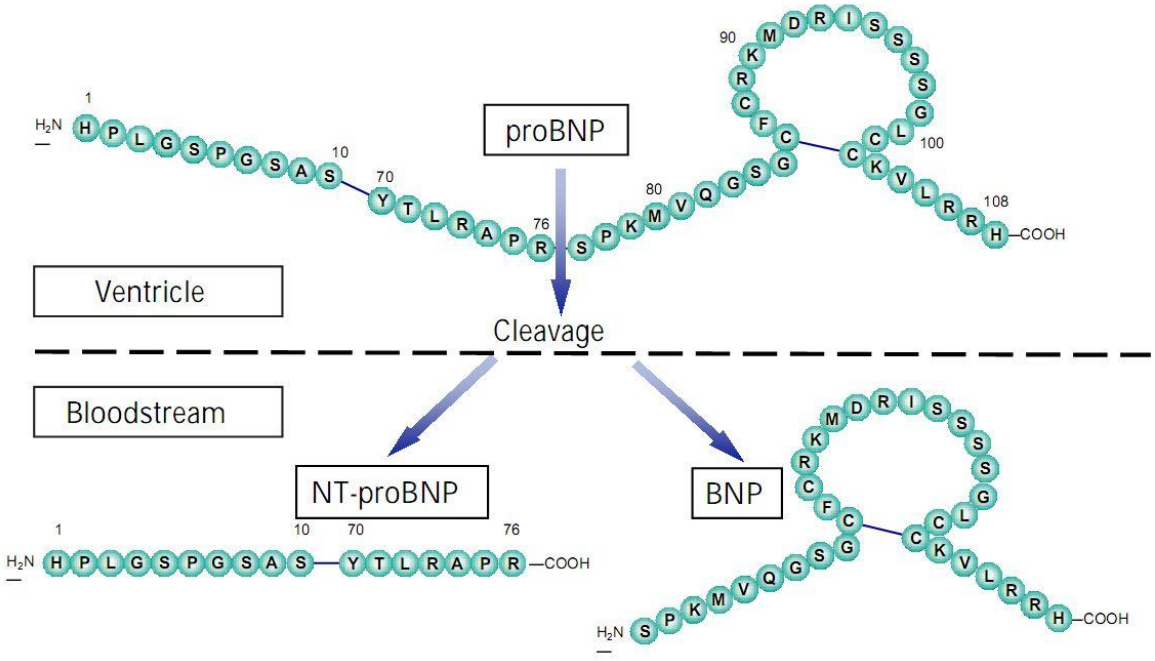
1. Study whether NT ProBNP is elevated in Acute Coronary Syndromes
2. To Study whether NT proBNP levels during an Acute Coronary Syndrome correlate specifically with symptoms like recurrent angina, exertional dyspnoea, palpitations, recurrent hospital admissions for ACS including Unstable Angina, NSTEMI and STEMI or death during the follow up.
3. To Study whether it predicts a deteriorating left ventricular function, and renal function.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Brain natriuretic peptide (BNP), also known as B-type natriuretic peptide is a 32 amino acid polypeptide secreted by the ventricles of the heart. BNP is named as such, because it was originally identified in extracts of porcine brain. In humans it is mainly produced in the cardiac myocytes of the left ventricular wall. Unlike ANP, whose major storage sites are in both the atria and ventricles, the major source of plasma BNP is the cardiac ventricles, suggesting that BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides. [(1)(2)]

Structure of NT ProBNP:



The release of BNP appears to be in direct proportion to ventricular volume and pressure overload. In reaction to stretch and tension of the myocardial wall the pro hormone proBNP splits into BNP which is hormonally active and the hormonally inactive remnant, a 76 amino acid N-terminal proBNP (NT-proBNP) by proteolytic cleavage. This process occurs under the influence of integrins, structures at the Z-disc of sarcomeres. After the stretch of these sarcomeres both peptides will be secreted in equimolar amounts into the circulation.

Circulating BNP acts as an antagonist of the renin angiotensin aldosterone system, and protects the body from plasma overload by inducing diuresis, natriuresis, vascular dilatation and inhibition of the sympathetic nerves system. BNP has antiremodeling and antifibrotic activity [(2)].

The **half life of BNP** is around 20 minutes and the half life of NT-proBNP is around 120 minutes [(1)].

Natriuretic Receptors :

1. Guanylyl cyclase-A (GC-A) also known as natriuretic peptide receptor-A (NPRA/ANP_A) or NPR1
2. Guanylyl cyclase-B (GC-B) also known as natriuretic peptide receptor-B (NPRB/ANP_B) or NPR2
3. Natriuretic peptide clearance receptor (NPRC/ANP_C) or NPR3

BNP binds to and activates the atrial natriuretic factor receptors NPRA, and to a lesser extent NPRB, in a fashion similar to atrial natriuretic peptide (ANP) but with 10-fold lower affinity. Both atrial natriuretic peptide and brain natriuretic peptide bind and activate GC-A, whereas CNP binds and activates GC-B. The biological half-life of BNP however is twice as long as that of ANP and that of NT-proBNP even longer, making these peptides better targets than ANP for diagnostic blood testing. [7]

BNP is cleared from the circulation by receptor-mediated endocytosis via the C-type natriuretic peptide receptor, as well as by enzymatic degradation via zinc-containing endopeptidases located on the vascular endothelial cells and in the renal tubules. Little is known on the exact clearance mechanism of NT-proBNP, although it has been suggested that the kidneys play a major role in this clearance [1][2].

Effect of BNP

The net effect of BNP and ANP is a decrease in blood volume and a decrease in cardiac output.

Relationship of BNP/NT-proBNP and gender

In healthy adults, gender differences in plasma levels of natriuretic peptides are found, with females having higher plasma levels. However, some of the studies found a gender difference for ANP/NT-ANP and not for BNP/NT-proBNP. This might reflect the age difference between men and women; because BNP/NT - proBNP were shown to be more affected by ageing as compared to ANP/NT-ANP, this age difference could be more powerful in BNP/NT-proBNP. [(22)]

BNP in Geriatric Age Group

This relationship between age and natriuretic peptide levels is a consequent to age-related changes in left ventricular compliance as well as a decreasing GFR [(1)(2)(7)]. Age stratification improves the ability of NT-proBNP to identify a high likelihood for acute heart failure (HF). The confirmation and exclusion cut-points for NT-proBNP will help the clinicians more confidently to utilize the marker in the evaluation of the dyspnoeic patient, preserving sensitivity for younger patients with suspected HF, while optimizing specificity for elderly patients. In

elderly non-systolic HF below the threshold for acute HF, >97% had an NT-proBNP value above the 'rule out' cut-point of 300 pg/mL [7].

NT-proBNP levels are higher in older female subjects when compared with age-matched male subjects, possibly due to a higher prevalence of diastolic abnormalities or more significant age-related reductions in GFR in women. There were no gender differences in younger age groups. The cut-off points proposed by PRIDE study is 1800 pg/mL for those >75 years [20]. Thejus et al Study on NT proBNP and Atrial Fibrillation takes cutoff value of NT-proBNP for diagnosis of heart failure as 125 pg/ml in the below 75 years age group and 450 pg/ml in the age group above 75 years [19]. The addition of this cut-point is relevant, as the age-related effects on NT-proBNP results are significant as the average age of patients with acute heart failure is rising.

Anemia and NT-proBNP levels

Anemia is a common phenomenon in HF and is related to the severity of the disease. Hb was related to BNP and NT-proBNP levels independent of severity of HF as measured by left ventricular ejection fraction (LVEF). But this is debatable. Studies in patients with

suspected coronary artery disease showed an independent association between Hb and BNP levels [21][1]**.** Anaemia results in elevated plasma volume, independent of the severity of Heart Failure.

Since BNP and NT-proBNP are released in response to ventricular volume overload, it is conceivable that BNP and NT-proBNP levels are higher in anaemic HF patients compared to non-anaemic HF patients. Additionally, patients with anaemia and renal dysfunction showed higher BNP and NT-proBNP levels when compared to anaemic patients without renal dysfunction [21]. Renal dysfunction was found to be a major cause of anaemia in HF patients, mediated by an erythropoietin production deficiency in the kidneys.

BNP in Acute Coronary Syndromes :

BNP has usefulness as a prognostic marker among patients with acute myocardial infarction. BNP has prognostic value across the full spectrum of patients with ACS, including those with UA/NSTEMI. [1][13][14][15]

In OPUS-TIMI 16, patients with elevated levels of BNP (>80 pg/ml) or NT-proBNP had a two to threefold higher risk of death by 10 months [29]. This finding was confirmed in the TIMI 11 and TACTICS-TIMI 18 trials. Together, these data suggest that measurement of NT-

proBNP in patients presenting with UA/NSTEMI adds importantly to our current tools for risk stratification [29].

Both the European Society of Cardiology and HFSA/AHF guidelines suggest that BNP assays are a useful adjunct to clinical assessment [29].

"Breathing Not Properly" a multinational study demonstrated that BNP was able to distinguish dyspnoea caused by heart failure from that caused by pulmonary disease with a high degree of predictive power and it was the strongest predictor in multiple logistic regression analysis of the diagnosis of heart failure [9]. In addition, this study was able to demonstrate the use of a cut-off 100 mg/dl for a normal NT-proBNP. The BNP test alone had a diagnostic accuracy of 81.2 percent, compared to 74.0 percent for clinical judgment alone. Although it may seem disconcerting that the addition of the physician assessment to the BNP measurement only barely improved diagnostic accuracy to 81.5 percent, the standard for diagnosis in this trial remained the clinical assessment by cardiologists, reviewing the totality of the clinical information. This trial established the role of BNP testing in the assessment of dyspnea in the emergency setting, and in general a BNP value of less than 100pg/ml is considered to have a high negative predictive value, whereas

concentrations greater than 400pg/ml have high positive predictive value for heart failure as the etiology of the dyspnoea [8][9][10].

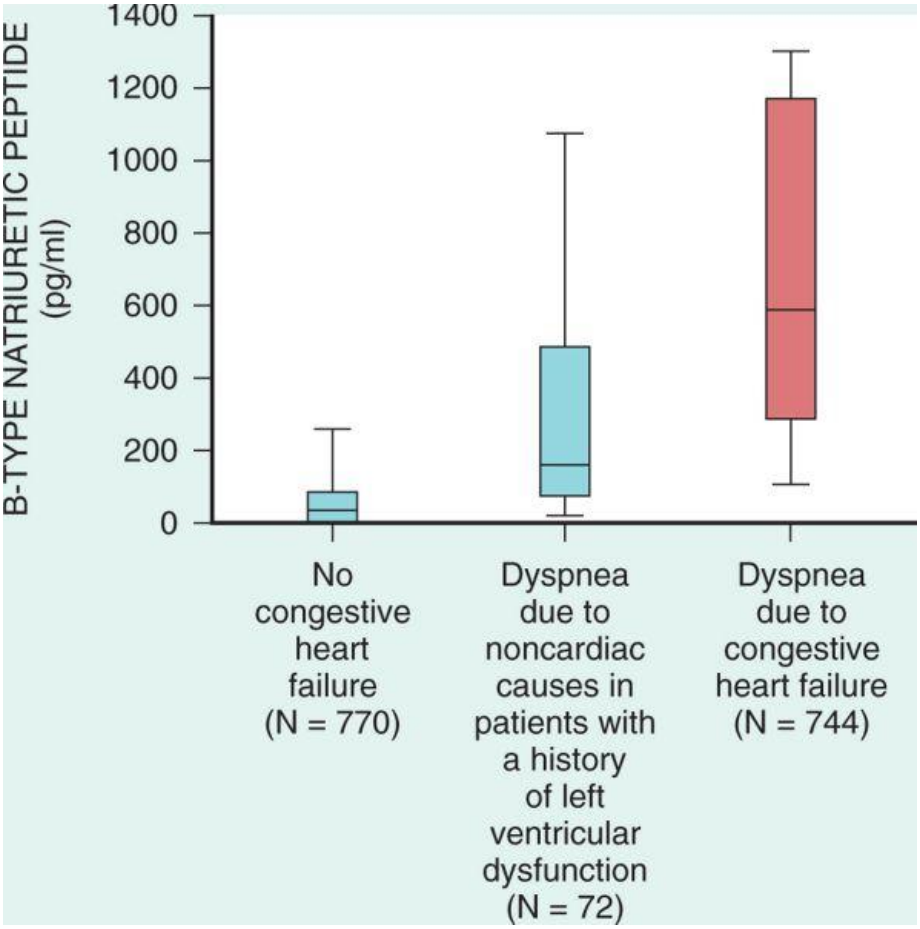
Given the larger mass of ventricle rather than atrial myocardium, the total amount of mRNA for BNP is higher in the ventricles than the atria. Natriuretic peptides are released early after STEMI, peaking at about 16 hours [13][14]. Evidence exists that natriuretic peptides released from the left ventricle during STEMI originate both from the infarcted myocardium as well as the viable noninfarcted myocardium [1][18]. The rise in BNP and N-terminal pro-BNP levels after STEMI correlates with infarct size and regional wall motion abnormalities[14]. Patients with anterior infarction, lower cardiac index and more significant congestive heart failure after STEMI have higher levels of N-terminal pro-BNP and BNP and such elevations correlate with a worse prognosis [18] .

Measurement of natriuretic peptides can provide useful information both early and late in the course of STEMI [19]. Patients with elevated levels 6 hours after the onset of symptoms have a marked increase in mortality even after adjusting for other known prognostic indicators. Conversely, patients with persistently elevated levels at 3 to 4 weeks after STEMI have an increased risk of cardiac-related mortality over the ensuing 5 to 10 years.

Several studies have shown that BNP and NT-proBNP levels have powerful prognostic value for death and MI in patients with Non ST Elevation Acute Coronary Syndromes , independent of markers of myocardial necrosis or inflammation[1][14][15] . The FRISC-II trial (144) found that BNP levels predicted the benefit of revascularization, but there was no such association in TACTICS - TIMI-18[29]. Serial BNP measurements can be used for dynamic risk profiling. Patients with normal troponin levels and low BNP levels are at very low risk of cardiovascular events [29].

Clinical significance of BNP in Heart Failure

Both BNP and NT-proBNP levels in the blood are used for screening of acute CHF. The plasma concentrations of both BNP and NT-proBNP are also typically increased in patients with asymptomatic or symptomatic left ventricular dysfunction. BNP accurately reflects current ventricular status. BNP is an independent predictor of high LV end-diastolic pressure and is more useful than ANP or norepinephrine levels for assessing mortality risk in patients with heart failure. (1)(10)(11)(28)



Reference: Braunwalds Textbook of Cardiology 7th edition.

For patients with Congestive Cardiac failure, BNP levels of more than 100 pg/mL have better than a 95% specificity and greater than a 98% sensitivity when comparing patients without heart failure to all patients with heart failure[1].

For patients with Congestive Heart Failure, BNP values will be above 100 pg per millilitre [11]. The Achilles heel of the NT proBNP molecule is the overlap in kidney disease in the heart failure patient population.

The BNP test is used as an aid in the diagnosis and assessment of severity of congestive heart failure. Natriuretic peptide concentrations correlate with filling pressures and both admission and pre-discharge BNP concentrations are predictive of outcomes [24]. The shorter half-life of BNP and the substantial renal clearance of NT-proBNP support the selection of the BNP assay for this potential diagnostic use. Changes in serial measures of BNP are predictive of outcomes in patients with AHF, beyond clinical and echocardiographic assessments and clinical studies are currently ongoing to assess the utility of serial inpatient BNP measures.

Hullsman-Berger et al found that using NT-proBNP measurement as a guide to intensive patient management, resulted in better clinical

outcome than multidisciplinary care alone in patients after hospitalization for heart failure [26]. In a multi-institutional trial, 278 patients were randomized to NT-proBNP guided intensive management (BM), multidisciplinary care, or usual care. After 12 months, patients in the BM group had fewer days of heart failure hospitalization (488 d) than patients in the multidisciplinary care group (1,254 d) or usual care group (1,588 d) ($p < 0.0001$ for both). In addition, first heart failure rehospitalization was lower with BM than multidisciplinary care (28% versus 40%, respectively and p value was 0.06. The combined end point of death or heart failure rehospitalization was lower in the BM group (37%) than in the multidisciplinary group (50%; $p < 0.05$). The death rate was 22% in both the BM and multidisciplinary groups, but 39% in the usual care group ($p < 0.02$) [26].

Pleural Effusion is common in cardiac failure. A pleural fluid N-terminal pro-brain natriuretic peptide more than 1500 pg/mL is virtually diagnostic of an effusion secondary to congestive heart failure[4].

Acute Dyspnoea Clinical Stratification with BNP levels

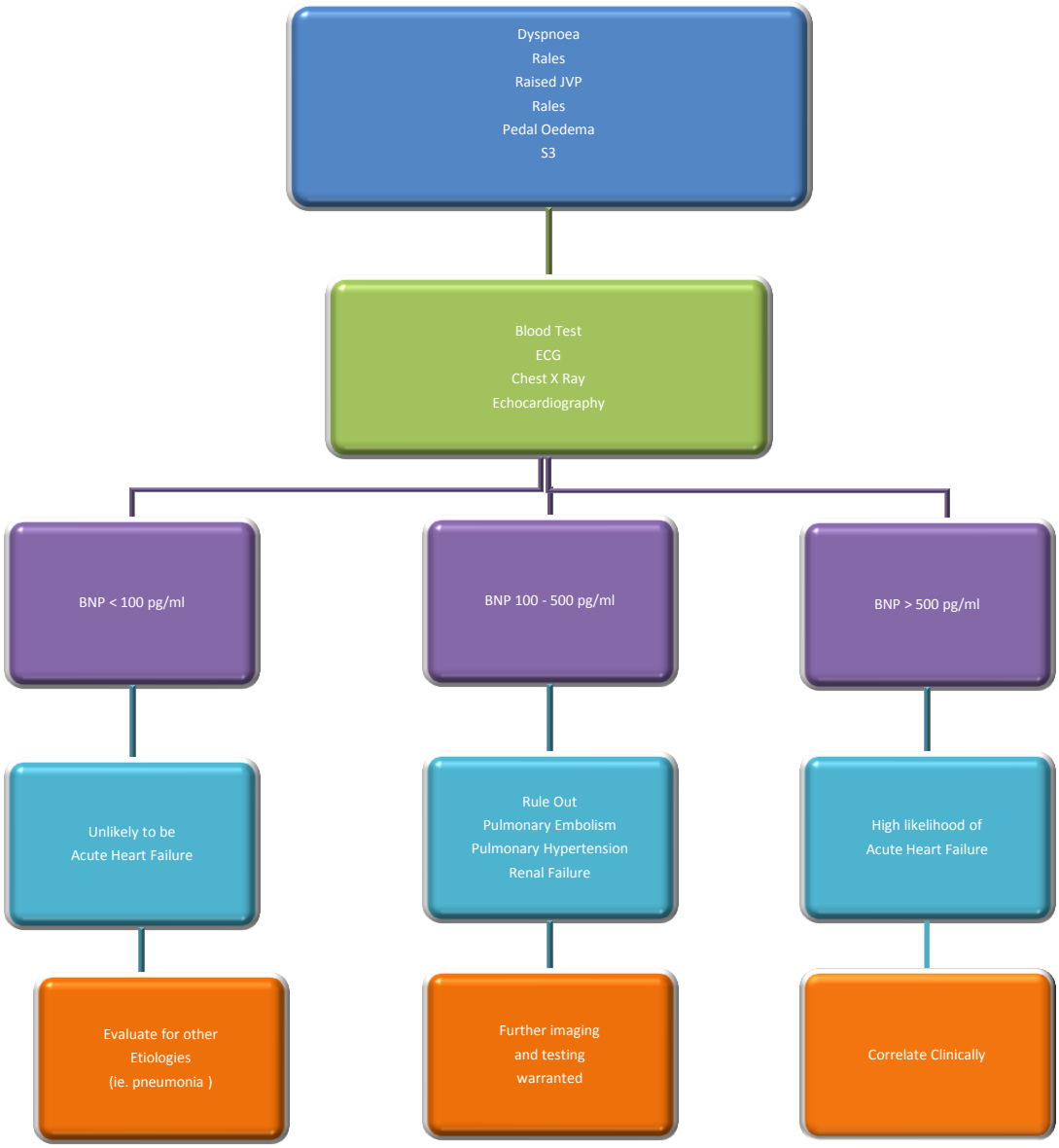


Diagram showing clinical stratification according to BNP levels.

Reference: Topol Textbook of Cardiology 3rd Edition [3].

NT-proBNP is cost-effective in the diagnosis and management of dyspnoeic patients in the emergency room [3].

Cardiac Examination

S_3 gallops or third heart sounds are detected in approximately 11 to 34 percent of patients admitted with Acute Heart Failure. An S_3 is fairly specific as an indicator of LV systolic dysfunction, and correlates with BNP levels. [(1)]

	LVEDP > 15 mmHg	LVEF < 50%	BNP > 100pg/ml
S_3			
Sensitivity	41 (26-58)	52 (31-73)	32 (20-46)
Specificity	92 (80-98)	87 (76-94)	92 (78-98)
Positive Predictive Value	81 (58-95)	57 (34-78)	85 (62-97)
Negative Predictive Value	65 (53-76)	84 (73-92)	48 (36-60)
Accuracy	69 (58-78)	78 (68-86)	56 (45-67)
S_4			
Sensitivity	46 (31-63)	43 (23-66)	40 (26-54)
Specificity	80 (66-90)	72 (59-82)	78 (61-90)
Positive Predictive Value	66 (46-82)	34 (18-54)	72 (52-87)
Negative Predictive Value	64 (51-76)	79 (66-88)	47 (34-60)
Accuracy	64 (54-74)	64 (54-74)	55 (44-66)
S_3 and/or S_4			
Sensitivity	68 (52-82)	74 (52-90)	57 (42-70)
Specificity	73 (59-85)	64 (52-76)	72 (55-86)
Positive Predictive Value	68 (52-82)	42 (26-58)	75 (59-87)
Negative Predictive Value	73 (59-85)	88 (75-95)	53 (38-67)
Accuracy	71 (61-80)	67 (56-76)	63 (52-73)

Adapted from Marcus GM, et al: JAMA 293:2238-2244, 2005.

BNP and Incidence of Atrial Fibrillation (AF)

Framingham Heart Study showed elevated BNP levels to be predictive of atrial fibrillation (AF), cardiovascular outcomes, and death. Just 68 subjects developed AF during the longitudinal study of men and women ≥65 years selected from four US communities. The group notes that NT-proBNP remained the strongest predictor of incident AF after adjustment for other variables including age, sex, medication use, blood pressure, echocardiographic variables, diabetes mellitus, and heart failure. Asselberg et al found that in the general population, elevated NT-proBNP levels at baseline predicted the development of AF when reassessed at 4 years [(27)]. The baseline median level was 62.2 pg/ml, in those who eventually developed atrial fibrillation compared to 35.7 pg/ml in those who did not. The difference was found to be highly significant statistically ($p = 0.001$). Values above the 80th percentile (97 pg /ml in women and 60 pg/ml in men) were associated with an odds ratio of 2.65 for the occurrence of AF. Mollmann et al found that baseline NT-proBNP above 900 pg/ml significantly predicts ($p<0.05$) persistence of AF at 4 weeks after DC version of lone atrial fibrillation [(19)].

NT ProBNP in Pulmonary Embolism

Elevations of NT-proBNP and BNP indicate myocardial stretch caused by right ventricular pressure overload. These patients also have an increased risk of a complicated hospital course, with a higher likelihood of recurrent pulmonary embolism, respiratory failure requiring mechanical ventilation, hypotension requiring vasopressors and death [41][43][51].

BNP in Cardiomyopathy

BNP levels were proposed as a test to discriminate between restrictive cardiomyopathy and constrictive disease, with concentrations approximately five times greater in the former compared with the latter. [2][3][67]

BNP in Aortic Stenosis

BNP and NT-proBNP are elevated in proportion to severity of AS and symptomatic status [1][23]. NT proBNP decreases after successful aortic valve replacement surgery. BNP serum level above 66 pg/mL detected symptomatic patients and those at risk for cardiovascular death.

Renal function and BNP/ NT- proBNP levels

Elevated levels of BNP were also independently related to renal dysfunction [32].This difference may be explained by differences in clearance as NT-proBNP is mainly cleared from the blood by the kidneys, while BNP is cleared mainly by neutral endopeptidases and natriuretic peptide clearance receptors.

This implies that the influence of renal dysfunction should be more pronounced on NT-proBNP levels compared to BNP levels. Implications for clinical practice indicate that haemoglobin and renal function should be taken into account when interpreting the elevated levels of BNP and NT-proBNP.

CKD influences the levels of B-type natriuretic peptide. In general, when the eGFR is less than 60 ml/min/1.73 m^2, a higher BNP cut off point of 200 pg/ml should be used in the diagnosis of heart failure. It is now well recognized that CKD (eGFR < 60 ml/min/1.73 m^2), when present in patients with HF, independently predicts poor outcomes [32][51]. Brain natriuretic peptide (BNP) antagonizes the renin angiotensin system and angiotensin II, and may serve as a biomarker of response to renal revascularization.

Silva et al. measured NT ProBNP in patients with uncontrolled hypertension and RAS (70 percent diameter stenosis), hypertension improved in 77 percent of those with elevated BNP levels, compared with group of five patients with a baseline BNP level less than or equal to 80 pg/ml (P = 0.001). If the BNP level fell more than 30 percent after successful stent placement, 94 percent (16 of 17 patients) had improvement in their blood pressure control [(51)].

But BNP with its physiological effects of vasodilators, diuretic, and natriuretic action do not appear to be sufficient to prevent the disease progression to Cardiorenal Syndrome Type II.

NT proBNP in severe sepsis and septic shock

NT-proBNP values are frequently increased in severe sepsis and septic shock. Values are significantly higher in nonsurvivors than survivors. NT-proBNP on day 3 in the intensive care unit is an independent prognostic marker of mortality in severe sepsis [(68)].

NT-proBNP Elevations in Adult Respiratory Distress Syndrome

NT-proBNP levels are elevated among patients with ARDS in a range typically considered consistent with heart failure. NT-proBNP concentrations are strongly associated with morbidity and mortality in ARDS [(69)]

NT - proBNP Predicts Stroke Risk

NT-proBNP is an independent marker of stroke risk[34][35], while other traditional risk factors like hypertension, left ventricular dysfunction were found not to be independent predictors. NT-proBNP was much better to point out which of the patients had a high risk for these cardiovascular diseases. According to Pedersen F, et al. [34][35], potential prognostic factors for stroke, including age, gender, systolic and diastolic blood pressure, atrial fibrillation, and NT-proBNP, were evaluated using Cox proportional hazards analysis. The investigators showed that NT-proBNP was a strong independent predictor of stroke risk in this population with hazard ratio 4.1.

Atrial Natriuretic Peptide

Atrial Natriuretic Peptide (ANP) is closely related to BNP and CNP (C-type natriuretic peptide). All share the same amino acid ring. ANP was discovered in 1981 by a team in Kingston, Ontario, Canada.

ANP or atrial natriuretic factor (ANF) or atrial natriuretic hormone (ANH), or atriopeptin, is a powerful vasodilator, and a polypeptide hormone secreted by heart muscle cells. It is involved in the homeostatic

control of body water, sodium, potassium and adipose tissue. ANP is produced, stored and released by the cardiac myocytes in the atria of the heart [(1)(2)(3)].

ANP is secreted in response to

1. Atrial distension or stretching of the vessel walls as in myocardial infarction or aortic stenosis.
2. Sympathetic stimulation of β-adrenoreceptors
3. Hypernatremia
4. Angiotensin-II
5. Endothelin
6. Exercise

ANP secretion increases in response to immersion of the body in water, which causes atrial stretch due to an altered distribution of intravascular fluid.

Surface receptors of natriuretic peptides.

1. Guanylyl cyclase-Also known as natriuretic peptide receptor-A (NPRA/ANP_A) or NPR1
2. Guanylyl cyclase-B (GC-B) also known as natriuretic peptide receptor-B (NPRB/ANP_B) or NPR2
3. Natriuretic peptide clearance receptor (NPRC/ANP_C) or NPR3

The vast majority of natriuretic peptide-dependent effects are mediated by elevations of intracellular cGMP concentrations. NPR-C functions mainly as a clearance receptor by binding and sequestering ANP from the circulation. All natriuretic peptides are bound by the NPR-C. Atrial natriuretic peptide and brain natriuretic peptide bind and activate GC-A

Physiological effects

ANP cause a reduction in blood volume and therefore a reduction in cardiac output and systemic blood pressure. Lipolysis is increased and renal sodium reabsorption is decreased. The overall effect of ANP on the body is to counter increases in blood pressure and volume caused by the renin-angiotensin system [(1)].

Renal Effects

- Dilates the afferent glomerular arteriole, constricts the efferent glomerular arteriole, and relaxes the mesangial cells. Thus increasing the glomerular filtration rate , resulting in greater excretion of sodium and water.
- Increases blood flow through the vasa recta which will wash the solutes out of the medullary interstitium. The lower osmolality of the medullary interstitium leads to less reabsorption of tubular fluid and increased excretion.

- Decreases sodium reabsorption in the proximal convoluted tubule and cortical collecting duct of the nephron via cGMP dependent phosphorylation of Epithelial sodium Chanel (ENaC).
- Inhibits renin secretion, thereby inhibiting the renin-angiotensin system.
- Reduces aldosterone secretion by the adrenal cortex.

Vascular

Relaxes vascular smooth muscle in arterioles and venules.

Cardiac

- Inhibits maladaptive cardiac hypertrophy

Adipose tissue

- Increases the release of free fatty acids from adipose tissue. Plasma concentrations of glycerol and nonesterified fatty acids are increased by IV infusion of ANP in humans.

Degradation

Regulation of the effects of ANP is achieved through gradual degradation of the peptide by the enzyme neutral endopeptidase (NEP).

C – Type Natriuretic Peptide:

C – type Natriuretic Peptide (CNP), encoded by a gene symbolized NPPC. The biologically active CNP consists of 22 amino acids. Unlike ANP and BNP, CNP does not have direct natriuretic activity. CNP was observed to be a selective endothelium-independent

venodilator compared to ANP. This is because CNP is a selective agonist for the B-type natriuretic receptor (NPRB) whereas ANP and BNP are selective for NPRA[(1)].

Other natriuretic factors

In addition to the mammalian natriuretic peptides (ANP, BNP, CNP), other natriuretic peptides with similar structure and properties have been isolated elsewhere in the animal kingdom. Tervonen (1998) described a salmon natriuretic peptide known as salmon cardiac peptide, while dendroaspis natriuretic peptide (DNP) can be found in the venom of the green mamba, a species of African snake

Pharmacological modulation

Neutral endopeptidase (NEP) is the enzyme that metabolizes natriuretic peptides. Several inhibitors of NEP are currently being developed to treat disorders ranging from hypertension to heart failure. Most of them are dual inhibitors. Omapatrilat (dual inhibitor of NEP and angiotensin-converting enzyme) developed by BMS did not receive FDA approval due to angioedema safety concerns. Other dual inhibitors of NEP with ACE/angiotensin receptor are currently being developed by pharmaceutical companies.

Nesiritide

B-type natriuretic peptide, discussed above as a diagnostic tool, is also be used in pharmacological doses for the treatment of AHF [(1)(2)]. Nesiritide (recombinant human BNP) is identical to the endogenous peptide and causes potent vasodilation in the venous and arterial systems including coronary vasculature. It also produces significant reductions in venous and ventricular filling pressures and a mild increase in cardiac output, with subsequent improvement in symptoms of dyspnoea. As with other vasodilators, nesiritide may reduce diuretic requirements. Nesiritide is indicated for treatment of patients with acutely decompensated congestive heart failure who have dyspnoea at rest or with minimal activity. It should not be administered for the indication of replacing diuretics, enhancing diuresis, protecting renal function, or improving survival. A bolus of 2 mg/kg followed by a 0.01 mg/kg/min infusion is the recommended starting dose for nesiritide. Nesiritide has clear effects on hemodynamics and is readily administered with limited need for frequent dose adjustments and an absence of tolerance, but its high cost, lack of clear clinical benefit beyond other less expensive and more readily titratable agents, and potential safety concerns, including increased mortality, have limited its use.

Evaluation Left Ventricular Systolic Function

Left ventricular size can be assessed from M – mode measurements of the left ventricular internal diameter (LVID). The cube formula is used to calculate left ventricular volume [(1)(2)(3)].

Left Ventricular Volume = $\pi/3$ x $LVID^3$

Calculation of Ejection fraction

Ejection fraction (EF) is the fraction of blood pumped out of ventricles with each heartbeat. The end-diastolic (EDV) and end-systolic volumes (ESV) are measured by the cube formula in M mode echocardiography [(1)(2)]. Stroke volume is the difference between the EDV and ESV.

$$EF = (EDV - ESV) / (EDV) \%$$

Grading of Left Ventricular Ejection Fraction [(1)]

Normal :	65 ± 8 %
Satisfactory :	45% – 55 %
Mild LV dysfunction :	35% – 45%
Moderate LV dysfunction :	25% - 45 %
Severe LV dysfunction :	< 25 %

Killip classification

Killip classification is a system used in acute myocardial infarction in order to risk stratify them. Individuals with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class [(42)].

Killip class I includes individuals with no clinical signs of heart failure.

Killip class II includes individuals with rales or crackles in the lungs, an S3, and elevated jugular venous pressure.

Killip class III describes individuals with frank acute pulmonary edema.

Killip class IV describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mmHg) and evidence of peripheral vasoconstriction like oliguria, cyanosis or sweating.

The Killip-Kimball classification has played a fundamental role in classic cardiology, having been used as stratifying criteria for many other studies. Worsening Killip class has been found to be independently associated with increasing mortality [(42)].

Thrombolysis in Myocardial Infarction risk score for unstable angina or non-ST (TIMI Score)

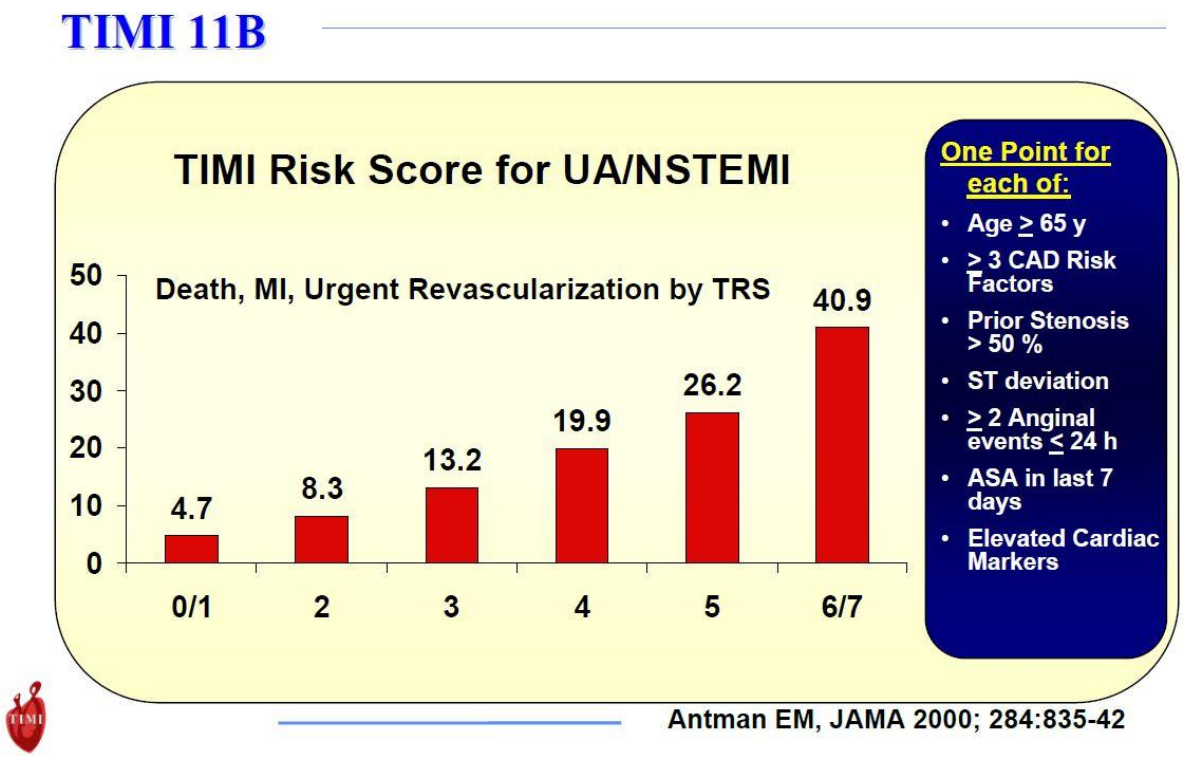
Thrombolysis in Myocardial Infarction (TIMI) Risk Score for unstable angina or non-ST-elevation myocardial infarction (NSTEMI) is a clinical prediction rule that was originally developed to predict the likelihood of morbidity in patients with unstable angina or NSTEMI. (1)(29)(5)

The TIMI Risk Score for unstable angina or NSTEMI has also been used to detect patients with chest pain who are at increased risk of acute coronary syndrome. (5)

Calculation

Single point is given to each of the parameters

- 65 years of age or older
- At least 3 risk factors for coronary artery disease (family history of coronary heart disease, hypertension, hypercholesterolemia, diabetes, current smoking)
- Prior coronary stenosis of 50% or more
- ST-segment deviation on electrocardiogram at presentation
- At least 2 Anginal events in prior 24 hours
- Use of aspirin in the last 7 days
- Elevated serum cardiac markers either Troponin T or CPK-MB



Interpretation

The risk of death, myocardial infarction or urgent myocardial revascularization is according to the number of points:

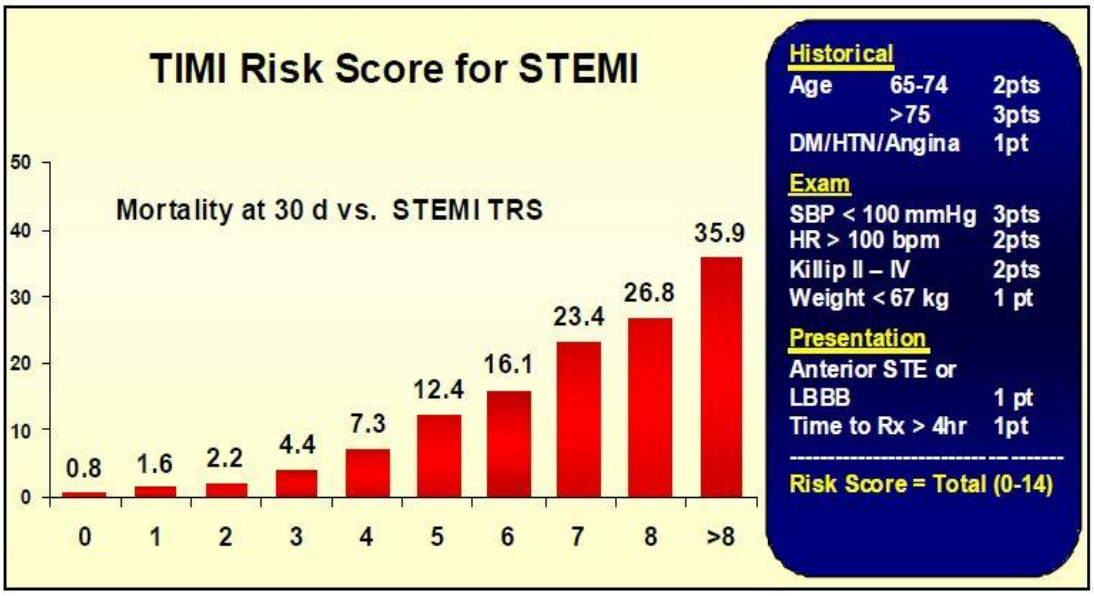
- 0-1 point: 5%
- 2 points: 8%
- 3 points: 13%
- 4 points: 20%
- 5 points: 26%
- 6-7 points: 41%

Among patients with unstable angina or NSTEMI, those with a TIMI risk score of 3 or more may benefit from invasive management (PTCA) according to the TACTICS randomized controlled trial [(29)].

TIMI Risk Score for ST-Elevation Myocardial Infarction (STEMI)

The TIMI risk score for ST elevation is based upon data from 15,000 patients with an ST segment elevation myocardial infarction eligible for fibrinolytic therapy. It is a simple arithmetic sum of eight independent predictors of mortality [29].

TIMI Risk Score for STEMI	
Historical	
Age 65-74 75 and above	2 points 3 points
Diabetes Mellitus / Hypertension or Angina	1 point
Examination	
Systolic Blood Pressure < 100	3 points
Heart Rate > 100	2 points
Killip II-IV	2 points
Weight < 67 kg	1 point
Anterior ST Elevation or Left Bundle Branch Block	1 point
Time to treatment > 4 hours	1 point
Risk Score = Total	**(0-14)**



Morrow DA, Circulation 2000;102:2031-7

The risk score is a weighted integer score based upon clinical risk indicators at presentation. For each patient, the score is calculated as the sum of points for each risk feature present (range 0–14). The risk score was developed using multi-variable methods.

METERIALS & METHODS

MATERIALS AND METHODS

Study Design:

Prospective Observational Study.

Study Population:

Patients less than 60 years of age admitted with Acute Coronary Syndromes in Medical Ward, GGH, Chennai, were taken into study

Inclusion Criteria:

Patients with Acute Coronary Syndromes with no prior history of cardiac disease.

Unstable Angina , NSTEMI , STEMI.

Age less than 60 years.

Exclusion Criteria:

Age more than 60 yrs.

Patients with Valvular Heart Disease

Patients with Anemia

Patients with Renal Failure

Ethical Clearance: Obtained.

Informed Consent: Obtained from all patients.

Methodology

A total of 70 patients with acute coronary syndromes were identified over a period of May 2010 to December 2010, according to the above criteria and were included in the study. Of these only 52 patients turned up for follow-up and participated in the study. Rest was omitted from the study.

A questionnaire was prepared. Noted the age, sex, address, phone number of the patient ,phone number of the relatives and in case the family had no phone , number of neighbours were recorded. Primary complaints like angina, dyspnoea, symptoms of cardiac failure were recorded. Risk factors for coronary artery disease like diabetes mellitus, systemic hypertension, smoking, hyperlipidemia, renal failure and other complaints if any were noted. Clinical examination included a detailed general examination including vital signs and systemic examination of cardiac, respiratory, gastrointestinal, and nervous systems. Killips Class was recorded if the patient was in acute MI. In NSTEMI,STEMI and unstable angina, TIMI scoring was also calculated.

Laboratory Investigations:

Blood urea and serum creatinine were used to rule out frank renal failure.

Electrocardiogram was taken to look for ST elevation or new onset left bundle branch block identified by comparison with previous ECG if available.

In all cases an initial Echocardiography was obtained to assess the left ventricular function and ejection fraction.

Within 2 to 24 hours of the onset of symptoms, NT-proBNP levels were measured in blood with Rapid NT proBNP Assay Kit.

Description of the NT proBNP Rapid Assay Kit :

The strips are coated with canine antibodies to human NT pro terminal end of Brain Natriuretic Peptide. It is a semi quantitative assay and it gives the measurement as < 100 pg / ml , 100 – 500 pg/ml and > 500 pg/ml. Values below 100pg/ml was considered as minimal or insignificant and values above 100 pg/ml was considered significant. Significant values in the range of 100 – 500 pg/ml is taken as moderately elevated and values above 500 pg/ml were taken as markedly elevated.

During subsequent visits:

All patients were asked for any recurrent symptoms like angina, palpitations, dyspnoea, any rehospitalization for cardiac problems including unstable angina , NSTEMI or STEMI in a period of 6 month follow up.

All patients were asked to come for a repeat Echocardiogram for assessing the left ventricular function and compared with the previous echocardiographic findings at the time of admission. In all patients renal function tests were repeated during the follow up. If the patients did not come for the follow up ,the patients or the relatives were contacted through phone or post to enquire about the further developments and to get information regarding rehospitalization and death elsewhere.

Investigations :

Parameter	**Method**
ECG	12 lead ECG
Urea	GLDH/urease
Creatinine	Picrate method
Haemoglobin	Acid Haematin Method
Troponin T or CPK -MB	Hs method
NT ProBNP	Elecsys Rapid Assay
Echocardiography	

Normal Values

Parameter	Normal Values	
Urea	7 – 20 mgs/dl	
Creatinine	M: 0.6 – 1.2mg/dl	F 0.5 –.9mg/dl
Echocardiography Ejection Fraction	Normal > 55 %	
Troponin T MI cut off level	0.0 to 0.01ng /ml > 0.1 ng / ml	
CPK - MB	0 – 5.5 ng / ml	
NT ProBNP Significant Cut Off Level in (< 60 years age)	> 100 pg / ml	

Statistical Analysis:

Statistical analysis was done with

1. SPSS software version 19

2. Microsoft Excel 2010.

Conflicts of interest: None

OBSERVATIONS & RESULTS

STUDY POPULATION CHARACTERISTICS

Study population included 52 patients admitted Acute Coronary Syndromes who never had history of any cardiac problems prior. All patients are under the age of 60. Youngest of them was 39 and the oldest person was 59 years of age. Average Age was 50.3 and median age was 51. As the levels of NT proBNP in elderly individuals tend to be elevated physiologically they are excluded from the study. Anemic and renal failure patients are also excluded. Out of 52, there were 38 male and 14 female patients. There were 14 Unstable Angina cases, 3 NSTEMI and 35 STEMI cases.

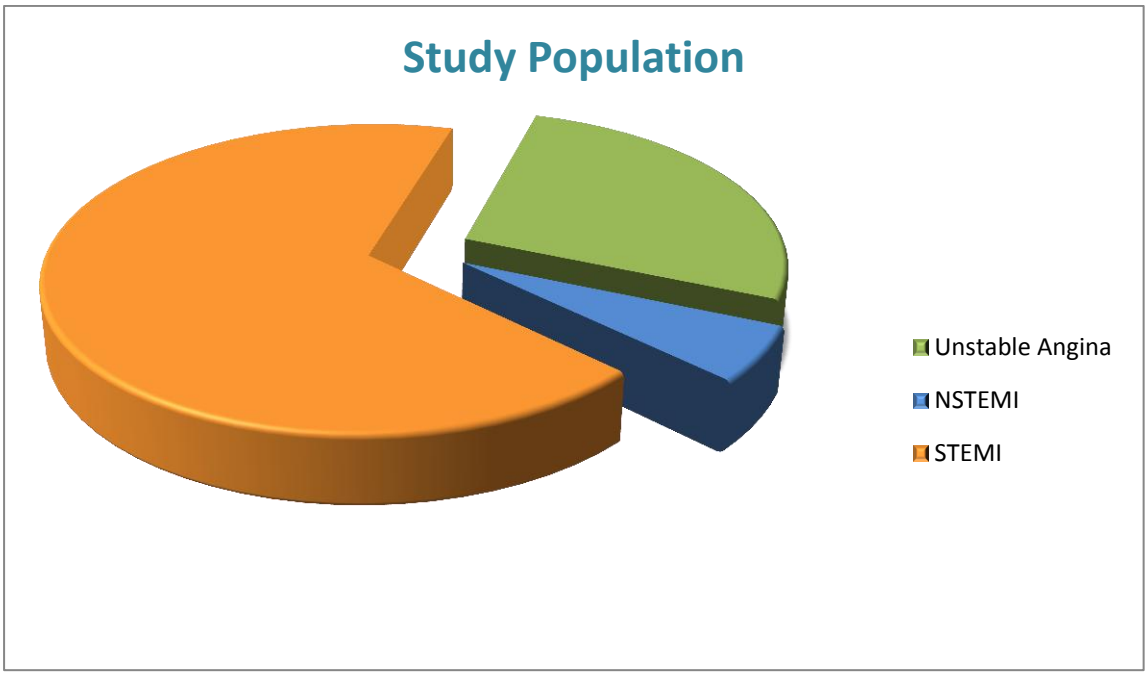


Figure 1: Category distribution of ACS patients.

Blood was taken 2 to 24 hours after the onset of symptoms for measurement of NT proBNP. Values were classified according to the Elecsys rapid assay kit reference value and recorded as below 100 pg/ml or minimal (not significant), between 100 to 500 pg/ml which was taken as moderately elevated (significant) and values above 500 pg/ml which was taken as markedly elevated (significant).

Levels of NT proBNP in various Acute Coronary Syndromes

NT ProBNP Levels	**Unstable Angina**	**%**	**NSTEMI**	**%**	**STEMI**	**%**
Normal (<100pg/ml)	**6**	**42.8**	**1**	**33.3**	**7**	**20**
Significant Elevation (>100pg/ml)	**8**	**57.2**	**2**	**66.6**	**28**	**80**
Total No: Patients	**14**		**3**		**35**	

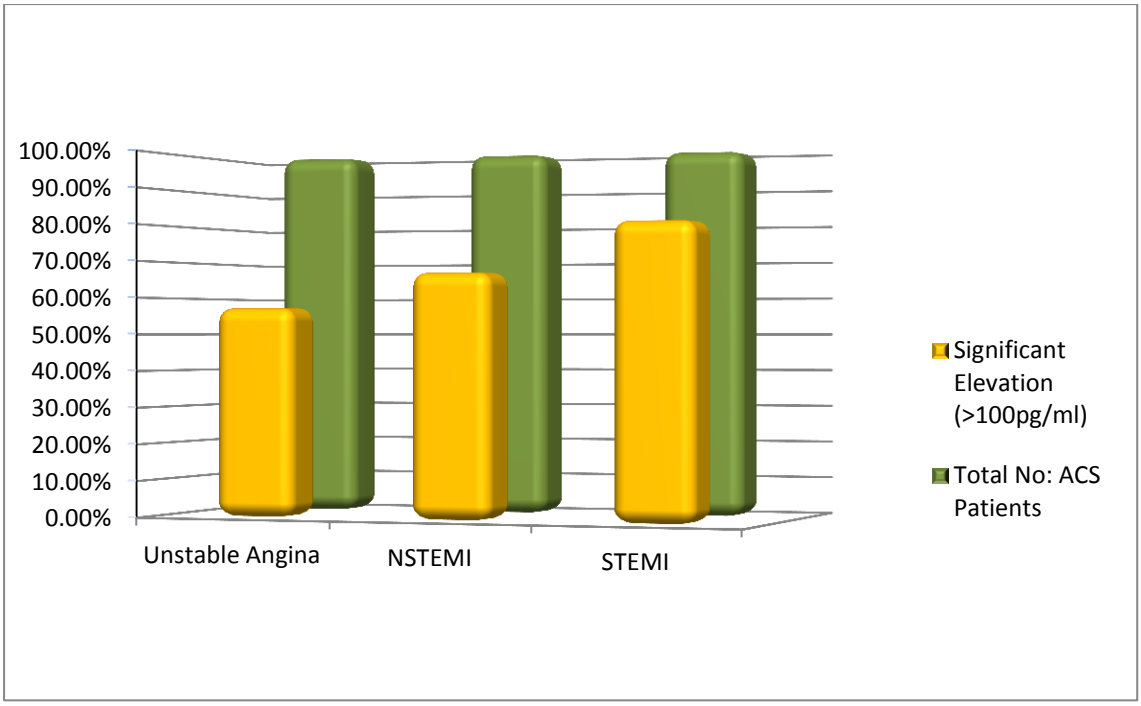


Figure 2: Showing incidence elevated NT proBNP level in various ACS

Here 80 % of patients with STEMI have elevated BNP levels and those with NSTEMI (66.6 %) and Unstable Angina (57.2 %) had lesser incidence of elevated NT proBNP. This was correlating with observations in other studies like James S K, Lindahl et al. GUSTO IV[(13)] and Fragmin and fast Revascularisation during Instability in coronary artery disease (FRISC)-II[)(15)].

Gender and NT ProBNP levels.

Gender and NT ProBNP Levels	NT ProBNP Levels		P Value (Fisher's Exact Test)
	Not elevated	Elevated	
Male (Percentage)	10 (26.3%)	28 (73.7%)	
Female (Percentage)	4 (28.6%)	10 (71.4%)	1.000

Gender and NT ProBNP Levels

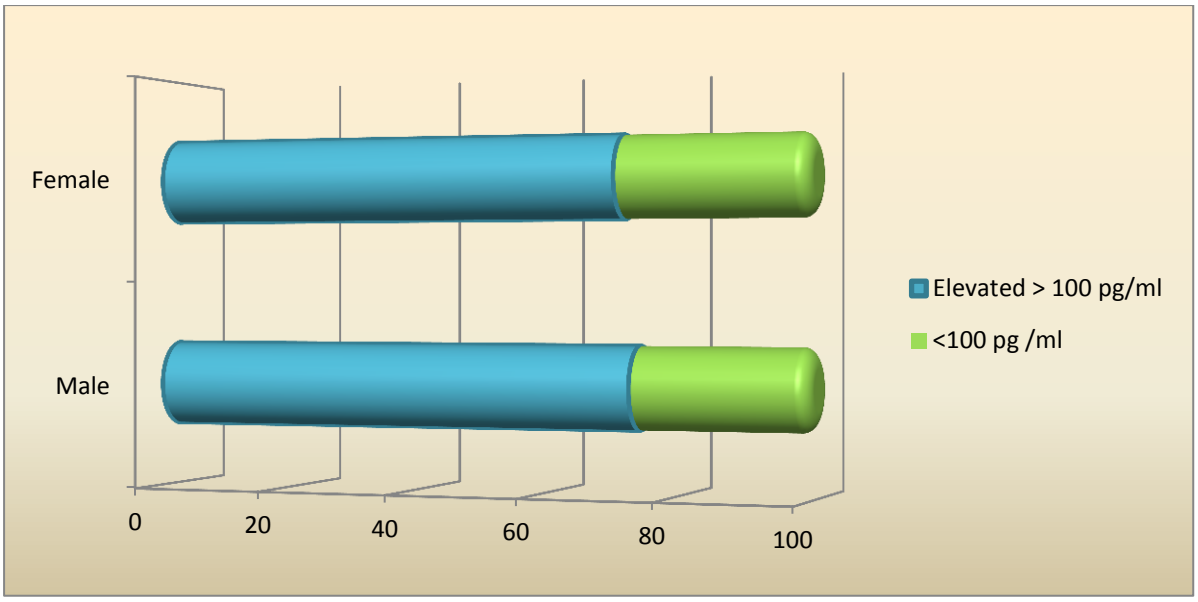


Figure 3: Percentage of male and female patients with elevated NT proBNP

As p value is 1.000 (>0.05) there was no correlation between gender and NT proBNP levels in the study group of patients under the age of 60 years with ACS.

Cardiac Enzymes and NT ProBNP Levels

Cardiac Enzymes and NT proBNP Levels		NT proBNP Levels		Total	P Value
		Not elevated	Elevated NT ProBNP		
Elevated	Count	9	26	35	1.000
	% within Cardiac Enzymes	(25.7%)	(74.3%)	(100.0 %)	
	% within NT proBNP Levels	[64.3%]	[68.4%]	[67.3%]	
Normal	Count	5	12	17	
	% within Cardiac Enzymes	(29.4%)	(70.6%)	(100.0 %)	
	% within NT proBNP Levels	[35.7%]	[31.6%]	[32.7%]	
Total	Count	14	38	52	
	% within Cardiac Enzymes	(26.9%)	(73.1%)	(100.0 %)	
	% within NT proBNP Levels	[100.0%]	[100.0%]	[100.0 %]	

RESULT

Study showed that there is no significant correlation (as P value is 1.0) between cardiac enzymes and NT proBNP levels. This is expected as NT-proBNP is elevated in unstable angina in addition to ST elevation myocardial infarction and NSTEMI. So this support the fact that they are independent variables even though NT proBNP is elevated in MI similar to CPK MB and Troponin T [(1)(2)(3)].

NT proBNP as a Prognostic Biomarker

Main aim of the study was evaluating the role of NT proBNP levels in an ACS patient for predicting the prognosis of an Acute Coronary Event in a 6 month follow up for any symptoms of recurrent angina, palpitations, dyspnea, rehospitalzations including unstable angina, Non ST elevation MI, STEMI, deterioration of left ventricular function, deterioration of renal functions and death.

This is the summary of the results in follow up period of 6 months

	Recurrent Symptoms in follow up							
NT ProBNP Levels	**Angina**	**Palpitation**	**Dyspnoea**	**Rehospitalization for UA or NSTEMI**	**LV Dysfunction**	**Renal Dysfunction**	**Rec STEMI**	**Death**
<100 pg/ml	**3**	**1**	**0**	**1**	**2**	**0**	**1**	**0**
100-500 pg/ml	**13**	**5**	**12**	**11**	**12**	**3**	**3**	**2**
Above 500pg/ml	**14**	**8**	**10**	**09**	**11**	**3**	**9**	**5**

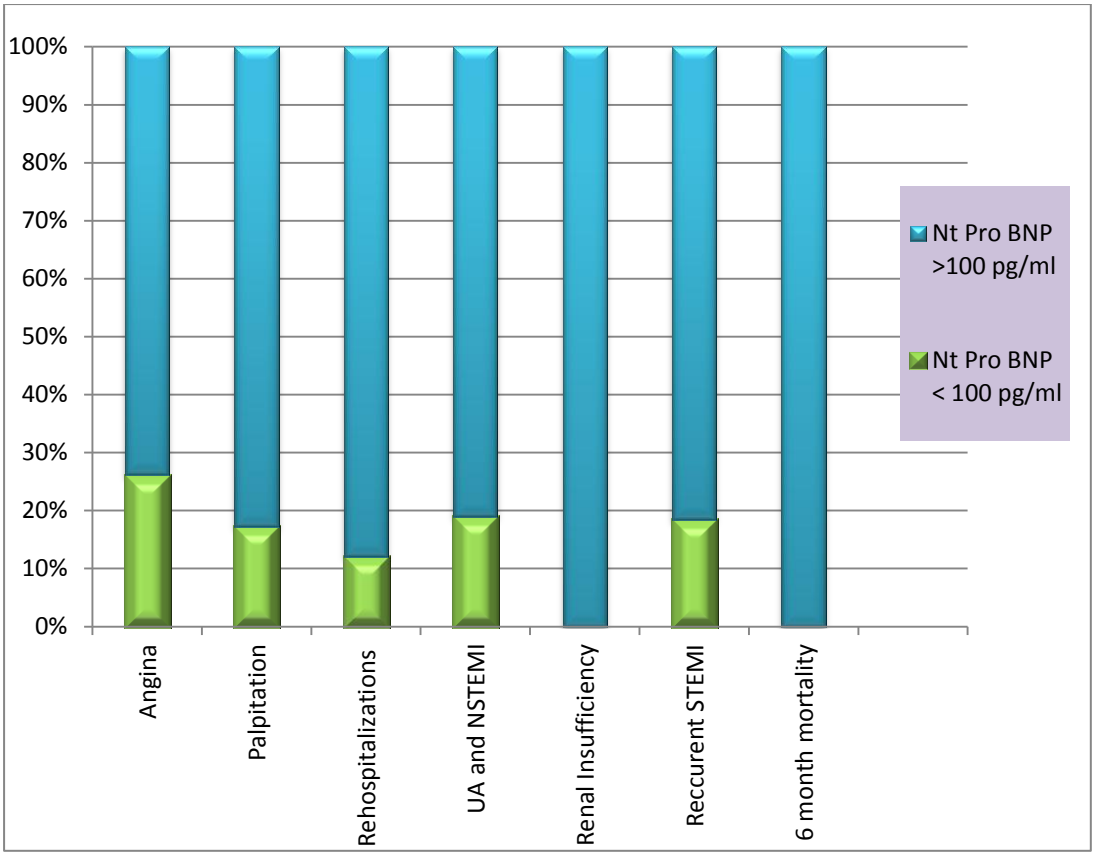


Figure 4: Showing NT ProBNP levels and occurrence of recurrent symptoms as percentiles in the follow up

All the recurrent symptoms in the follow up like angina, palpitation, hospital admissions for unstable angina and NSTEMI, development of left ventricular dysfunction, deterioration of renal functions, recurrent ST elevation myocardial infarction and death were more common in patients with initial NT proBNP levels more than 100 pg/ml. There was no mortality in patients with NT proBNP levels below 100 pg/ml. It was noted that none of the patients with NT proBNP level below 100 pg/ml, progressed to renal failure.

In depth analysis of each outcome is done and the result was evaluated.

NT ProBNP Level Elevation and Recurrent Angina

NT ProBNP Levels Elevation		Angina		Total	P Value
		Yes	No		
< 100 pg/ml (Minimal)	Count	3	11	14	0.002
	% within NT ProBNP Levels Elevation	(21.4%)	(78.6%)	(100.0%)	
	% within Angina	[10.0%]	[50.0%]	[26.9%]	
100-500 pg/ml(Moderate)	Count	14	9	23	
	% within NT ProBNP Levels Elevation	(60.9%)	(39.1%)	(100.0%)	
	% within Angina	[46.7%]	[40.9%]	[44.2%]	
>500 pg/ml (Marked)	Count	13	2	15	
	% within NT ProBNP Levels Elevation	(86.7%)	(13.3%)	(100.0%)	
	% within Angina	[43.3%]	[9.1%]	[28.8%]	
Total	Count	30	22	52	
	% within NT ProBNP Levels Elevation	(57.7%)	(42.3%)	(100.0%)	
	% within Angina	[100.0%]	[100.0%]	[100.0%]	

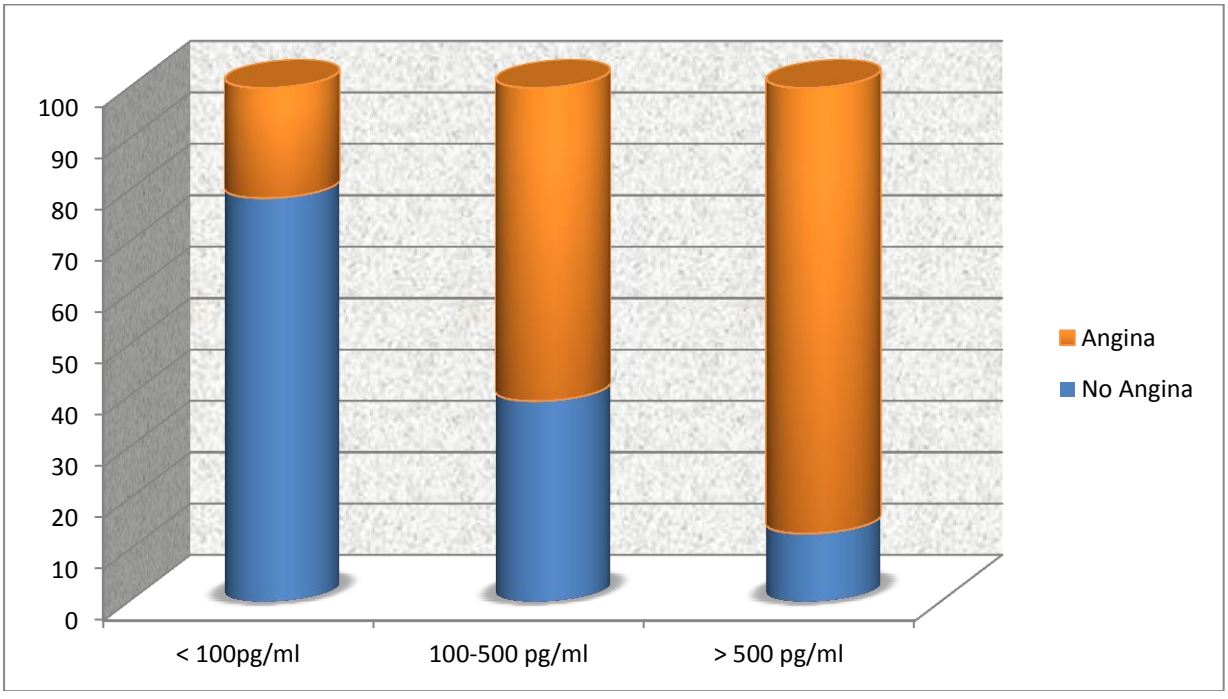


Figure 5: Showing Percentage of incidence of recurrent anginas

NT-ProBNP Levels above 100 pg/ml and Angina

NT ProBNP Levels	Angina		Total	P Value
	Yes	No		
< 100 pg/ml	3	11	14	.001
>100 pg/ml	27	11	38	

60.9 % of the patients with 100-500 pg/ml of NT proBNP level had recurrent angina while 86.7% of the patients with NT proBNP values above 500 pg/ml developed recurrent angina. As the P value is 0.001 even a 100-500 pg/ml (Moderate) elevation of NT proBNP above 100pg/ml itself was a good predictor for this outcome.

Result - There is a significant increase in incidence of recurrent angina in Acute Coronary Syndrome patients with NT proBNP levels above 100 pg/ml.

Elevated NT ProBNP Levels and Palpitations

	NT ProBNP Levels Elevation	Palpitations		Total	P Value
		Yes	No		
< 100 pg/ml (Min)	Count % within Nt ProBNP Levels Elevation % within Palpitations	1 (7.1%) [7.1%]	13 (92.9%) [34.2%]	14 (100.0%) [26.9%]	.015
100-500 pg/ml (Moderate)	Count % within NT ProBNP Levels Elevation % within Palpitations	5 (21.7%) [35.7%]	18 (78.3%) [47.4%]	23 (100.0%) [44.2%]	
>500 pg/ml (Marked)	Count % within NT ProBNP Levels Elevation % within Palpitations	8 (53.3%) [57.1%]	7 (46.7%) [18.4%]	15 (100.0%) [28.8%]	
Total	Count % within NT ProBNP Levels Elevation % within Palpitations	14 (26.9%) [100.0%]	38 (73.1%) [100.0%]	52 (100.0%) [100.0%]	

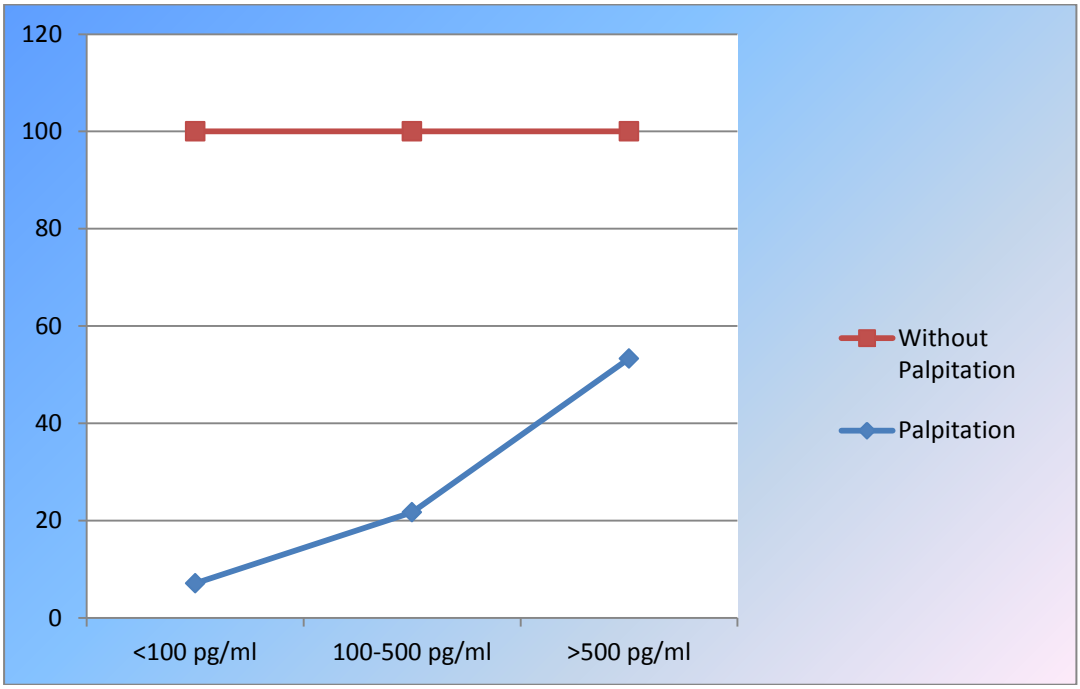


Figure 6: Incidence of palpitations in patient with different levels of NT proBNP

Result: There is a significant positive correlation between NT proBNP elevation and recurrent palpitations. The P value was 0.015.

Elevated NT ProBNP Levels and Dyspnoea

NT ProBNP Levels Elevation (pg/ml)		Dyspnoea		Total	P Value
		Yes	No		
< 100 pg/ml (Min) <100	Count	0	14	14	.001
	% within NT ProBNP Levels Elevation	(.0%)	(100.0%)	(100.0%)	
	% within Dyspnoea	[.0%]	[46.7%]	[26.9%]	
100-500 pg/ml(Moderate) 100-500 Pg/ml	Count	12	11	23	
	% within NT ProBNP Levels Elevation	(52.2%)	(47.8%)	(100.0%)	
	% within Dyspnoea	[54.5%]	[36.7%]	[44.2%]	
>500 pg/ml (Marked) >500	Count	10	5	15	
	% within NT ProBNP Levels Elevation	(66.7%)	(33.3%)	(100.0%)	
	% within Dyspnoea	[45.5%]	[16.7%]	[28.8%]	
Total	Count	22	30	52	
	% within NT ProBNP Levels Elevation	(42.3%)	(57.7%)	(100.0%)	
	% within Dyspnoea	[100.0%]	[100.0%]	[100.0%]	

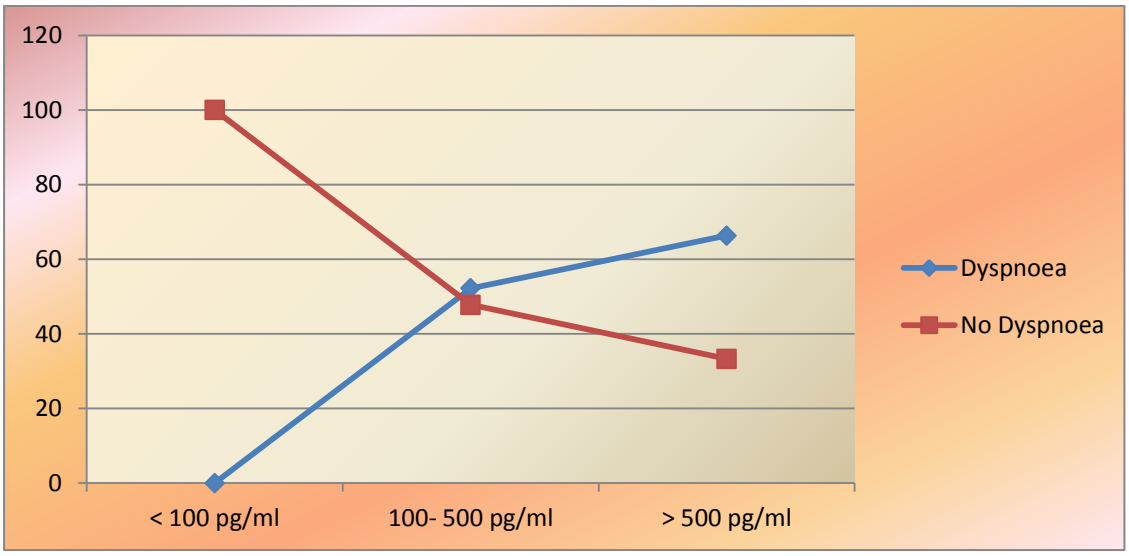


Figure 7: Chart comparing NT proBNP levels and percentage of incidence of recurrent dyspnoea in the follow up.

Result: Dyspnoeic episodes were increasing with the level of NT proBNP. In chi square test the P value is 0.001 which is very significant at 1% level.

NT ProBNP Levels Elevation and Hospital Admission for Unstable Angina and NSTEMI

NT ProBNP Levels Elevation		Hospital Admissions		Total	P Value
		Yes	No		
< 100 pg/ml (Min)	Count	1	13	14	0.009
	% within NT ProBNP Levels Elevation	(7.1%)	(92.9%)	(100.0%)	
	% within Hospital Admission	[4.8%]	[41.9%]	[26.9%]	
100-500 pg/ml(Moderate)	Count	11	12	23	
	% within NT ProBNP Levels Elevation	(47.8%)	(52.2%)	(100.0%)	
	% within Hospital Admission	[52.4%]	[38.7%]	[44.2%]	
>500 pg/ml (Marked)	Count	9	6	15	
	% within NT ProBNP Levels Elevation	(60.0%)	(40.0%)	(100.0%)	
	% within Hospital Admission	[42.9%]	[19.4%]	[28.8%]	
Total	Count	21	31	52	
	% within NT ProBNP Levels Elevation	(40.4%)	(59.6%)	(100.0%)	

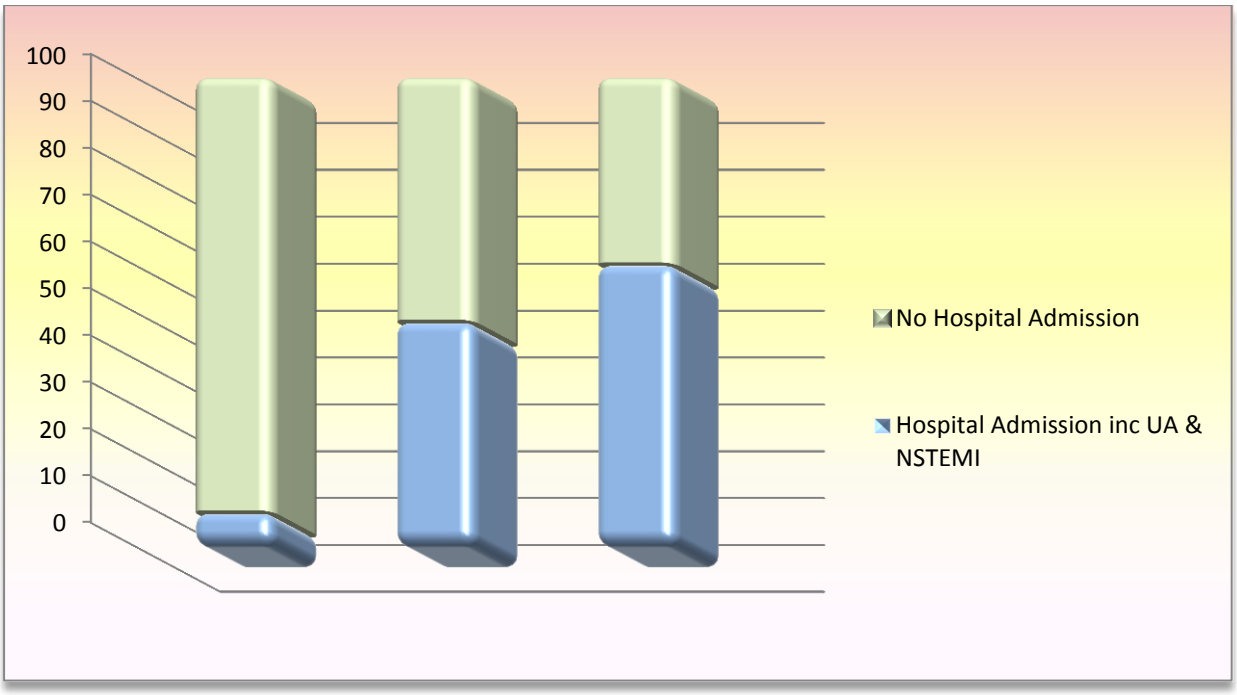


Figure 8: Percentage of Hospital Admissions including UA and NSTEMI in patients with different NT proBNP levels.

As p value is 0.009 (< 0.05) there is a significant correlation between elevated NT proBNP levels and rehospitalization for unstable angina and NSTEMI.

Elevated NT proBNP Levels and LV Dysfunction

		LV Dysfunction		Total	P value
		Deterioration	No Deterioration		
< 100 pg/ml (Min)	Count	2	12	14	
	% within NT ProBNP Levels Elevation	(14.3%)	(85.7%	(100.0%)	
	% within LV Dysfn	[8.0%]	[44.4%]	[26.9%]	
100-500 pg/ml(Moderate)	Count	12	11	23	
	% within NT ProBNP Levels Elevation	(52.2%)	(47.8%	(100.0%)	.006
	% within LV Dysfn	[48.0%]	[40.7%]	[44.2%]	
>500 pg/ml (Marked)	Count	11	4	15	
	% within NT ProBNP Elevation	(73.3%)	(26.7%)	(100.0%)	
	% within LV Dysfn	[44.0%]	[14.8%]	[28.8%]	

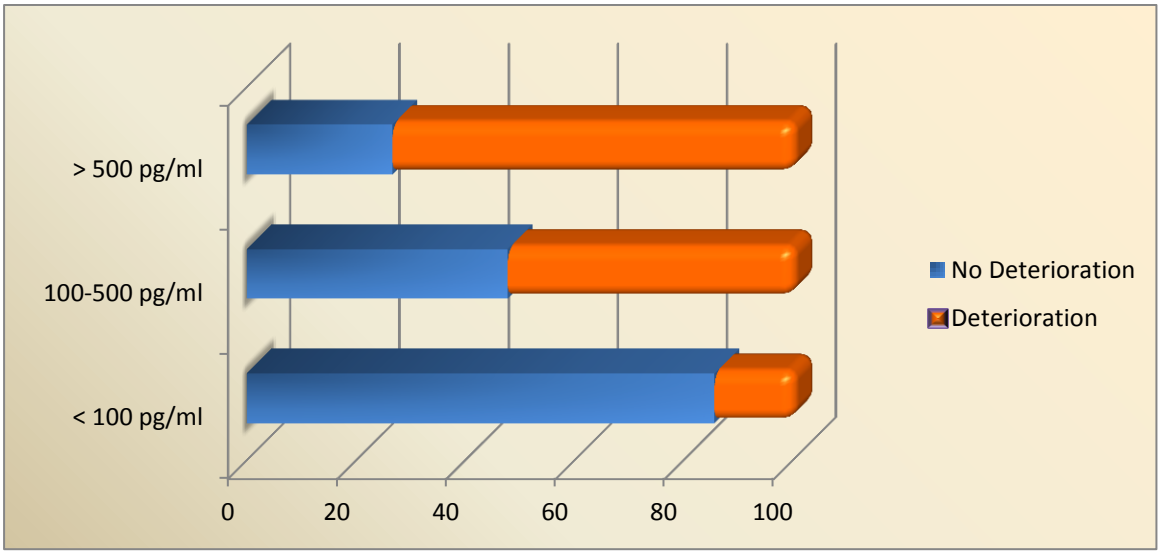


Figure 9: Percentage of development of left ventricular dysfunction in ACS patients with elevated NT proBNP levels

Result:

Elevated NT ProBNP levels correlated significantly with development of left ventricular dysfunction in the 6 month follow up. P value was 0.006

Elevated NT-ProBNP Levels and Renal Function

NT ProBNP Levels Elevation		Renal Function		Total	P Value
		Normal	Raised		
< 100 pg/ml (Min)	Count	14	0	14	.231
	% within NT ProBNP Elevation	(100.0%)	(.0%)	(100.0%)	
	% within Renal Function	[30.4%]	[.0%]	[26.9%]	
100-500 pg/ml(Moderate)	Count	20	3	23	
	% within NT ProBNP Elevation	(87.0%)	(13.0%)	(100.0%)	
	% within Renal Function	[43.5%]	[50.0%]	[44.2%]	
>500 pg/ml (Marked)	Count	12	3	15	
	% within NT ProBNP	(80.0%)	(20.0%)	(100.0%)	
	% within Renal Function	[26.1%]	[50.0%]	[28.8%]	

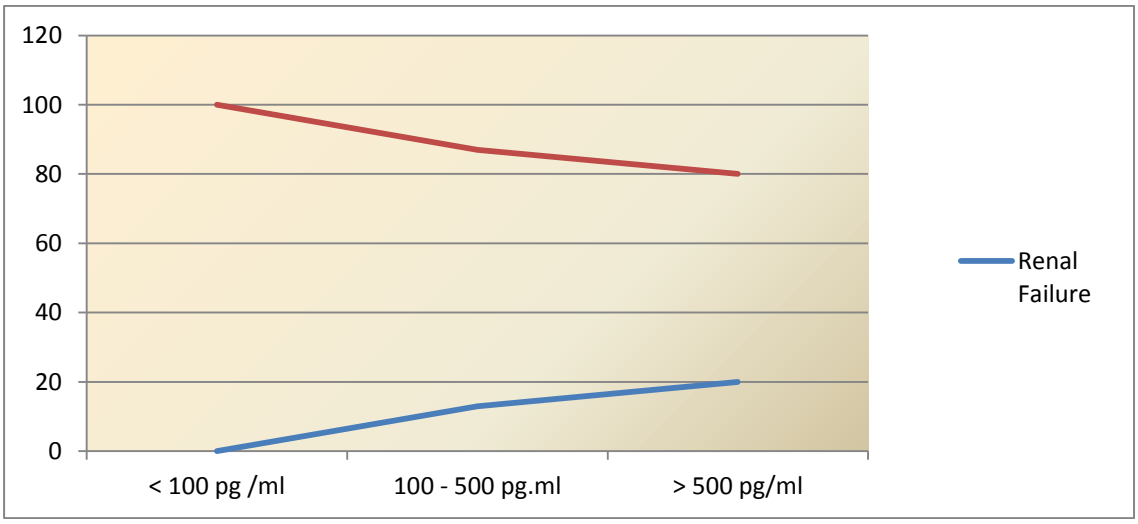


Figure 10: Percentage of patients developing elevated renal parameters in ACS with different NT proBNP levels

Comparing elevated NT proBNP with deterioration of renal function, the Pearson Chi Square test gives the P value as 0.231. So there is only a positive correlation of renal failure with elevated NT proBNP, but the correlation was not statistically significant.

Elevated NT ProBNP Levels and Recurrent Myocardial Infarction

NT ProBNP Elevation		Rec MI		Total	P value
		Yes	No		
< 100 pg/ml (Minimal)	Count	1	13	14	
	% within NT ProBNP Elevation	(7.1%)	(92.9%)	(100.0%)	
	% within Rec MI	[7.7%]	[33.3%]	[26.9%]	
100-500 pg/ml(Moderate)	Count	3	20	23	.001
	% within NT ProBNP Elevation	(13.0%)	(87.0%)	(100.0%)	
	% within Rec MI	[23.1%]	[51.3%]	[44.2%]	
>500 pg/ml (Marked)	Count	9	6	15	
	% within NT ProBNP Elevation	(60.0%)	(40.0%)	(100.0%)	
	% within Rec MI	[69.2%]	[15.4%]	[28.8%]	
Total	Count	13	39	52	
	% within NT ProBNP Elevation	(25.0%)	(75.0%)	(100.0%)	
	% within Rec MI	[100.0%]	[100.0%]	[100.0%]	

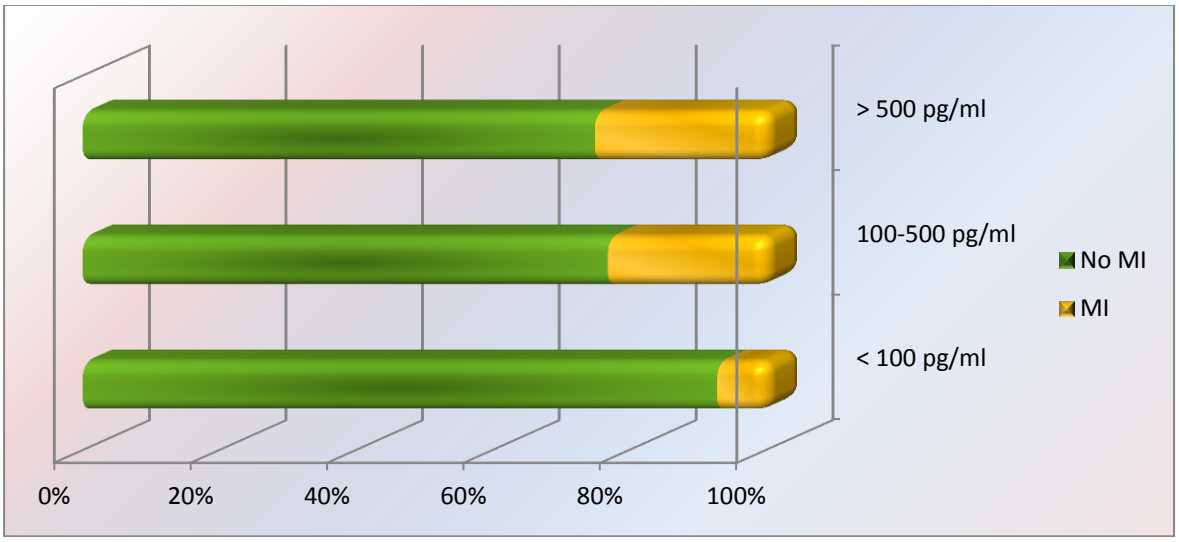


Figure 11: Percentage of MI during follow in various NT proBNP groups

There is a significant correlation between NT proBNP elevation and recurrent myocardial infarction with levels > 100pg/ml. So NT proBNP is a good predictor of recurrent myocardial infarction in an ACS patient.

Predictive Value of NT proBNP

When NT proBNP levels were compared for the correct percentage of predictions the results were as follows.

T-Test

Group Statistics

	NT ProBNP Levels	N	Mean	Std. Deviation	Std. Error Mean	Risk
TIMI Score	Not elevated	14	2.07	.917	.245	
	Elevated NT ProBNP	38	2.47	.893	.145	0.159

Observed outcome after 6 months	Predicted		
	Outcome		Percentage Correct
	Survived	Death	
Survived	43	2	95.6
Death	1	6	85.7
Overall Percentage			94.2

When NT proBNP level was evaluated as a risk prediction model, as per the Hosmer–Lemeshow statistical analysis which was used as goodness of fit for logistic regression models, the result obtained was that elevated NT proBNP levels were able to identify the outcome as death in 85.7 % of cases and it predicted survival in 95.6 % cases correctly.

Result: Initial proBNP levels predicted mortality correctly in 85.7 % of cases.

Elevated NT-ProBNP Level and Mortality

NT ProBNP Elevation		Outcome		Total	P Value
		Survive	Death		
< 100 pg/ml (Min)	Count	14	0	14	
	% within NT ProBNP Elevation	(100.0%)	(.0%)	(100.0%)	
	% within Outcome	[31.1%]	[.0%]	[26.9%]	
100-500 pg/ml(Moderate)	Count	21	2	23	.021
	% within NT ProBNP Elevation	(91.3%)	(8.7%)	(100.0%)	
	% within Outcome	[46.7%]	[28.6%]	[44.2%]	
>500 pg/ml (Marked)	Count	10	5	15	
	% within NT ProBNP Elevation	(66.7%)	(33.3%)	(100.0%)	
	% within Outcome	[22.2%]	[71.4%]	[28.8%]	
Total	Count	45	7	52	
	% within NT ProBNP Elevation	(86.5%)	(13.5%)	(100.0%)	
	% within Outcome	[100.0%]	[100.0%]	[100.0%]	

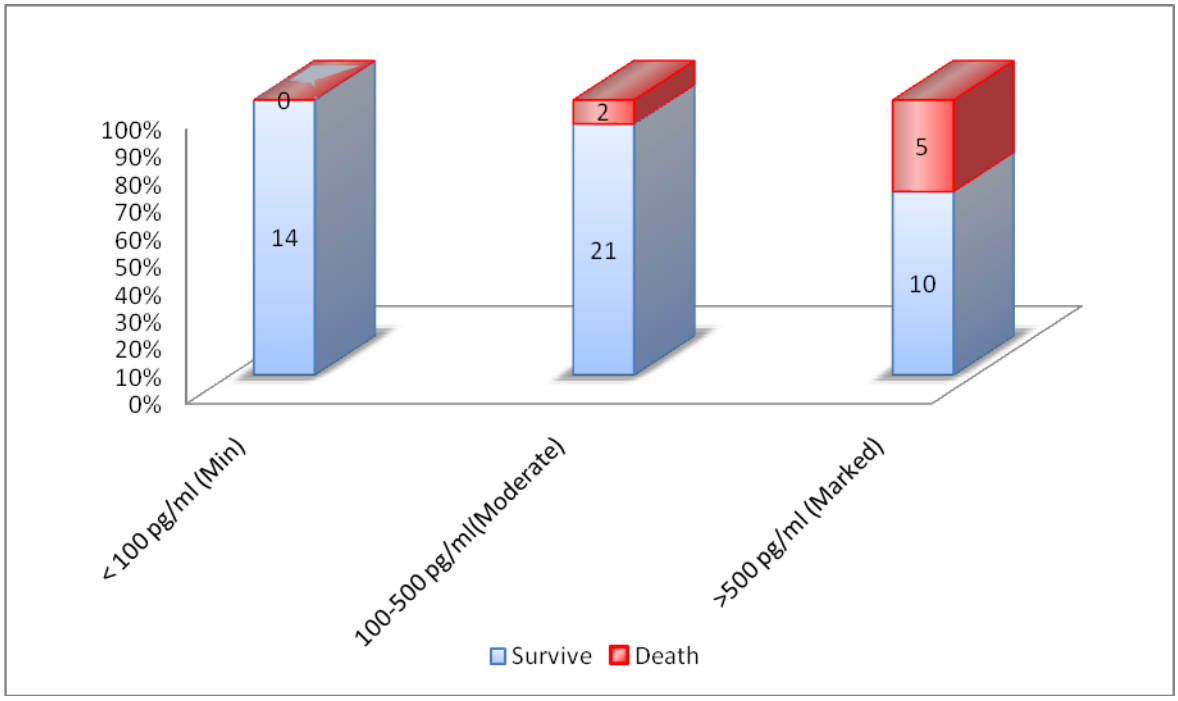


Figure 12: Percentage of mortality in ACS patient in various NT proBNP groups.

In this study out of 52 ACS patients 7 patients died. It is to be noted that none of the patients in the group with low NT proBNP level died in the 6 month follow up. Out of seven patients died, two patients had NT proBNP level between 100 and 500 pg/ml while 5 had levels above 500pg/ml. Patients with elevated NT proBNP above 100 pg/ml had significant mortality rate as the P value was 0.021.

Table comparing markedly elevated NT proBNP (above 500 pg/ml) with mortality

NT ProBNP Levels	Mortality		Total	P Value
	Yes	No		
<500 pg/ml	2	35	37	
>500 pg/ml	5	10	15	.003

When the NT proBNP levels were above 500pg/ml there was 33% mortality rate and P value was even more significant at 0.003. But NT proBNP level above 100 pg/ml itself was statistically significant. Hence this study concluded that there is a significant correlation between the mortality and elevated BNP and the cutoff level can be taken as above 100 pg/ml.

Result: NT proBNP is a good predictor of mortality in patients with ACS.

TIMI Scoring and NT proBNP

Although not being the primary objective of the study, it was interesting to note that risk stratification in TIMI scoring for UA & NSTEMI and risk stratification by NT proBNP levels were comparable.

TIMI Score and NT-ProBNP Levels		NT ProBNP Levels		Total	P Value
		Not elevated	Elevated NT ProBNP		
5%	Count	5	8	13	
	% within TIMI Score	(38.5%)	(61.5%)	(100.0%)	
	% within NT ProBNP Levels	[35.7%]	[21.1%]	[25.0%]	
8%	Count	3	6	9	
	% within TIMI Score	(33.3%)	(66.7%)	(100.0%)	
	% within NT ProBNP Levels	[21.4%]	[15.8%]	[17.3%]	.525
13%	Count	6	22	28	
	% within TIMI Score	(21.4%)	(78.6%)	(100.0%)	
	% within NT ProBNP Levels	[42.9%]	[57.9%]	[53.8%]	
20%	Count	0	2	2	
	% within TIMI Score	(.0%)	(100.0%)	(100.0%)	
	% within NT ProBNP Levels	[.0%]	[5.3%]	[3.8%]	
Total	Count	14	38	52	
	% within TIMI Score	(26.9%)	(73.1%)	(100.0%)	
	% within NT ProBNP Levels	[100.0%]	[100.0%]	[100.0%]	

In patients with ACS, NT proBNP levels did not significantly correlate with TIMI scoring for risk stratification in UA and NSTEMI. NT proBNP and TIMI scoring tend to be independent variables. Hence NT proBNP tends to be an independent predictor for risk and it may be possible to combine them.

DISCUSSION

DISCUSSION

The study subjects were patients with Acute Coronary Syndromes including Unstable Angina, NSTEMI and STEMI. All the patients included were less than 60 years of age. Patients with prior history of cardiac problems or renal failure were excluded as they might already be having an elevated NT proBNP level.

A single blood sample for NT ProBNP level was taken between 2 hours and 24 hours after the onset of symptoms.

Out of 52 subjects 38 patients had elevated NT proBNP of more than 100 pg/ml. Percentage of elevated levels were seen more in STEMI (80 %) followed by NSTEMI (66.6 %) and Unstable angina (57.2 %). This correlates well with other studies conducted [13][14][15].

The study found no relationship between gender and NT proBNP levels (P Value 1.00). Other studies quote that NT proBNP is elevated slightly more in female sex but all those studies had included geriatric population [22].

Cardiac Enzymes elevation in ACS and NT proBNP had no correlation (P value - 1.00) with each other. Cardiac enzymes are elevated only in STEMI, NSTEMI, and not in Unstable Angina. But the NT proBNP levels were raised in unstable angina also. NT proBNP and Cardiac enzymes tend to be independent variables.

Evaluating NT proBNP as a prognostic biomarker, this study found that patients with elevated levels had recurrent symptoms and poor quality of life more commonly than those with normal levels, in a 6 month follow up period. NT proBNP elevation was associated with **Recurrent Angina (P value – 0.002)**, **Palpitations (P value 0.015)**, **Dyspnoea (P Value – 0.001)** and more **frequent cardiac related hospital admissions including unstable angina and NSTEMI (P Value - 0.009)**. Patients with elevated NT proBNP levels also had more chances for **deterioration of left ventricular function (P Value - 0.006)** as quantified by the left ventricular ejection fraction, in the follow up echocardiography.

Patients with Elevated NT ProBNP levels (> 100 pg / ml) had another **STEMI within the 6 month follow up (P Value – 0.001)** when compared to those without. This is in concordance with the very few studies done earlier in this regard [(6)(12)(13)].

When NT proBNP levels were compared to renal function impairment, there was a positive correlation. Patients with consistently deteriorating renal functions (6 out of 52 patients) as measured by serum creatinine had elevated NT proBNP level. It was however statistically insignificant (P Value - 0.231). This is in contrast to other studies which found NT proBNP as a good predictor for deteriorating renal

functions[1][32]. But this study population had other risk factors like diabetes mellitus, hypertension and atherosclerosis which could have contributed to the development of renal failure.

Initial proBNP levels predicted mortality correctly in 85.7 % of our cases as per Hosmer Lemeshow statistical analysis test. So NT proBNP has got a good positive predictive value for mortality. When NT proBNP was evaluated for predicting mortality, those patients with NT proBNP levels above 500 pg/ml had higher mortality (P Value 0.003). When the NT proBNP level cutoff was taken as 100 pg/ml, it was still significantly associated with **mortality (P Value – 0.021)**. Hence NT proBNP value of more than 100 pg/ml itself is a good predictor of mortality.

We compared the risk stratification of TIMI scoring for Acute Coronary Syndromes including Unstable Angina, NSTEMI and STEMI with NT proBNP levels. Both of them had good predictability individually. NT proBNP scoring was not superior to TIMI (P Value – 0.525). But the advantage was that while using NT proBNP, only a single blood value was necessary, avoiding the recall disadvantage of TIMI scoring. So NT proBNP is recommended for risk stratification in acute coronary syndromes.

We recommend further studies to combine TIMI scoring and NT ProBNP for an even better predictability.

LIMITATIONS OF THE STUDY

The major limitation of the study was the smaller number of subjects.

Being a tertiary care center, the proportion of patients with more severe disease and multiple risk factors were getting admitted more than those with milder disease. So this study had more STEMI patients than NSTEMI or Unstable Angina patients, which is not reflecting the incidence pattern of the disease in the general population.

Geriatric age group was not included specifically because NT proBNP levels are normally elevated in them, and the normal cut off values in this age group not being well defined. This will exclude a major portion of patients with ACS.

Women would be developing coronary artery disease later in their life than the male counterpart, so in our study female subjects were relatively less because study excludes patients above 60 years of age.

CONCLUSION

CONCLUSION

- NT proBNP is a reliable prognostic biomarker.
- NT proBNP is elevated more commonly in STEMI than in NSTEMI or Unstable Angina
- During follow up NT proBNP can be used to predict recurrent symptoms like angina, palpitations, dyspnoea, recurrent hospital admissions and progression to left ventricular dysfunction.
- NT proBNP also had a good predictive value for recurrent Unstable Angina , NSTEMI, STEMI and cardio vascular mortality.
- The cut off level of NT proBNP for prognostic end points can be taken as values above 100 pg/ml.
- NT proBNP levels were independent of the gender in the below 60 age group.
- NT ProBNP as an independent variable in risk stratification is comparable to TIMI risk scoring.
- So TIMI scoring may be combined with NT proBNP for better prediction of cardiovascular outcome in patients with acute coronary syndromes.

RECOMMENDATIONS

RECOMMENDATIONS

- NT proBNP should be used as a prognostic biomarker in Acute Coronary Syndromes.
- More intense monitoring is required in patients with elevated NT proBNP levels.
- Further studies may be undertaken to combine NT proBNP and TIMI scoring system for a better risk stratification in patients with Unstable Angina, NSTEMI and STEMI.

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ANNEXURES

ANNEXURES

NT ProBNP as a prognostic Biomarker in ACS – PROFORMA

Name:

Age:

Sex:

IP.NO:

Address:

Phone Number of the patient:

Phone Number of Relatives / Neighbours :

Presenting Complaints:

Angina:

Recurrent Chest Pain:

Palpitation

Dyspnoea:

Orthopnoea:

Oliguria:

Co-morbid Illness: DM ☐ SHT ☐ Dyslipidemia ☐

History of prior treatment:

Others if any:

EXAMINATION:

Vital Signs: Pulse Rate BP

Body Weight (in kg)

CVS:

RS:

CNS

Abdomen:

Killips Class:

Investigations For All Patients:

S.No	Parameter	Method
1.	Complete blood count	Automated flow cytometry
2.	ECG	12 lead ECG
3.	Urea	GLDH/urease
4.	Creatinine	Picrate method
5.	Echocardiography	
6.	Troponin T or CPK -MB	Hs method
8.	NT ProBNP	Elecsys Rapid Assay

Time to Treatment < 4 hours Yes / No

TIMI Scoring:

NT proBNP level:

Below 100 pg/ml ☐

100 – 500 pg/ml ☐

Above 500 pg/ml ☐

DIAGNOSIS:

Six Month Follow Up for Recurrent Symptoms:

Chest Pain: Yes / No

Palpitation : Yes / No

Dyspnoea : Yes / No

LV Dysfunction : Yes / No

Renal Dysfunction : Yes / No

Hospital Admissions : Yes / No

Recurrent Unstable Angina : Yes / No

Recurrent NSTEMI : Yes / No

Recurrent STEMI : Yes / No

Final Outcome : Survived / Expired

Master Chart

S.No	Name	Age	Sex	Symptoms	Risk Factors fo	S. Cr	ECG	Cardiac Enzymes	Diagnosis	TIMI Score	Treatment	NT ProBNP	LV Functio	Recurrent Symptoms within 6 months							
												Pg /ml		Angina	Palpitations	Dyspnoea	Hospital Admissions inc	LV Function	Renal Function	Rec STEMI	Final outcome : Death / Survived
1	Murugan	45	M	Chest Pain, SOB	Smoker, Diabetic	1	ST elevation	Elevated	AWMI	4	SK	100-500	Normal	Yes	No	Yes	Yes	Mild Lv D	Normal	No	Survived
2	Babu	56	M	Chest Pain	Smoker, Alcoholic	0.8	T inversion	Normal	UA	1	Heparin	100-500	Normal	Yes	No	No	No	Mild Lv D	Normal	No	Survived
3	Perumal	55	M	Giddiness SOB	DM Hypercholestrolemia	1.1	ST Elevation	Elevated	IWMI	2	SK	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
4	Muniammal	48	F	Chest Pain	No	0.9	Non Sp Changes	Normal	UA	1	Heparin	100-500	Normal	No	No	Yes	Yes	Mild LV d	Normal	No	Survived
5	Balaji	55	M	Chest Pain	SHT	1	ST Elevation	Elevated	Ext AWMI	3	SK	>500	Mild Lv Dys	No	Yes	Yes	Yes	Mild LV d	Normal	Yes	Survived
6	Sekhar	40	M	Chest Pain	SHT family History	0.9	ST Elevation	Elevated	AWMI	3	SK	<100	Normal	Yes	Yes	No	Yes	Mild Lv D	Normal	No	Survived
7	Mani	44	M	Chest Pain	Smoker, Alcoholic	0.8	ST Elevation	Elevated	ASMI	3	SK ,elective PCI	>500	Mild LV Dys	No	Yes	No	No	Mild LV d	Normal	No	Survived
8	Jayaraj	50	M	Chest Pain	Alcoholic SHT	0.8	T inversion	Elevated	NSTEMI	2	Heparin	>500	Mild Lv Dys	Yes	No	No	No	Mod LV d	Normal	Yes	Survived
9	Nizamuddin	51	M	Chest Pain SOB	Smoker Family Hist	1	ST Elevation	Elevated	IWMI	3	SK	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
10	Bhaskar	58	M	Chest Pain SOB	Smoker	1.1	ST Elevation	Elevated	Ext AWMI	3	SK	100-500	Mod Lv Dys	Yes	No	Yes	No	Mod LV d	Raised	No	Survived
11	Kuppan	53	M	Chest Pain	Smoker	0.8	ST Elevation	Elevated	ASMI	3	SK	>500	Mild Lv Dys	Yes	Yes	No	Yes	Mild LV d	Normal	No	Survived
12	Jyothilakshmi	50	F	Chest Pain SOB	No	1	ST Elevation	Elevated	Ext AWMI	3	SK	100-500	Normal	Yes	Yes	Yes	Yes	Mild LV d	Normal	No	Survived
13	Prabhakaran	52	M	Pain Pulmonary Oedema	SHT Smoker Dyslipidemia	0.7	ST Elevation	Elevated	Ext AWMI	4	SK	>500	Mild Lv Dys	Yes	Yes	Yes	Yes	Mod LV d	Normal	Yes	Expired
14	Sreenivasan	39	M	Chest Pain	Smoker Family Hist	0.9	ST Elevation	Elevated	AWMI	3	SK	100-500	Normal	No	No	No	No	Mild LV d	Normal	No	Survived
15	Vinod Kumar	40	M	Chest Pain	No	0.8	Non Sp Changes	Normal	UA	1	Heparin ,PCI elective	<100	Normal	No	No	No	No	Normal	Normal	No	Survived

Master Chart

S.No	Name	Age	Sex	Symptoms	Risk Factors fo	S. Cr	ECG	Cardiac Enzymes	Diagnosis	TIMI Score	Treatment	NT ProBNP	LV Function	Recurrent Symptoms within 6 months							
												Pg /ml		Angina	Palpitations	Dyspnoea	Hospital Admissions inc	LV Function	Renal Function	Rec STEMI	Final outcome : Death / Survived
16	Karthikeyan	54	M	SOB Giddiness Pain	No	0.9	ST Elevation	Elevated	ASMI	3	SK	100-500	RMWA	Yes	No	No	No	Mild LV d	Normal	Yes	Expired
17	Ravi	46	M	Chest Pain SOB	DM SHT	1	ST Elevation	Elevated	Inferolateral MI	3	SK	<100	Normal	Yes	No	No	No	Normal	Normal	No	Survived
18	Mangammal	55	F	Chest Pain	DM	1	T inversion	Normal	UA	1	Heparin	>500	Mild Lv Dys	Yes	Yes	Yes	Yes	Mod LV d	Raised	Yes	Survived
19	Thirumoorthy	55	M	Chest Pain	No	1	T inversion	Normal	UA	1	Heparin	100-500	Normal	No	No	No	No	Normal	Normal	No	Survived
20	Deen Dayal	48	M	Chest Pain	Smoker	0.8	T inversion	Elevated	NSTEMI	2	Heparin	<100	Normal	Yes	No	No	No	Normal	Normal	Yes	Survived
21	Prabhu	50	M	Chest Pain SOB	Smoker Hypercholestrolemia	0.8	ST elevation	Elevated	IWMI	3	SK	100-500	Normal	Yes	No	No	No	Mild Lv D	Normal	No	Survived
22	Kalaiselvi	45	F	Chest Pain	DM	1	Non Sp Changes	Normal	UA	1	Heparin	100-500	Mild Lv Dys	Yes	Yes	Yes	Yes	Mild Lv D	Raised	No	Survived
23	Jayalakshmi	56	F	Chest Pain	DM SHT	1	ST elevation	Elevated	ASMI	3	SK	>500	Mild Lv Dys	Yes	No	Yes	No	Mod LV d	Normal	Yes	Expired
24	Seth Mohammed	55	M	SOB Giddiness Pain	Smoker	0.6	ST elevation	High Normal	Evolved IWMI	3	Heparin	>500	Normal	Yes	No	No	Yes	Mild LV d	Raised	Yes	Survived
25	Arumugam	55	M	Chest Pain SOB	Smoker SHT	0.7	ST elevation	Elevated	Ext AWMI	3	SK	>500	Moderate Lv Dys	Yes	Yes	Yes	No	Severe Lv	Normal	Yes	Expired
26	Elizabeth	42	F	Chest Pain	DM	1	T inversion	Normal	UA	1	Heparin	100-500	Moderate Lv Dys	Yes	No	No	Yes	Severe Lv	Raised	No	Survived
27	Chinnappaiyan	51	M	Chest Pain	No	0.6	T inversion	Normal	UA	1	Heparin	<100	Normal	No	No	No	No	Normal	Normal	No	Survived

Master Chart

S.No	Name	Age	Sex	Symptoms	Risk Factors fo	S. Cr	ECG	Cardiac Enzymes	Diagnosis	TIMI Score	Treatment	NT ProBNP	LV Functior	Recurrent Symptoms within 6 months							
												Pg /ml		Angina	Palpitations	Dyspnoea	Hospital Admissions inc	LV Function	Renal Function	Rec STEMI	Final outcome : Death / Survived
28	Karunakaran	56	M	Chest Pain	Recent CVA SHT Dyslipidemia	0.8	ST elevation	Normal	AWMI	3	Heparin ,PCI elective	100-500	Mild Lv Dys	Yes	No	No	No	Mod LV d	Normal	No	Survived
29	Ayesha Beegum	58	F	Chest Pain	No	1	ST elevation	Elevated	Evolved ASMI	3	Heparin	<100	Mild Lv Dys	No	No	No	No	Mild Lv D	Normal	No	Survived
30	Murugan	57	M	Chest Pain	No	1.1	ST elevation	Elevated	Inferolateral MI	3	SK	100-500	Mild Lv Dys	Yes	No	No	No	Mild LV d	Normal	No	Survived
31	Geetha	50	F	SOB Giddiness Pain	No	0.7	Non Sp Changes	Normal	UA	1	Heparin	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
32	Senthil Kumar	40	M	Giddiness	Smoker	0.7	ST elevation	Elevated	AWMI	2	SK	100-500	Normal	No	No	No	No	Normal	Normal	No	Survived
33	Anbazhagan	55	M	SOBChest Pain	SHT	0.5	Non Sp Changes	Normal	UA	1	Heparin	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
34	Hari Babu	44	M	Chest Pain	No	0.9	ST elevation	Elevated	ASMI 2VD	3	SK ,elective PCI	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
35	Joseph	53	M	Chest Pain	Smoker	0.8	ST, CHB	Elevated	IWMI	3	SK	>500	Normal	Yes	No	Yes	Yes	Mild LV d	Raised	No	Survived
36	Andal	44	F	Chest Pain	No	0.8	ST elevation	Elevated	Ext AWMI	3	SK	>500	Mild Lv Dys	Yes	Yes	Yes	Yes	Mod LV d	Normal	No	Survived
37	Karthikeyan	52	M	Chest Pain SOB	Smoker	0.9	ST elevation	High Normal	Evolved IWMI	2	Heparin	100-500	Moderate Lv Dys	Yes	Yes	Yes	Yes	Mod LV d	Normal	No	Survived
38	Balaji	38	M	Chest Pain	Smoker Family Hist	0.8	ST elevation	Elevated	AWMI	3	SK	>500	Mild Lv Dys	Yes	Yes	Yes	Yes	Mod LV d	Normal	No	Survived

Master Chart

S.No	Name	Age	Sex	Symptoms	Risk Factors fo	S. Cr	ECG	Cardiac Enzymes	Diagnosis	TIMI Score	Treatment	NT ProBNP	LV Functior	Recurrent Symptoms within 6 months							
												Pg /ml		Angina	Palpitations	Dyspnoea	Hospital Admissions inc	LV Function	Renal Function	Rec STEMI	Final outcome : Death / Survived
39	Alamelu	57	F	Chest Pain	No	0.9	Non Sp Changes	Elevated	NSTEMI	2	Heparin	100-500	Mild Lv Dys	Yes	No	Yes	Yes	Mod LV d	Normal	Yes	Expired
40	Elangovan	50	M	Chest Pain	No	0.9	Non Sp Changes	Normal	UA	1	Heparin	100-500	Mild Lv Dys	Yes	No	No	No	Mod LV d	Normal	No	Survived
41	Kumaravel	49	M	Chest Pain	SHT Smoker	0.7	ST elevation	Elevated	IWMI	3	SK	>500	Mild Lv Dys	Yes	No	No	No	Mod LV d	Normal	Yes	Expired
42	Santhi	55	F	Abdominal Pain	No	0.9	ST elevation	Elevated	IWMI	2	SK	>500	Mild Lv Dys	Yes	No	Yes	No	Mod LV d	Normal	No	Survived
43	Mohan	47	M	Chest pain	No	1	ST elev, QS	Elevated	Evolved ASMI	3	Heparin	100-500	Normal	No	No	Yes	Yes	Mild LV dy	Normal	No	Survived
44	Lalitha	50	F	Chest Pain	No	0.6	Non Sp Changes	Elevated	UA	2	Heparin	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
45	Dasprakash	49	M	Chest pain	Smoker SHT	0.8	ST elevation	Elevated	Evolved AWMI	3	Heparin	>500	Moderate Lv Dys	Yes	No	Yes	Yes	Severe Lv	Normal	Yes	Expired
46	Jayakumar	48	M	Chest Pain	Alcoholic SHT	1	ST elevation	Elevated	Inferolateral MI	3	SK	100-500	Mild Lv Dys	No	No	No	No	Normal	Normal	No	Survived
47	Sasikala	56	F	Chest Pain	No	0.5	ST dep, T inv	Normal	UA	1	Heparin	100-500	Mild Lv Dys	Yes	Yes	Yes	No	Mild Dysf	Normal	Yes	Survived
48	Manimegalai	55	F	Chest Pain	No	0.9	Non Sp Changes	Normal	UA	1	Heparin	<100	Normal	No	No	No	No	Normal	Normal	No	Survived
49	Raja	50	M	chest pain	No	1	ST elevation	Elevated	Evolved ASM	3	Heparin	100-500	Normal	No	No	Yes	Yes	Mod LV d	Normal	No	Survived
50	Palani	59	M	Chest Pain	Smoker	0.9	ST elevation	Normal	Evo AWMI	2	Heparin	100-500	Mild Lv Dys	No	No	Yes	Yes	Mild LV dy	Normal	No	Survived
51	Parthiban	55	M	Chest Pain	SHT DM	0.7	ST elevation	Elevated	IWMI	3	SK	100-500	Mild Lv Dys	No	Yes	Yes	Yes	Mild LV dy	Normal	No	Survived
52	Mani	42	M	Chest Pain	Smoker	0.8	ST elevation	Elevated	AWMI	3	SK	<100	Normal	No	NO	No	No	Normal	Normal	No	Survived

Patient consent form

Title

"ROLE OF NT PRO BNP LEVELS IN PREDICTING THE PROGNOSIS IN ACUTE CORONARY SYNDROMES"

Study Centre : Institute of Internal Medicine, Madras Medical College
Patient's name :
Patient's age :
Identification number :

I confirm that I have understood the purpose of the procedures of the above study. I have had the opportunity to ask questions and all my questions have been answered satisfactorily. ☐

I understand that my participation in the study is entirely voluntary and that I am free to withdraw from the study at any time without my legal rights being affected ☐

I understand that sponsors of the study, others working on sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and any future research that may be conducted in relation to it; even if I withdraw from the study I agree to this access. However I understand that my identity will not be revealed in any information released to third parties unless required by law. I agree not to restrict the use of any data or results arising from the study. ☐

I agree to take part in the above the study and to comply with the instructions given during the study and inform about any change in my health status to the investigator. ☐

I hereby give permission to undergo complete clinical examination and investigations as part of the study. ☐

Signature of the patient

Patient's name and address place date

Signature of the investigator

Investigator's name place date

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-600 003

Telephone 25363970
Fax 044 2535115
L.Dis:No.14597/ME5/Ethics Dean/MMC/2010 Dated : 12.05.2010

Title of the work : " Role of NT PRO BNP Levels in Predicting the Prognosis in Acute Coronary Syndromes "

Principal Investigator : Dr. Anoop C. Haridas.
Designation : PG in MD General Medicine
Department : Madras Medical College & GGH, Ch-3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 12th May 2010 at 2.p.m in Pharmacology Seminar Hall, Madras Medical College, Chennai -3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
4. You should not deviate form the area of the work for which you applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulation of the institution(s).
7. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC,CHENNAI

CHAIRMAN
IEC,MMC, CHENNAI

DEAN
MADRAS MEDICAL COLLEGE,
CHENNAI -3