A STUDY ON "PROGNOSTIC VALUE OF ADMISSION GLYCOSYLATED HEMOGLOBIN AND BLOOD GLUCOSE IN NONDIABETIC PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION"

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DECLARATION

I solemnly declare that the dissertation titled "***A STUDY ON PROGNOSTIC VALUE OF ADMISSION GLYCOSYLATED HEMOGLOBIN AND BLOOD GLUCOSE IN NONDIABETIC PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION***" was done by me from MARCH 2017 TO AUGUST 2017 under the guidance and supervision of **PROF. DR. K. NAMASIVAYAM MD.**

This dissertation is submitted to **THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY** towards the partial fulfilment of the requirement for the award of MD Degree in General Medicine (Branch I).

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LIST OF ABBREVIATIONS USED

ACS – ACUTE CORONARYSYNDROME

ADA –AMERICAN DIABETES ASSOCIATION

AGE - ADVANCED GLYCOSYLATION ENDPRODUCTS

ARIC - ATHEROSCLEROSIS RISK IN COMMUNITIES

CAC - CORONARY ARTERY CALCIFICATION

CAD – CORONARY ARTERY DISEASE

CI - CONFIDENCE INTERVAL

DCCT - DIABETES CONTROL AND COMPLICATIONS TRIAL

DIGAMI - DIABETES MELLITUS INSULIN GLUCOSE INFUSION IN ACUTE MYOCARDIAL INFARCTION.

DM – DIABETES MELLITUS

ECG-ELECTROCARDIOGRAM

FBS – FASTING BLOOD SUGAR

FPG - FASTING PLASMA GLUCOSE

HBA1C - GLYCATED EMOGLOBIN

HDL - HIGH DENSITY LIPOPROTEIN

HERS – HEART AND ESTROGEN/PROGESTIN REPLACEMENT STUDY

HI-5 - THE HYPERGLYCEMIA: INTENSIVE INSULIN INFUSION IN INFARCTION (HI-5) STUDY

HPLC – HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

LBBB - LEFT BUNDLE BRANCH BLOCK

LDL - LOW DENSITY LIPOPROTEIN

LV - LEFT VENTRICULAR

MBG - MEASURED BLOOD GLUCOSE

MRFIT - MULTIPLE RISK FACTOR INTERVENTION TRIAL

NHANES - NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

NICE – SUGAR TRIAL - THE NORMOGLYCEMIA IN INTENSIVE CARE EVALUATION AND SURVIVING USING GLUCOSE ALGORITHM REGULATION

NSTE - NON ST ELEVATION

OGTT- ORAL GLUCOSE TOLERANCE TEST

PCI - PERCUTANEOUS CORONARY INTERVENTION

PPG- POSTPRANDIAL GLUCOSE

RCA-RIGHT CORONARY ARTERY

RV – RIGHT VENTRICLE

STEMI – ST- ELEVATION MYOCARDIAL INFARCTION

TAMI - THROMBOLYSIS AND ANGIOPLASTY IN MYOCARDIAL INFARCTION TRIAL

UA – UNSTABLE ANGINA

UKPDS- UK PROSPECTIVE DIABETES STUDY

CONTENTS

INTRODUCTION

It is a well-known fact that Diabetes and cardiovascular diseases go hand in hand together. Many patients presenting with cardiovascular diseases are either suffering from diabetes or are in prediabetic state.[1]

Many studies pointed out the fact that even milder abnormalities of blood glucose level (even below the diagnostic threshold of diabetes mellitus) are associated with increased cardiovascular risk[2-3].

It is well accepted that hyperglycemia is commonly present in patients admitted with acute STEMI. It is associated with increased risk of death or adverse cardiovascular events in patients both with and without previous history of diabetes mellitus[4].

Patients belonging to the prediabetes group often have other cardiovascular risk factors, including hypertension and dyslipidemia, and are at increased risk for cardiovascular disease[142]

The treatment goals for people with prediabetes are the same as for the general population. But since they are at risk for cardiovascular diseases, an increased vigilance is warranted to identify and treat these and other cardiovascular risk factors (e.g., smoking).

In patients with no prior history of diabetes who present with a macrovascular complication that is ; Myocardial infarction , hyperglycaemia might be due to a previously undiagnosed diabetes or due to stress hyperglycaemia or due to a

prediabetic state. This can lead to a poor outcome in patients in the form of shock , failure or arrhymias[143]

So both stress hyperglycaemia in non-diabetic patients and high random blood sugar in diabetic patients are having adverse prognostic effects in patients with ACS. However the effect of recently elevated blood sugar as measured by HbA1c has still not been consistently reported as a bad prognostic indicator.

Though many studies have been done[**143**] on this interesting subject, the results are not significantly conclusive on either side.

Available data suggests that hyperglycaemia on admission is an indicator of short term mortality in patients admitted with acute STEMI but its efficacy in predicting the long term mortality is still unclear.[**144**]

It has been noted that among patients with high risk non ST elevation acute coronary syndrome [NSTE- ACS] also that a substantial proportion of patients admitted with high risk NSTE ACS had previously undiagnosed DM (12.2%) or prediabetes (10.8%) as defined by HbA1c or FBS after admission.[145]

In nondiabetic patients, HbA1c could be utilised for risk stratification of CAD and its severity; independent of traditional cardiovascular risk factors.[146]

These factors aroused curiosity which led into this study which probes into the prognostic significance of glycated haemoglobin and admission RBS in non-diabetics admitted with acute STEMI.

Moreover this study enables risk stratification. Early identification of high risk groups enables initiation of specific intervention strategies and it may help us to improve the prognosis in these patients. It also helps in identifying a previously undiagnosed group of diabetics.

This is of importance because there is a global increase in the number of patients suffering from cardiovascular disease with underlying insulin resistance, prediabetes and overt diabetes mellitus which go unrecognized.

AIMS & OBJECTIVES OF THE STUDY

To determine the association between both acute hyperglycemia or stress hyperglycemia if present , that is denoted by the admission blood glucose at the time of presentation and chronic hyperglycemia which is denoted by HbA1c and short term clinical outcome in non-diabetic patients with STEMI

Short term clinical outcome means :

- Presence of Arrhythmias / Cardiogenic shock/ LV failure during hospital admission.
- Ejection fraction in Echocardiogram whether
  - Normal – 50-70%
  - Mild LV dysfunction– 40 -49%
  - Moderate LV dysfunction– 30-39%
  - Severe LV dysfunction- <30%

HbA1c is divided into three ranges

- Normal – <5.6%,
- Impaired or prediabetes – 5.7 -6.4%
- Diabetes - >/= 6.5%

Main aim is to find out the association this HbA1c ranges with adverse cardiac events as mentioned above.

Along with that any association between admission RBS (either above or below 200) with any adverse cardiac events as mentioned above .

Other Objectives:

- Age & gender distribution of various HbA1c ranges & blood sugar
- Any relationship between tobacco use , alcoholism & sedentary lifestyle with various ranges of HbA1c.
- Lipid profile normal or high and its relation with HbA1c .
- Occurrence of anterior wall (AW) or inferior wall (IW) & ranges of HbA1c and blood glucose.
- Correlation between admission blood glucose with various ranges of HbA1c

REVIEW OF LITERATURE

DIAGNOSIS OF DIABETES[5]

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a75-g oral glucose tolerance test (OGTT) or A1C criteria

- FPG >/= 126mg/dl (7.0 mmol/L)*

. (Fasting is defined as no caloric intake for at least 8 h.)

OR

- 2-h PG>/=200 mg/dL (11.1 mmol/L) during an OGTT*.

The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

- A1C>/=6.5% (48 mmol /mol)*.

The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

OR

A random plasma glucose >/=200 mg/dL (11.1 mmol/L).

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis*.(In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.)

DIAGNOSIS OF ST- ELEVATION MYOCARDIAL INFARCTION[147]

ECG criteria

The ECG is paramount to the diagnosis of STEMI and should be obtained within 10 minutes of presentation.

If the diagnosis of STEMI is in doubt, serial ECGs may help to elucidate the diagnosis.

Classic findings include :

- Peaked upright T waves is the first ECG manifestation of myocardial injury.
- ST elevations correlate with the territory of injured myocardium .

Diagnostic ECG criteria for STEMI

When ST elevations reach threshold values in two or more anatomically contiguous leads, a diagnosis of STEMI can be made.

- In men >40 years of age, threshold value for abnormal ST-segment elevation at

  the J point is ≥2 mm in leads V2 and V3 and >1 mm in all other leads. men ,<40 years of age, threshold value for abnormal ST-segment elevation at the J point in leads V2 and V3 is >2.5 mm.
- In women, the threshold value of abnormal is ST-segment elevation at the J point is >1.5 mm in leads V2 and V3 and >1 mm in all other leads.

- In right-sided leads (V3R and V4R), the threshold for abnormal ST elevation at the J point is 0.5 mm, except in males ,30 years in whom it is 1 mm.
- Right sided leads should be obtained in all patients with evidence of inferior wall ischemia to rule out right ventricular (RV) ischemia. RV infarction can occur with proximal right coronary artery (RCA) lesions.
- In posterior leads (V7, V8, and V9), the threshold for abnormal ST elevation at the J point is 0.5 mm.
- All patients with ST-segment depression in leads V1 to V3, inferior wall STelevation, or tall R waves in V1 to V3 should have posterior leads placed in order to diagnosis a posterior wall MI. Posterior STEMIs are usually due to occlusion of the circumflex artery and are often misdiagnosed as UA/NSTEMI.

R waves in V1 or V2 represent Q waves of the posterior territory.

- Circumflex artery ischaemia may be electrocardiographically silent.
- The presence of reciprocal ST-segment depression to the opposite of the infarct territory increases the specificity for acute MI.
- New LBBB. Suggests a large anterior wall MI with a worse prognosis

Criteria for ST-segment Elevation for Prior LBBB or RV-paced Rhythm [148]

ECG changes

- ST-segment elevation greater than 1 mm in the presence of a positive QRS complex (concordant with the QRS)

- ST-segment elevation greater than 5 mm in the presence of a negative QRS complex (disconcordant with the QRS)
- ST-segment depression greater than 1 mm in V1–V3 ECG leads,

Q waves.

Development of new pathologic Q waves is considered diagnostic for transmural MI but may occur in patients with prolonged ischemia or poor collateral supply.

The presence of Q waves only is not an indication for acute reperfusion; It is very helpful to have an old ECG to compare to inorder to determine chronicity.

Diagnostic criteria include:

- In leads V2 and V3, a pathologic Q wave is ≥0.02 s, or a QS complex in V2 or V3. An isolated Q wave in lead V1 or lead III is normal.
- In leads other than V1 through V3, presence of a Q wave ≥0.03 s and ≥0.1 mV deep or a QS complex in any two contiguous leads suggest prior MI.
- R wave ≥0.04 s in V1 and V2 and R/S ratio ≥1 with a positive T wave suggest prior posterior MI (in the absence of RVH or right bundle branch block RBBB)

Cardiac Etiologies of ST-elevation

- Prior MI with aneurysm formation
- Aortic dissection with coronary involvement
- Pericarditis

- Myocarditis
- LV hypertrophy or aortic stenosis (with strain)
- Hypertrophic cardiomyopathy
- Coronary vasospasm (Cocaine, Prinzmetal angina)
- Early repolarization (normal variant)
- Brugada syndrome

Other Etiologies of ST elevation

- Pulmonary embolism
- Hyperkalemia

HbA1c (GLYCATED HEMOGLOBIN)[6]

Glycated hemoglobin are HbA1c reflects average glycemia over approximately 3 months and has strong predictive value for diabetes complications [7,8]. Thus, A1C testing should be performed routinely in all patients with diabetes at initial assessment and as part of continuing care.

Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained.

The frequency of A1C testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment. The use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters between patients and providers.

Patients with type 2 diabetes with stable glycemia well within target may do well with A1C testing only twice per year. Unstable or intensively managed patients (e.g., pregnant women with type 1 diabetes) may require testing more frequently than every 3 months[9].

Discovery of HbA1c

Samuel Rahbar (May 12, 1929 - November 10, 2012) was an Iranian scientist who discovered the linkage between diabetes and HbA1c, a form of hemoglobin used primarily to identify plasma glucose concentration over time[10].

Later **Antony Cerami** found that HbA1c levels reflected urine glucose levels in humans , offering additional evidence that the HbA1c may be a helpful tool for people with diabetes[11].

Over the next few decades, the Diabetes Control and Complications Trial (DCCT)[12] and UK Prospective Diabetes Study (UKPDS)[13] showed that blood glucose control, as assessed using HbA1c, prevented the complications of diabetes.

Without HbA1c, this would have been nearly impossible to demonstrate.

Milestones in history of HbA1c[14]

- 1966 –Holmquist and Schroeder identified five subtypes of haemoglobin A including HbA1c.
- 1968- Rahbar recognises HbA1c is elevated in Diabetes.
- 1975- Koenig and Cerami suggested that HbA1c is related to metabolic control.
- 1993- DCCT identified HbA1c as a potent marker in patients with type1 DM.
- 1998-UKPDS established HbA1c as a valuable marker in patients with type 2 DM.
- 2010-ADA recommends HbA1c for diagnosing diabetes and prediabetes

As the author Dr Rahbar quoted

" The first patient who presented the unusual fast-moving hemoglobin was identified for further study. A 67-year-old female named Zobaydeh Khatoon was traced to Vaziri Hospital. Upon review of her hospital chart labelled

"DIABETIC," we found out that she was suffering from a severe uncontrolled diabetes mellitus. At first this was considered to be a coincidence. A person with hereditary abnormal haemoglobin could also suffer from diabetes. But when the same observation was made in several other blood samples in the following weeks, and all the patients were found to be diabetic, the possibility of a real relationship could no longer be ignored "[16].

Structure of HbA1c

Glycated hemoglobins are minor components of human haemoglobin **(**Hb). These are formed non enzymatically by condensation of glucose or other reducing sugars with chains of hemoglobin A. The subfraction HbA1c, a nonenzymatic glycation at the amino-terminal valines of the β-chain.

When blood glucose enters the erythrocytes it glycosylates the ε-amino group of lysine residues and the amino terminals of hemoglobin. The fraction of haemoglobin glycosylated, normally about 5%, is proportionate to blood glucose concentration. Since the half-life of an erythrocyte is typically 60 days, the level of glycosylated hemoglobin (HbA1c) reflects the mean blood glucose concentration over the preceding 6–8 weeks. Measurement of HbA1c therefore provides valuable information for management of diabetes mellitus. **[141]**

SIGNIFICANCE OF HBA1C IN HEALTH AND DISEASE

The global prevalence of diabetes is predicted to rise from 135 million in 1995 to 300 million by 2025. In the US alone, 70 million diabetic patients with their associated complications cost $3 billion a year.

Large prospective studies such as the DCCT, UKPDS, EDIC, and EPIC-NORFOLK multicentre clinical studies were designed to investigate the long-term risks of complications of diabetes and their correlation with HbA1c levels. Nearly 10,000 publications on HbA1c have appeared in the literature in the past 30 years.

What we learned from these studies is:

- Diabetes mellitus increases the risk of cardiovascular diseases.
- HbA1c concentrations predict cardiovascular risk in people with diabetes[12-13].
- HbA1c concentrations predict mortality continuously across the whole population distribution in people without diabetes and at concentrations below those used to diagnose diabetes.
- Adequate blood pressure control and lipid control can reduce the HbA1c concentration
- HbA1c may provide a practical screening tool for diabetes or impaired glucose Tolerance[16].

The EURODIAB Prospective Complication Study reported an association of HbA1c with inflammatory markers of endothelial function in diabetes[18]

- HbA1c is strongly and consistently associated with all inflammatory markers tested including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF).
- Measures of inflammation were associated with diabetes, duration glycemic control, the advanced glycation end products pentosidine, body mass index (BMI), triglycerides, HDL (inversely), and systolic/blood pressure. These factors were directly associated with HbA1c.
- Measures of inflammation were strongly associated with markers of endothelial dysfunction including soluble vascular cell adhesion molecule-1 and soluble E-selectin.
- A close link between poor glycemic control, inflammation, and vascular endothelial dysfunction has also been demonstrated in type 2 diabetes.
- HbA1c may reflect the biological activities of hyperglycemia, Amadori products,and AGEs, all of which induce inflammation.
- AGE pentosidine was strongly associated with the general score of inflammatory markers independent of HbA1c.

LIMITATIONS OF HBA1C[6]

The A1C test is an indirect measure of average glycemia and, as such is subject to limitations.

- Conditions that affect red blood cell turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's MBG levels.
- For patients in whom A1C/estimated average glucose (eAG) and measured blood glucose appear discrepant, clinicians should consider the possibilities of altered red blood cell turnover
- A1C does not provide a measure of glycemic variability or hypoglycemia.
- For patients prone to glycemic variability, especially patients with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from MBG and A1C.
- Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol (1,5-AG) are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C .

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HbA1c and microvascular complications.

The Diabetes Control and Complications Trial (DCCT), a prospective randomized controlled trial of intensive versus standard glycemic control in patients with type 1 diabetes, showed definitively that better glycemic control is associated with significantly decreased rates of development and progression of microvascular (retinopathy and diabetic kidney disease) and neuropathic complications[19]

Methods of estimation of HbA1c

- HPLC method – affected by hemoglobinopathies.
- Immunoturbidimetric assays – affected by hemoglobinopathies.
- Colorimetric enzymatic method – new standard in the HbA1c estimation.

DIABETES AND CARDIOVASCULAR MORTALITY

MYOCARDIAL INFARCTION BEFORE DIAGNOSING DIABETES

Sometimes prediabetic state or overt diabetes may first be diagnosed in patients presenting with acute STEMI. A second mechanism is that the stress of MI unmasks or worsens the tendency towards hyperglycemia.

The frequency with which this may happen was demonstrated in a prospective study of 181 patients with an acute MI and no previous diagnosis of diabetes in whom the fasting blood glucose and two-hour blood glucose after a standard load were serially measured[21].

Impaired glucose tolerance was present in 35 percent at hospital discharge and 40 percent three months later. The respective values for previously undiagnosed diabetes were 31 and 25 percent using oral glucose tolerance test criteria and 10 and 13 percent when only the fasting blood glucose was used.

The Hemoglobin A1C concentration on admission was an independent predictor for abnormal glucose tolerance at three months, indicating that the metabolic abnormality preceded the infarction and that the hyperglycemia was not entirely attributed to stress.

These findings strongly suggest that the fasting plasma glucose concentration and Hemoglobin A1c should be measured during hospitalization in nondiabetic patients with an acute MI and that elevated values be repeated after discharge to identify those at increased risk.

Whether an oral glucose test should be part of the standard evaluation remains uncertain.

An increase in cardiovascular risk before the diagnosis of diabetes was also noted in a report from the Nurses' Health Study in which approximately 5 percent of over 115,000 initially non diabetic women developed type 2 diabetes at 20 year follow-up [22]. These women had a multivariate adjusted relative risk for MI before the diagnosis of diabetes of 3.17 (95 percent CI 2.61 to 3.85).

There appears to be a graded rise in cardiovascular risk with increasing degrees of glucose intolerance below the definition of overt diabetes [23-29].

In a meta-analysis of 20 studies that included almost 100,000 people, there was a curvilinear increase in the risk for a cardiovascular event with increasing glucose intolerance.[23]

When compared to patients with a fasting glucose of 75 mg/dL (4.2 mmol/L), the risk of an event was higher in patients with a fasting glucose of 110 mg/dL (6.1 mmol/L) or a two-hour glucose of 140 mg/dL (7.8 mmol/) (relative risk 1.33 and 1.58, respectively) [23].

Among survivors in the Framingham Heart Study, the HbA1c concentration was significantly related to prevalent cardiovascular disease in women but not men[25].

For each 1 percent increase in HbA1c (eg, from 5 to 6 percent), the relative odds of cardiovascular disease was 1.39 (95% CI 1.06-1.83)[25].

In a review of over 10,000 men and women, a 1 percentage point increase in HbA1c was associated with a relative risk for all-cause mortality of 1.24 (95% CI 1.14-1.34) in men and 1.28 (95% CI 1.06-1.32) in women [28].

The relative risk was not changed (1.26) when patients with known diabetes or cardiovascular disease or an HbA1c ≥7 percent were excluded.

The increase in risk was also independent of other major cardiovascular risk factors. The rates of cardiovascular disease and mortality were lowest at HbA1c values less than 5 percent, a finding that has also been noted in another study [29].

It has been suggested that the two-hour glucose has greater predictive value than the fasting glucose [21, 26].Similar findings have been noted in other studies in which higher glucose levels two hours after an oral glucose tolerance test were also more closely associated than fasting glucose levels with cardiovascular risk factors[30,31].

There is a graded rise in cardiovascular risk with increasing hyperglycemia in patients with overt diabetes. The magnitude of this effect was illustrated in a meta-analysis of 13 prospective cohort studies (10 in type 2 diabetes, including the UKPDS)[13]. For every one-percentage point increase in glycosylated hemoglobin (HbA1c), the relative risk for any cardiovascular event was 1.18 (95% CI 1.10-1.26).

There may also be an association between HbA1c and the extent of coronary disease. This was suggested in a review of 315 patients with diabetes who underwent coronary angiography because of chest pain [32].

The mean HbA1c increased progressively in patients with 0, 1, 2, or 3-4 vessel disease (6.7, 8.0, 8.8, and 10.4, respectively, a trend that was highly significant). There was no significant difference among the four groups in the duration of diabetes or the prevalence of smoking, hypertension, or dyslipidemia.

As noted above, there is also a graded rise in cardiovascular risk with increasing degrees of glucose intolerance below the definition of overt diabetes [23-27].

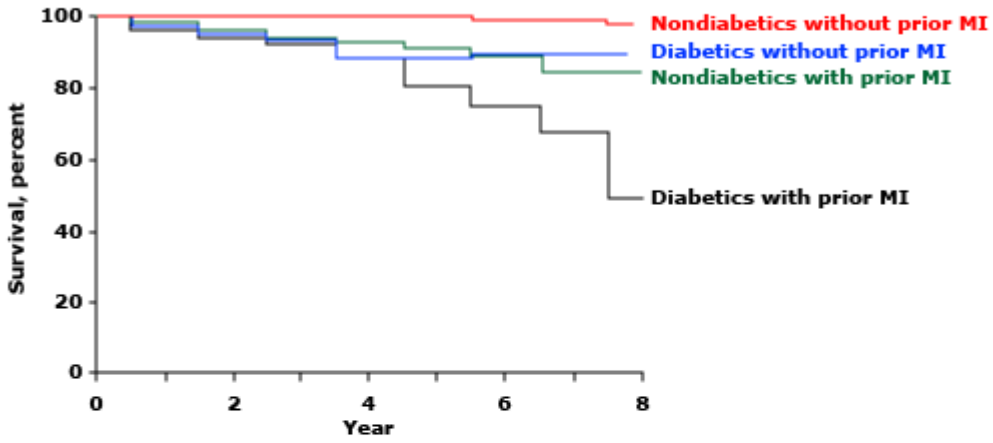
Effect of glycemic control — Strict glycemic control is recommended in both type 1 and type 2 diabetes because of demonstrated benefits in terms of microvascular disease. Protection against macrovascular disease is established only in type 1 diabetes.

Protection against macrovascular disease with strict glycemic control has not been established in type 2 diabetes.

Strict glycemic control appears to be important in patients with an acute MI. Patients with diabetes mellitus are at increased risk for myocardial infarction (MI) and diabetes is considered a coronary risk equivalent by the National Cholesterol Education Program [33].

Type 2 diabetic patients without a prior MI have the same risk of developing an MI as nondiabetic patients who have already had an MI [34].

DIABETES INCREASES CORONARY HEART DISEASE MORTALITY WITH OR WITHOUT A PRIOR MYOCARDIAL INFARCTION (MI) [34]



In a seven-year follow-up of 1059 subjects with type 2 diabetes and 1378 patients without diabetes, persons with diabetes, with or without a prior myocardial infarction (MI), had a greater mortality from coronary disease compared to those without diabetes (42 versus 16 percent for those with a prior MI and 15 versus 2 percent for those without a prior MI). The rate of coronary death and fatal and nonfatal MI in persons with diabetes without a prior MI was the same as in those without diabetes with a prior MI, providing part of the rationale for considering type 2 diabetes a coronary heart disease equivalent.

Data from: Haffner SM, Lehto S, Ronnemaa T, et al. N Engl J Med 1998; 339:229.

Graphic 80251 Version 6.0

In the acute setting, the evidence of benefit from strict glycemic control with insulin therapy in patients with acute MI is limited. The evidence in other groups of patient is inconsistent.

HYPERGLYCEMIA AND OUTCOME AFTER ACUTE MI

The association between hyperglycemia and outcome after acute MI has been evaluated in two settings: the short-term predictive value of the admission serum glucose in patients with and without diabetes and the long-term increase in risk in patients with diabetes.

Predictive value of admission glucose

There is a positive association between the serum glucose at the time of MI and mortality in patients with and without diabetes [35-40].

The prognostic significance of what has been presumed to represent stress hyperglycemia was addressed in an analysis of 15 trials that reported in-hospital mortality after an MI in relation to admission serum glucose concentrations [35].

The analysis comes to the following conclusions of these trials in which the admission glucose were random and may have represented fasting or postprandial states:

In patients without diabetes, those with glucose concentrations between 110 and 143 mg/dL (6.1 to 8 mmol/L) had a 3.9-fold higher risk of death compared to patients with lower glucose concentrations. Glucose values between 144 and 180 mg/dL (8 to 10 mmol/L) were associated with a three-fold higher risk of heart failure or cardiogenic shock.

Diabetic patients with glucose concentrations ≥180 to 196 mg/dL (10 to 11 mmol/L) also had an increased risk of death compared with normoglycemic diabetic patients (relative risk 1.7), but this relative risk was lower than in non-diabetics.

In addition to the admission value, a graded relationship has been found between the fasting glucose obtained within 24 hours of admission and 30-day mortality [41,42].

The possible mechanisms by which stress hyperglycemia is associated with worse outcomes were evaluated in a review of 460 consecutive patients with STEMI who were treated with primary percutaneous coronary intervention (PCI); 322 (70 percent) had a serum glucose ≥140 mg/dL (7.8 mmol/L) on admission, but only 14 percent had a history of diabetes[43].

The patients with hyperglycemia were significantly less likely to have TIMI grade 3 (normal) flow before PCI compared to those with normoglycemia (12 versus 28 percent, adjusted odds ratio 2.6 for the absence of reperfusion). The decreased TIMI flow rate might be due to endothelial damage or hypercoagulable state due to underlying hyperglycemia.

The impairment in coronary flow might reflect a prothrombotic state or endothelial dysfunction associated with hyperglycemia, more severe disease leading to a greater stress response, or hyperglycemia might be a marker for some other determinant of outcome.

Despite the observation of worse outcomes in patients with higher glucose concentrations on admission and within 24 hours, the available studies do not rule out

the possibility that high blood glucose in this setting is a marker for a sicker patient, as opposed to being causative for worse outcomes.

A review of 4224 patients in trials of fibrinolysis or primary PCI in patients with STEMI found a U-shaped relationship between the serum glucose (mostly admission values) and the 30-day rate of death or recurrent MI [44].

The following findings were noted in patients with hypoglycemia, defined as blood glucose values of <81 mg/dL (4.5 mmol/L), euglycemia, defined as blood glucose values of 81 to 99 mg/dL (4.5 to 5.5 mmol/L), and severe hyperglycemia, defined as blood glucose values >199 mg/dL (11.0 mmol/L).

- The 30-day mortality rate in the three groups was 4.6, 1.0, and 4.7 percent, respectively
- The 30-day rate of recurrent MI or death in the three groups was 10.5, 4.2, and 7.2 percent, respectively

. The risk was also significantly increased in patients with blood glucose values between 150 and 199 mg/dL (8.3 and 11.0 mmol/L, odds ratio 2.93). The U-shaped relationship was seen in both diabetic and nondiabetic patients.

Similar findings (higher mortality with both hyperglycemia on admission and hypoglycemia during hospitalization) were noted at two years in a review of 713 consecutive patients with diabetes and non-ST elevation acute coronary syndrome [45]. Both persistent hypoglycemia and hyperglycemia were found to be better predictors of mortality than admission glucose in a separate study [46].

It is not yet clear from these data whether treatment-induced hypoglycemia is driving increased risk. One analysis of hyperglycemia in patients with acute MI found that spontaneous hypoglycemia was associated with increased hospital mortality, but not hypoglycemia associated with insulin therapy [47].

Other medical factors, such as malnutrition, hepatic or renal disease or sepsis may be playing a role in these observational data.

WORST OUTCOME IN DIABETIC PATIENTS

The long-term outcome after an acute MI is worse in diabetic patients than nondiabetic patients with both a non-ST elevation MI (NSTEMI) and an ST elevation MI (STEMI).

The adverse effect is manifested by increases in mortality and nonfatal cardiovascular end points (such as reinfarction or heart failure) [34,48].

Diabetic patients tend be older and to have a greater prevalence of comorbidities compared to patients without diabetes [48]. However, the increase in risk persists after adjustment for these differences. The data supporting these conclusions is presented separately.

UNDIAGNOSED DIABETES IN PATIENTS WITH STEMI

The frequency with which patients with an acute MI have undiagnosed diabetes was addressed in a prospective study in which glucose metabolism (via fasting blood glucose and oral glucose tolerance test) was evaluated in 181 consecutive patients with an acute MI and no prior history of diabetes [49].

The criteria for diagnosing diabetes were a fasting plasma glucose ≥126 mg/dL (6.1 mmol/L) and/or two-hour postload plasma glucose above 200 mg/dL (11.1 mmol/L). The respective values for impaired glucose tolerance were a fasting plasma glucose between 110 and 125 mg/dL (6.1 to 6.9 mmol/L) and a two hour postload plasma glucose between 140 and 200 mg/dL (7.8 to 11.1 mmol/L).

The following findings were noted:

- Prediabetes was present in 35 percent at hospital discharge and 40 percent three months later. The respective values for previously undiagnosed diabetes were 31 and 25 percent at these time periods. However, the incidence of previously undiagnosed diabetes was much lower (10 and 13 percent) when only the fasting blood glucose was used, as suggested by the American Diabetes Association. Whether the same patients had abnormal glucose metabolism at discharge and three months is not clear.
- Independent predictors for abnormal glucose tolerance at three months were the Hemoglobin A1C concentration on admission and the fasting blood glucose on day four. The former observation, which indicates that the metabolic abnormality preceded the infarction, and the persistence of abnormal glucose tolerance at three months suggest that the hyperglycemia during hospitalization cannot be simply explained as stress hyperglycemia in some patients.

The presence of elevated levels of Hb A1c found in most of these patients makes stress hyperglycemia a less likely diagnosis.

At the least, these findings strongly suggest that the fasting plasma glucose concentration and hemoglobin A1c should be measured during hospitalization in nondiabetic patients with an acute MI and that elevated values be repeated after discharge to identify those at increased risk.

VALUE OF GLYCEMIC CONTROL

Evidence from which recommendations for glycemic control in patients with acute myocardial infarction (MI) comes from studies in three populations: critically ill patients (a minority of whom have an acute MI) in intensive care units; patients admitted with acute MI; patients admitted to general medical wards.

Critically ill patients

Randomized trials have assessed the efficacy of strict glycemic control (target blood glucose 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) compared to standard care (180-200 mg/dl; 10.0-11.1 mmol/L) in patients admitted to an intensive care unit (ICU). .

Although initial single-center studies suggested a strong benefit, mainly in post-surgical patients, these data have not been replicated by others. The largest of the randomized trials in ICU patients, the NICE-SUGAR trial, found an increase in the rate of death at 90 days with intensive glucose control (81-108 mg/dl; 4.5-6.0 mmol/L) as compared to those whose blood glucose was maintained between 144-

180 mg/dl (8.0 to 10.0 mmol/L) [47]. In addition, the data from these studies may or may not apply to patients with myocardial infarction.

Patients with acute MI who might be labelled critically ill include those with hemodynamic or electrical instability, acute heart failure, or co-existent serious acute illnesses such as acute exacerbation of obstructive lung disease requiring respiratory support or acute blood loss requiring transfusion.

STUDIES OF PATIENTS WITH ACUTE MI

A number of trials have attempted to address the value of intensive insulin therapy and/or glycemic control specifically in patients with an acute MI. None was as large and well designed as the aforementioned ICU trials and each has important flaws. Furthermore, none of the trials achieved the level of glucose control that would have been considered intensive in the ICU trials.

DIGAMI trial

In the DIGAMI trial, 620 diabetic patients with an acute MI were randomly assigned to an insulin-glucose infusion for 24 hours followed by subcutaneous insulin four times daily for ≥3 months or standard treatment with insulin therapy only if clinically indicated [50]. The target blood glucose level for patients assigned to the insulin-glucose infusion was 126 to 196 mg/dL (7 to 10.9 mmol/liter).

With respect to glycemic control, the following findings were noted:

- At randomization, the mean blood glucose was about 280 mg/dL (15.6 mmol/L). The blood glucose was significantly lower with intensive insulin at 24 hours (173 versus 211 mg/dL [9.6 versus 11.7 mmol/L]) and hospital discharge (148 versus 162 mg/dL [8.2 versus 9.0 mmol/L])

- At randomization, the HbA1c was 8.1 percent. The reduction in HbA1c was significantly greater with intensive insulin therapy at three months (1.1 versus 0.4 percent) and one year (0.9 versus 0.4 percent).

Mortality was significantly lower in the group assigned to more aggressive insulin therapy at one year (19 versus 26 percent) and at 3.4 years (33 versus 44 percent) [36,50].

The greatest reduction in mortality was seen in low-risk patients who had not been receiving insulin prior to the infarction.

Since DIGAMI also included an outpatient insulin therapy component, the isolated effect of glycemic control in-hospital could therefore not be easily assessed.

DIGAMI-2 trial

The value of insulin therapy was further addressed in the DIGAMI-2 trial.In this patients with type 2 diabetes and acute MI were randomly assigned to one of three glucose management strategies:

- Group 1- inpatient insulin infusion/outpatient intensive subcutaneous insulin therapy;

- Group 2- inpatient insulin infusion/outpatient standard treatment;
- Group 3- inpatient/outpatient routine glucose management according to local practice[51] .

Although it was anticipated that mortality rates would be lowest in group 1, they were similar in all three groups. However, there were a number of problems with this study that interfere with interpretation of the results:

- Glycemic control, which was expected to be the best in group 1, was also similar in the three groups.
- The overall event rate was lower than expected in all groups (perhaps due to implementation of other secondary prevention strategies), which may have attenuated any statistical differences between groups.
- The trial was stopped earlier than planned due to a failure to recruit an adequate number of patients; since less than 50 percent of the required patients were recruited, the power to detect a difference among the treatment groups was substantially reduced.

HI-5 trial

The possible benefit of more intensive glucose control in patients with an acute MI with either a history of diabetes or an admission blood glucose ≥140 mg/dL (7.8 mmol/L) was evaluated in the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study[52].

In this trial, 240 such patients were randomly assigned to conventional therapy or to an insulin/dextrose infusion to maintain the blood glucose between 72

and 180 mg/dL (4 and 10 mmol/L) for at least 24 hours. After 24 hours, the patients were managed with standard care by their own physicians with a recommend HbA1c of less than 7 percent.

There was no difference in the primary end point of mortality in-hospital or at three or six months. However, HI-5 was seriously flawed by the small number of patients, lack of blinding, maintenance of glycemic control for only 24 hours, and failure to attain a significant difference in mean 24-hour blood glucose between the intensive therapy and control groups (149 versus 162 mg/dL [8.3 versus 9.0 mmol/L]).

Subset analysis found that patients who had a mean blood glucose ≤144 mg/dL (8.0 mmol/L) during the first 24 hours had large reductions in mortality in-hospital (0 versus 7 percent) and at three and six months (2 versus 11 percent). The possible mortality benefit in this subgroup analysis is consistent with the above surgical ICU trial but needs to be confirmed in patients with an acute MI.

OBSERVATIONAL EVIDENCE

Additional evidence supporting a benefit from glycemic control comes from an observational study of 7820 hyperglycemic patients (admission blood glucose ≥140 mg/dL 7.8 mmol/L) hospitalized with acute myocardial infarction [53].

After multivariable adjustment, lower mean postadmission glucose levels were associated with better all-cause in-hospital mortality. There was no difference in mortality rates between insulin-treated and non-insulin treated patients irrespective of mean postadmission glucose level.

DIABETES AND CARDIOVASCULAR MORTALITY

The importance of the association between diabetes and CHD can be illustrated by findings from the Framingham Heart Study and the Multiple Risk Factor Intervention Trial (MRFIT).

In the Framingham Heart Study, the presence of diabetes doubled the age-adjusted risk for cardiovascular disease in men and tripled it in women[20]

Diabetes remained a major independent cardiovascular risk factor even when adjusting for advancing age, hypertension, smoking, hypercholesterolemia, and left ventricular hypertrophy.

The National Cholesterol Education Program report from the United States and guidelines from Europe consider type 2 diabetes to be a CHD equivalent, thereby elevating it to the highest risk category [54, 55]. This classification was based in part upon the observation that patients with type 2 diabetes without a prior MI (mean age 58) were at the same risk for MI (20 and 19 percent, respectively) and coronary mortality (15 versus 16 percent) as patients without diabetes who had a prior MI (mean age 56)[34].

Similar observations were noted in MRFIT[56]. Among 5163 men who reported taking medications for diabetes (mostly type 2), 9.7 percent died from cardiovascular disease over a 12 year period; the comparable cardiovascular death rate in the 342,815 men not taking medications for diabetes was 2.6 percent. This difference was independent of age, ethnic group, cholesterol level, systolic blood pressure, and

tobacco use. However, among diabetic men, the increase in cardiovascular risk rose more steeply than in nondiabetics with the addition of each of these risk factors.

The Emerging Risk Factors Collaboration group performed a meta-analysis of 102 studies that included 530,083 patients with no history of MI, angina, or stroke at the initial study visit [57].

After adjusting for other risk factors, patients with diabetes had an overall risk of CHD twice that of patients without diabetes (HR 2.0, 95%CI 1.8-2.2), with a similarly higher risk of cardiac death (HR 2.3, 95% CI 2.1-2.6) and non-fatal MI (HR 1.8, 95% CI 1.6-2.0).

Although most patients in the above studies had type 2 diabetes, the relative risk for cardiovascular disease compared to nondiabetics of similar age is even greater in those with type 1 diabetes [58,59].

This was illustrated in a review of 292 patients with type 1 diabetes [58]. After age 30, CHD mortality increased rapidly, particularly in patients with renal disease. The cumulative CHD mortality was 35 percent by age 55, compared to 8 and 4 percent in nondiabetic men and women, respectively, in the Framingham Heart Study. Similar relationships were noted for nonfatal MI and angina.

The age at which an individual transitions to a high risk for cardiovascular disease category is another way to demonstrate the powerful risk imparted by the presence of diabetes mellitus. This relationship was evaluated in a retrospective, population-based cohort of Canadians using a large provincial health claims database[60].

The transition to a high-risk category (10 year event rate risk of greater than 20 percent) occurred at a younger age for men and women with type 2 diabetes than for nondiabetic patients (mean difference 15 years). Using a broad definition of cardiovascular disease, the age of onset of high-risk was 41 and 48 years for men and women with diabetes, respectively.

Extent of coronary disease

Most [61-68] but not all [69] studies have found that the extent of the disease in the coronary arteries is greater among diabetic patients. As an example, the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial provided coronary angiographic data obtained during an acute myocardial infarction [65].

TAMI included 148 diabetic and 923 nondiabetic patients in whom cardiac catheterization was performed at 90 minutes and seven to ten days after thrombolytic therapy [65]. Compared to the nondiabetics, the diabetic patients had a significantly higher incidence of multivessel disease (66 versus 46 percent) and a greater number of diseased vessels.

Multivessel CHD is also common in asymptomatic patients with type 2 diabetes, particularly those with two or more coronary risk factors other than diabetes [70]. There also may be an association between the extent of coronary disease and the degree of glycemic control.

Temporal trends

The incidence of cardiovascular disease has declined substantially in adults with and without diabetes over the last 50 years. The magnitude of this effect and the persistence of greater risk in diabetic patients were illustrated in a report from the Framingham Heart Study of participants seen between 1950 and 1966 and between 1977 and 1995 [71].

The age and sex-adjusted rate of cardiovascular events (myocardial infarction, CHD death, or stroke) decline from 287 to 147 per 10,000 person years in participants with diabetes (a 49 percent decline) and from 85 to 54 cardiovascular events in those without diabetes (a 35 percent decline). Diabetes was still associated with a two-fold increase in risk (multivariable-adjusted hazard ratio 1.96, 95% CI 1.44-2.66). The reductions in risk were similar in men and women.

However, different findings were noted in a report from the National Health and Nutrition Examination Survey (NHANES), which evaluated the time periods of 1971 to 1975 and 1982 to 1984 [72].

There was smaller decline in cardiovascular mortality over time in diabetic men (13 versus 36 percent in nondiabetic men), while the risk by 23 percent in diabetic women (compared to a 27 percent decline in risk in nondiabetic women).

A possible explanation for the difference in findings is that the Framingham Heart Study compared outcomes over a much longer period, beginning in the 1950s and ending in the 1990s. In addition, the diagnosis of diabetes was confirmed in the Framingham report compared to a patient-reported clinician diagnosis in NHANES.

Myocardial infarction

Diabetes is associated with an increased risk of myocardial infarction (MI). In the worldwide INTERHEART study of patients from 52 countries, diabetes accounted for 10 percent of the population-attributable risk of a first MI [73].

The importance of diabetes as a risk factor for MI was demonstrated in a study that compared the seven year incidence of MI in 1373 nondiabetics and 1059 patients with type 2 diabetes in Finland.

Type 2 diabetics without a prior infarction were at the same risk for MI (20 and 19 percent, respectively) and coronary mortality (15 versus 16 percent) as nondiabetics with a prior MI. The risk of infarction was greatest in diabetics with a prior MI and lowest in nondiabetics without a prior MI (45 and 4 percent, respectively). These findings were independent of other risk factors such as total cholesterol, hypertension, and smoking.

Similar findings have been noted in other studies [74,75], including a much larger series of 13,790 patients in a population-based cohort from the Atherosclerosis Risk In Communities (ARIC) study in the United States [74].

At nine years of follow-up, there were 634 cardiac deaths or nonfatal MIs (4.6 percent). Event rates varied among patients with or without diabetes and with or without a history of MI as follows:

- No diabetes and no MI – 3.9 percent
- Diabetes and no MI – 10.8 percent
- No diabetes and prior MI – 18.9 percent

- Diabetes and prior MI – 32.2 percent

These relationships may vary with gender. In another report from Finland, prior MI was a greater risk factor for CHD mortality than diabetes without a prior MI in men (hazard ratio 1.78), but diabetes without a prior MI was a greater risk factor in women (hazard ratio 1.75) [76].

In addition to the increase in mortality, diabetic patients are also more likely to experience a complication associated with an MI, including postinfarction angina and heart failure.

Possible contributory factors are that diabetic patients are more likely to have multivessel disease [70] and fewer coronary collateral vessels [77].

Asymptomatic CHD in Diabetic patients

In addition to the increase in cardiovascular events, patients with type 2 diabetes also have a high rate of asymptomatic coronary disease as determined by the presence of coronary artery calcification (CAC) on electron beam CT scanning and by inducible silent ischemia on stress imaging [77].

In addition to an increased rate of structural disease, patients with type 2 diabetes also have reduced myocardial flow reserve, a reflection of coronary vasodilator capacity [78,79]. This abnormality is inversely related to glycemic control [78]..

Silent ischemia and infarction

Some diabetic patients have a blunted appreciation of ischemic pain, which may result in atypical anginal symptoms, silent ischemia, or even silent infarction.

Silent ischemia in diabetes is thought to be caused at least in part by autonomic denervation of the heart [80-83]..

In support of this hypothesis is the observation that the uptake of metaiodobenzylguanidine (MIBG), a norepinephrine analog, is reduced in diabetic patients with silent ischemia [82]. This finding is suggestive of sympathetic denervation, which has also been seen with positron emission tomography [79,84].

Furthermore, regional heterogeneity in sympathetic innervation can predispose to myocardial electrical instability that may lead to life-threatening arrhythmias [84].

Another component of decreased perception of myocardial ischemia is that diabetic patients have a prolongation of the anginal perceptual threshold during exercise testing, ie, the time from onset of ischemic changes on the electrocardiogram to the onset of angina [85] The longer the threshold, the greater the exercise capacity and the more severe the ischemia.

Diabetic patients also have an increased frequency of silent ST segment depression and coronary perfusion abnormalities during stress testing. Although the supportive data are presented separately, the potential magnitude of silent CHD can be illustrated by the results of the following study.

The rate of silent ischemia was evaluated in an observational study of 1899 asymptomatic patients with type 2 diabetes age ≤60 years (mean age 53) [20]

The patients underwent stress testing with dipyridamole myocardial contrast echocardiography (MCE) and follow-up coronary angiography if the MCE were abnormal. The stress test was abnormal in 60 percent, 65 percent of whom had significant coronary disease on angiography.

This report also evaluated the relationship between the number of risk factors and the presence of silent ischemia. Sixty percent of patients had ≥2 CHD risk factors (dyslipidemia, hypertension, smoking, a positive family history of premature CHD, or the presence of microalbuminuria).

The two risk groups (≥2 versus 0 or 1 risk factors) had equivalent rates of an abnormal stress test (60 percent) and of significant coronary disease on angiography (65 percent). However, the patients with ≥2 risk factors had more severe coronary disease with significantly higher rates of three-vessel disease (33 versus 8 percent), diffuse disease (55 versus 18 percent), and vessel occlusion (31 versus 4 percent); they also had a lower rate of single vessel disease (29 versus 54 percent).

Diabetes is associated with an increased frequency of unrecognized MI, as well as silent ischemia, at least in men [80,86,87.] In a report from the Framingham Heart Study, for example, the fraction of infarctions that were detected on routine electrocardiograms but unrecognized clinically was more than twice that in nondiabetic men (39 versus 18 percent)[86].

In comparison, diabetic women were less likely to have silent infarction, a finding also noted in a report from the HERS trial [88].

THE IMPACT OF GLYCEMIC CONTROL ON CARDIOVASCULAR RISK.

Patients with diabetes have a greater burden of atherogenic risk factors than nondiabetics, including hypertension, obesity, lipid abnormalities, and elevated plasma fibrinogen [89,90]. Many of these risk factors are also present in the prediabetic state prior to conversion to overt type 2 diabetes [91].

Patients with the constellation of abdominal obesity, hypertension, diabetes, and dyslipidemia are considered to have the metabolic syndrome (also called the insulin resistance syndrome or syndrome X), which is associated with increased cardiovascular risk.

The CHD risk in patients with diabetes varies widely with the intensity of these risk factors. The evidence is strongest for hypertension, elevated low density lipoprotein, smoking, the metabolic syndrome, hyperglycemia, and microalbuminuria. The following discussion is limited to the unique aspects of coronary risk factors in patients with diabetes.

Hypertension

The general role of hypertension as a risk factor for cardiovascular disease and its importance in patients with diabetes are discussed in detail elsewhere.

Summarized briefly, hypertension is present at diagnosis in many patients with type 2 diabetes, but generally does not occur until after the onset of renal disease

in patients with type 1 diabetes [92]. The most compelling evidence for the importance of hypertension in diabetes comes from the United Kingdom Prospective Diabetes Study (UKPDS) [93].

The following findings were noted at nine year follow-up:

- Each 10 mmHg reduction in updated mean systolic pressure was associated with a 12 percent risk reduction in any complication related to diabetes (including cardiovascular disease); the lowest risk occurred at a systolic pressure below 120 mmHg.
- A similar relationship was noted with fatal or nonfatal MI as the incidence fell from 33.1 per 1000 patient years at an updated mean systolic pressure ≥160 mmHg to 18.4 per 1000 patient years at an updated mean systolic pressure below 120 mmHg.

Based upon these and other observations, antihypertensive therapy is warranted in all patients with diabetes [94]. The optimal goal blood pressure and choice of antihypertensive drugs in such patients are discussed in detail separately.

Dyslipidemia

There are a number of differences in the lipid profile between diabetics and nondiabetics that may contribute to the increase in atherosclerosis [95,96]. The serum lipid abnormalities differ somewhat in patients with type 1 and type 2 diabetes [96].

●The lipid pattern in patients with type 1 diabetes is largely related to glycemic control. The Diabetes Control and Complications Trial (DCCT) found that patients

with type 1 diabetes (mean HbA1c 8.8 percent) had similar serum lipid values as nondiabetic individuals in the Lipid Research Clinics (LRC) prevalence study except for young women, who had somewhat higher serum total cholesterol and lower high-density lipoprotein (HDL) cholesterol concentrations [97]. In comparison, worse glycemic control is characteristically associated with hypertriglyceridemia and low HDL-cholesterol concentrations [95,98].

●Among patients with type 2 diabetes, insulin resistance, relative insulin deficiency, and obesity are associated with hypertriglyceridemia, low serum HDL cholesterol concentrations, and occasionally high serum LDL cholesterol and lipoprotein(a) values [95,96]. This pattern of lipid abnormalities can be detected before the onset of overt hyperglycemia and is thought to be due in part to hyperinsulinemia and/or insulin resistance [99].

For any serum lipoprotein concentration, diabetic patients have more coronary disease than nondiabetic patients. This increase in risk may be due in part to qualitative differences in the lipoprotein fractions or to the presence of other pro atherosclerotic metabolic changes. Among these changes are high serum concentrations of small dense LDL particles, enhanced oxidative modification of LDL, and elevations in serum lipoprotein(a) [96].

The association of elevated LDL cholesterol with cardiovascular risk in many epidemiologic studies has been reinforced by randomized clinical trials showing that statin therapy improves outcomes in diabetics, including those without clinical evidence of CHD and those with values below 116 mg/dL [100,101].

Non-HDL cholesterol (total cholesterol minus HDL cholesterol, which includes all cholesterol present in lipoprotein particles considered to be atherogenic; LDL, lipoprotein(a), intermediate-density lipoprotein, and very-low-density lipoprotein), appears to be a particularly strong predictor of CHD in both men and women with diabetes [102].

Smoking

As in nondiabetics, smoking in patients with diabetes increases cardiovascular morbidity and mortality, raises serum LDL cholesterol, and can impair glycemic control [103]. This increase in risk is gradually reduced with smoking cessation.

Sex

The increase in CHD risk in patients with diabetes is greater in women than in men [24,104]. The magnitude of this effect was illustrated in a meta-analysis of 37 studies of almost 450,000 patients with type 2 diabetes: the summary relative risk for fatal CHD in patients with diabetes was 3.5 in women and 2.1 in men. The excess risk is at least in part due to diabetes being more commonly accompanied by other cardiovascular risk factors in women.

Microalbuminuria

Microalbuminuria is the earliest clinical manifestation of diabetic nephropathy and is associated with an increased risk of cardiovascular disease in both diabetic and nondiabetic patients.

The magnitude of the predictive value of microalbuminuria was illustrated in a review of over 9000 participants in the HOPE (Heart Outcomes Prevention Evaluation) trial [105]. The presence of microalbuminuria was associated with an increased relative risk of the primary aggregate end point (myocardial infarction, stroke, or cardiovascular death) in those with and without diabetes (1.97 and 1.61, respectively) [105]. The risk of an adverse cardiovascular event increased progressively with increased absolute levels of microalbuminuria.

A similar impact of microalbuminuria was found among participants in the LIFE trial [106]. The urine albumin-to-creatinine ratio was measured in 7143 nondiabetic subjects (median value 1.16 mg/mmol [10.2 mg/g]) and 1063 subjects with diabetes (median value 3.05 mg/mmol [26.9 mg/g]). For every 10-fold increase in the albumin-to-creatinine ratio, the risk of cardiovascular death, MI or stroke increased by 39 percent and the risk of cardiovascular death by 47 percent among diabetics. The respective increases in risk for nondiabetics were 57 and 98 percent.

Annual cardiovascular death rates also increase with worsening diabetic nephropathy. This was illustrated in an analysis of 5097 subjects in the United Kingdom Prospective Diabetes Study [107]. Annual cardiovascular death rates for no nephropathy, microalbuminuria, macroalbuminuria, and elevated plasma creatinine concentration or renal replacement therapy were 0.7, 2.0, 3.5, and 12.1 percent, respectively [107].

Exercise

Regular exercise is associated with a lower risk of both CHD and cardiac death for both primary and secondary prevention. However, most of the evidence comes from long-term observational studies in which those who exercise regularly have significantly less CHD. Unfortunately, this type of evidence is subject to bias, since the decision to exercise is only one of the many choices made in adopting a healthy life style (eg, cessation of smoking). Thus, attribution of exercise as a prevention of CHD is confounded by other favorable reductions in risk characteristics.

Similar observational studies have been performed in patients with diabetes:

●In a prospective cohort study of 2896 diabetic adults, those who walked for at least two hours per week had lower cardiovascular mortality rates when compared with inactive individuals (HR 0.66; 95 percent CI 0.45 to 0.96; 1.4 versus 2.1 percent per year, respectively) [108].

Lack of moderate alcohol intake

The consumption of a moderate amount of alcohol may have health benefits, particularly with regard to coronary disease.

The effect of light to moderate alcohol consumption in diabetic patients was evaluated in the Physicians' Health Study of 87,938 subjects who were free of myocardial infarction, cancer, or liver disease at baseline; 2790 had diabetes [109]. After a 5.5 year follow-up, diabetic patients who consumed alcohol on a weekly or

daily basis had a significantly lower risk of death from CHD than those who rarely or never consumed alcohol (adjusted relative risk 0.67 and 0.42). The risk reduction was similar to that seen in nondiabetics.

Similar benefits of moderate alcohol consumption were noted in diabetic women in the Nurses' Health Study, which evaluated 5103 women with a diagnosis of diabetes at ≥30 years of age who were free of CHD, stroke, or cancer at baseline [110]. Compared to diabetic women reporting no alcohol intake, the adjusted relative risk for nonfatal or fatal coronary heart disease for diabetic women reporting a daily intake of 0.1 to 4.9 grams of alcohol (<0.5 drinks) or ≥5 grams (≥0.5 drinks) was 0.72 and 0.45, respectively.

Hyperhomocysteinemia

An elevated serum concentration of homocysteine is a known risk factor for atherosclerosis and is associated with an increased risk of myocardial infarction and death. The risk appears to be greater in patients with diabetes as illustrated in a review of 2484 men and women aged 50 to 75 years [111]. After adjusting for major cardiovascular risk factors, the odds ratio for five year mortality for hyperhomocysteinemia was 2.51 for diabetics compared to 1.34 for nondiabetics. For each 5 μmol/L increment in serum homocysteine concentrations, the odds ratio for diabetics and nondiabetics was 1.60 and 1.17, respectively.

Mechanisms of increased risk

A variety of mechanisms may contribute to the increase in CHD risk in patients with diabetes in addition to the effects on blood pressure and lipid metabolism. A complete review is beyond the scope of this discussion [112].

Endothelial dysfunction

Endothelial dysfunction has been documented in diabetic patients who have normal coronary arteries and no other risk factors for coronary disease [112-120].The degree of impairment is related to the duration of diabetes, but a defect can occur acutely in patients who develop postprandial hyperglycemia despite having a normal fasting plasma glucose [121].

The presence of insulin resistance alone may be associated with coronary endothelial dysfunction [122,123]. In a study of 50 insulin-resistant and 22 insulin-sensitive Mexican-American subjects without glucose intolerance, CHD, hypertension, cigarette use, or dyslipidemia, endothelium-dependent coronary vasomotor function was abnormal (as assessed by myocardial blood flow response to a cold pressor test) in the insulin-resistant compared to the insulin-sensitive group [122].

Platelet activation

Diabetes has a number of effects on platelet function that may predispose to coronary thrombosis. These include increased primary and secondary platelet aggregation [124-126], increased platelet activation [127] with release of the contents of alpha-granules, including thromboglobulin and platelet factor 4 [128], enhanced binding

of fibrinogen to the glycoprotein IIb/IIIa complex, located on the platelet surface, an effect which may be due in part to an increase in the number of glycoprotein IIb/IIIa receptors on the platelet surface.

The altered platelet function in diabetics may be mediated in part by elevated blood glucose. In one study of 42 patients with stable coronary artery disease, the fasting blood glucose was an independent predictor of platelet-dependent thrombosis [129]. This relationship was continuous and graded and was even evident in a range of glucose levels considered to be normal. Plasma insulin levels were not associated with platelet-mediated thrombosis.

Coagulation abnormalities

In addition to platelet activation, diabetes also predisposes individuals to abnormalities in various pathways involved in coagulation, hemostasis, and fibrinolysis [130]. The following are among the abnormalities that have been described.

●Diabetes is associated with an increase in plasma fibrinogen, which is a cardiovascular risk factor [131-133]. Elevated plasma fibrinogen is also associated with other cardiovascular risk factors including older age, increased body mass, smoking, total cholesterol, and triglycerides [133].

●Fibrinolytic activity is reduced [134,135]. Although circulating tissue-type plasminogen activator (tPA) levels are normal or increased in the plasma of diabetics, tPA activity is decreased because of increased plasma concentrations of and enhanced binding to its inhibitor, plasminogen activator inhibitor (PAI-1) [136,137]. Elevations in PAI-1, presumably due to increased synthesis, are also found in atheromata obtained from

type 2 diabetic patients undergoing atherectomy, probably reflecting increased levels in the vessel wall [138].

Plaque composition

Plaque composition may differ in diabetics and affect coronary risk. In a histologic study of atherectomy specimens from patients with and without diabetes, coronary tissue from diabetics contained a greater amount of lipid-rich atheroma, more macrophage infiltration, both of which are associated with a greater risk for plaque rupture, and a higher incidence of thrombosis [139]. However, plaques from younger patients with type 1 diabetes at autopsy were characterized by dense fibrous tissue and few foam cells, which should enhance plaque stability [140].

METHODOLOGY

1) This study is a single center prospective observational study of patients in our hospital admitted in intensive care medicine unit with acute ST elevation MI.
2) The study was done in the intensive care unit of Thanjavur Medical college which is manned by the residents and professors of Department of Internal Medicine.
3) A total of 127 patients were admitted in the ICU with STEMI during the study period, out of which only 50 patients met the inclusion criteria.
4) Fifty non-diabetic patients admitted in the intensive care medicine unit with acute ST elevation MI diagnosed with 12 lead electrocardiogram were selected for the study.
5) The period of study was for 6 months. (March 2017 to August 2017)
6) Informed Consent from the patient was taken as per the approval of the ethical committee.
7) All patients in the study underwent the following based on a proforma:
    a. Detailed history of
        i. Chest pain- whether present or absent. Duration was not noted.
        ii. Palpitation- whether present or absent
        iii. Giddiness – whether present or absent
        iv. Breathlessness – whether present or absent.

v. Past history of hypertension/Dyslipidemia/Coronary artery disease is considered present or absent based on patient history.
vi. History of sedentary life style
vii. History of Smoking
viii. History of Alcoholism
ix. Family history of Coronary artery disease

b. Detailed examination was done which included:
i. General examination including JVP
ii. Vitals including Blood Pressure, Pulse Rate
iii. Examination of Cardiovascular system
iv. Examination of Respiratory system
v. Examination of other systems

c. Investigations done included:
i. 12 lead Electrocardiogram
ii. Complete blood count
iii. Admission Random Blood sugar
iv. HbA1c
v. Lipid Profile
vi. Trans thoracic Echocardiogram

8) Inclusion Criteria
a. Patient with acute STEMI diagnosed with 12 lead ECG treated with fibrinolysis.
b. Both males and females

9) Exclusion Criteria

a. Patients with Diabetes mellitus

b. Patients with Hb less than 7 mg/dl

c. Patients with Haemoglobinopathy or Hypothyroidism

d. Patient's refusal to participate.

- All the patients were admitted in the intensive care unit of our hospital. They were included in the study based on the inclusion and exclusion criteria.
- Acute STEMI was diagnosed based on the ECG criteria as mentioned before.
- Random blood sugar sample (venous blood) at the time of admission was collected.
- HbA1c was done for the patient using standard laboratory techniques approved by DCCT.
- All of them were treated with fibrinolysis using Injection Streptokinase as per standard protocol.
- They were followed up during the whole days of hospital stay and were watched for any complications.
- Complications were identified early and adequate treatment was given as per standard guidelines.
- They were observed till discharge from the hospital or death .
- Post fibrinolysis Echocardiogram was done to assess the ejection fraction.

- Cardiogenic shock is defined as systemic hypo perfusion sustained systolic arterial hypotension <90 mmHg .
- LV failure- As per the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines patients having cardinal clinical symptoms of dyspnea and fatigue and signs of HF, namely edema and rales were considered to have heart failure.
- Ejection fraction

- Ejection fraction

- Normal – 50-70%
- Mild LV dysfunction– 40 -49%
- Moderate LV dysfunction– 30-39%
- Severe LV dysfunction- <30%

- Lipid profile

  S.cholesterol > 200mg/dl – high

  S.cholesterol < 200mg/dl - low

DATA MANAGEMENT AND ANALYSIS

Data was entered into Microsoft Excel. Master chart was prepared.Statistical Analysis was done using software GraphPad Prism version 5 and SPSS v24. Numerical values were reported using mean and standard deviation or median. Categorical values are reported using number and percentages. Correlation was obtained using Pearson correlation coefficient. Probability value (p) value less than 0.05 was considered a statistically significant.

RESULTS

1.AGE AND GENDER DISTRIBUTION IN THE STUDY POPULATION

Table 1: Age and gender distribution in the study population

S. No	Age (in years)	Overall		Male gender		Female gender	
		N	%	n	%	n	%
1	≤40	7	14	7	100	0	0
2	40 – 60	27	54	21	77.8	6	22.2
3	≥60	16	32	13	81.3	3	18.8

Data are expressed as percentages with absolute numbers.

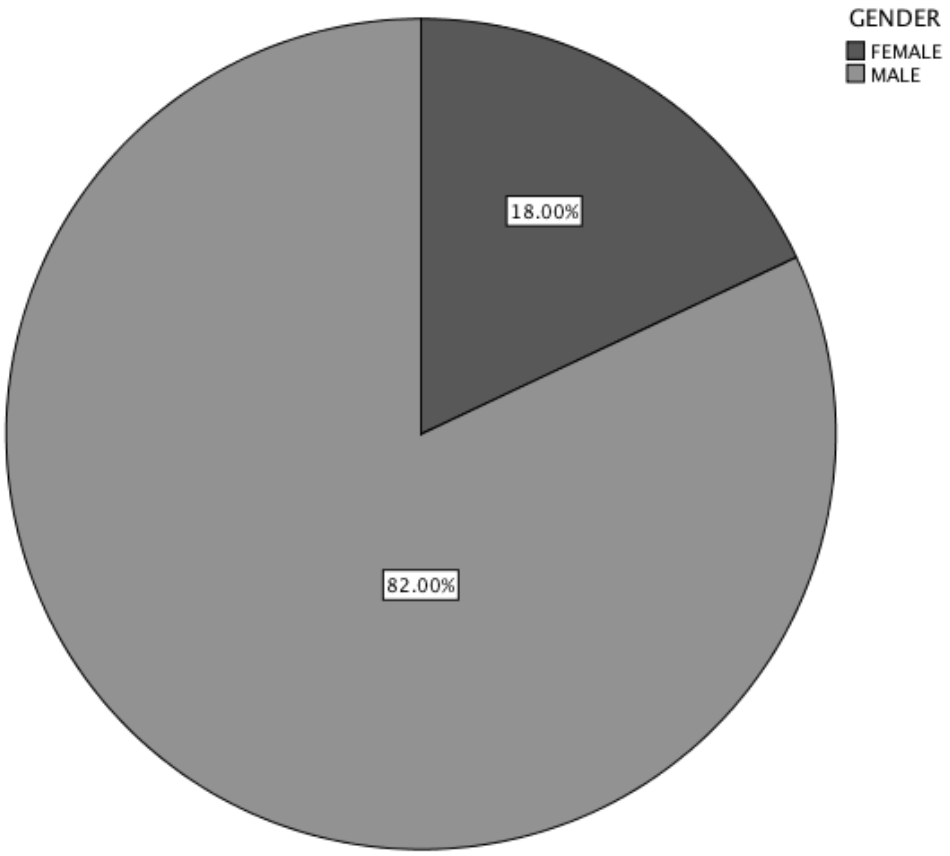


Figure 1: Pie chart representation of age of the study population

Table 2: Comparison of age & gender in different groups of the study population

S. No	Parameter	Normal group			Prediabetes group			Diabetic group		
		n	Mean	SD	n	Mean	SD	N	Mean	SD
1	Overall	16	54.19	15.76	14	57.71	6.35	20	55.6	8.04
2	Male gender	13	51.6	16.5	12	58.5	6.38	16	54.81	8.79
3	Female gender	3	65	0	2	52.5	3.53	4	58.75	2.5

Data are expressed as mean with standard deviation. Two-way ANOVA with multiple comparison of the row means was used to test the statistical differences between the means of the group and no statistical difference was seen between the groups.

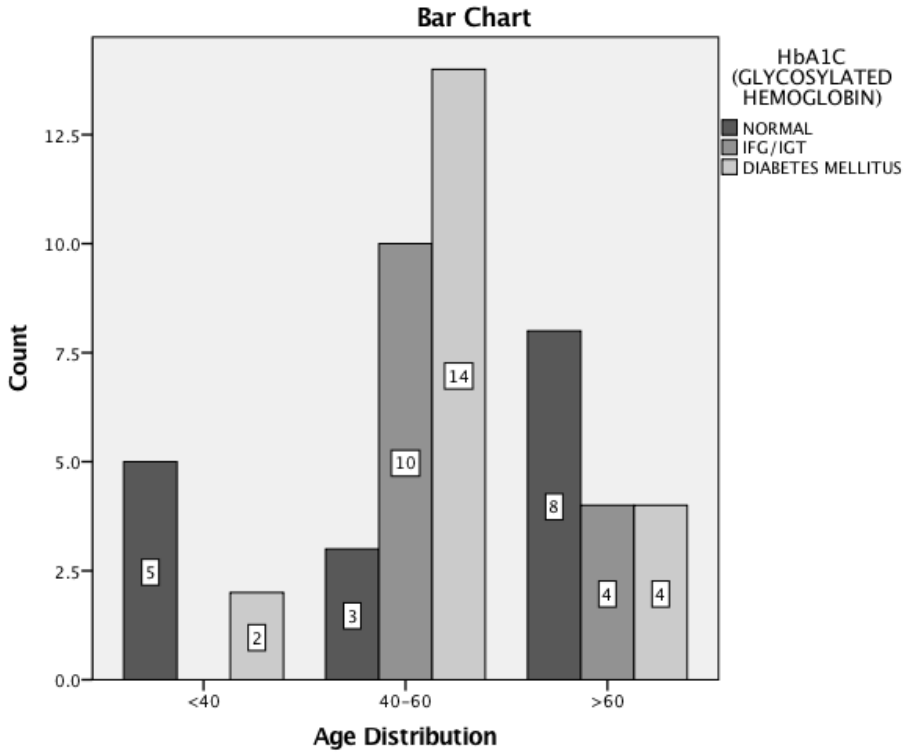


Figure 2: Bar chart of Age distribution in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

Table 3: Comparison of gender in different groups of the study population

Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value (odds ratio)
		N	%	n	%	n	%	
Gender	Male	13	31.7	12	29.3	16	39	0.9 (NS)
	Female	3	33.3	2	22.2	4	44.4	

Data are expressed as percentages with absolute numbers.

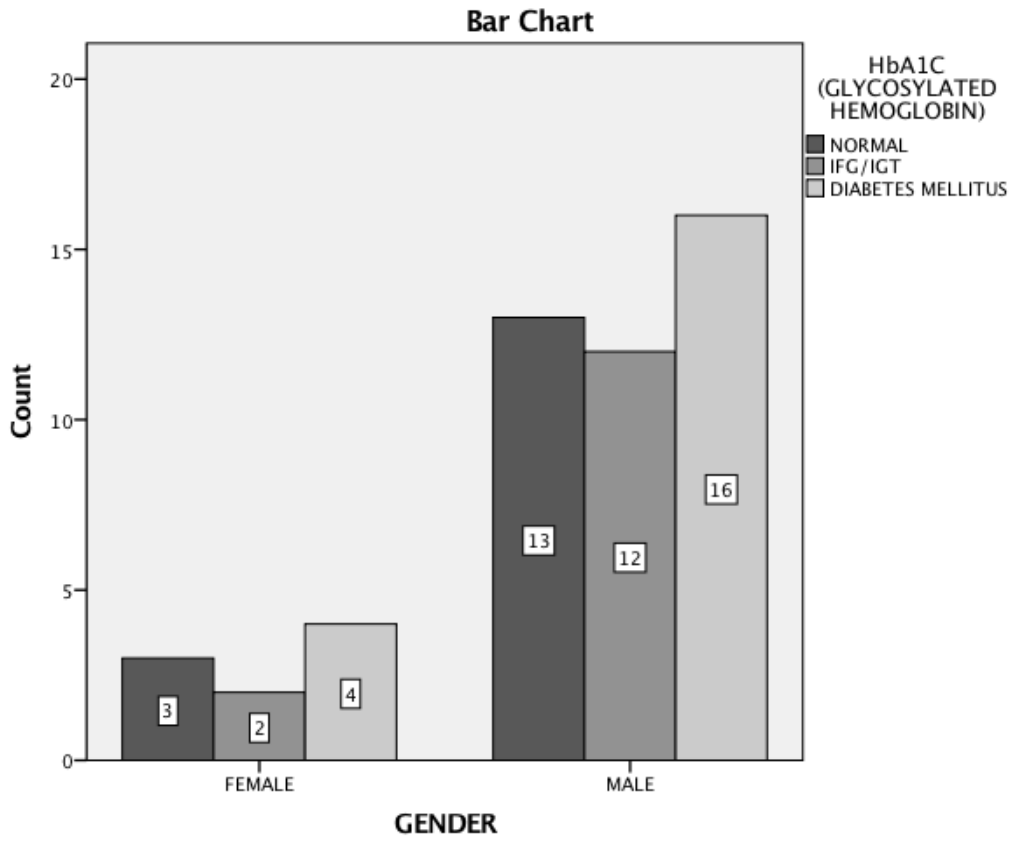


Figure 3: Bar chart of Gender in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

2. CLINICAL PRESENTATION

Table 4.Distribution of history of chest pain and other cardiac symptoms between the groups in the study population

S. No	Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value (odds ratio)
			n	%	n	%	n	%	
1	History of chest pain	Present	16	32	14	28	20	40	NA
		Absent	0	0	0	0	0	0	
2	History of other cardiac symptoms	Present	8	29.6	6	22.2	13	48.1	0.41 (NS)
		Absent	8	34.8	8	34.8	7	30.4	

Data are expressed as percentages with absolute numbers.

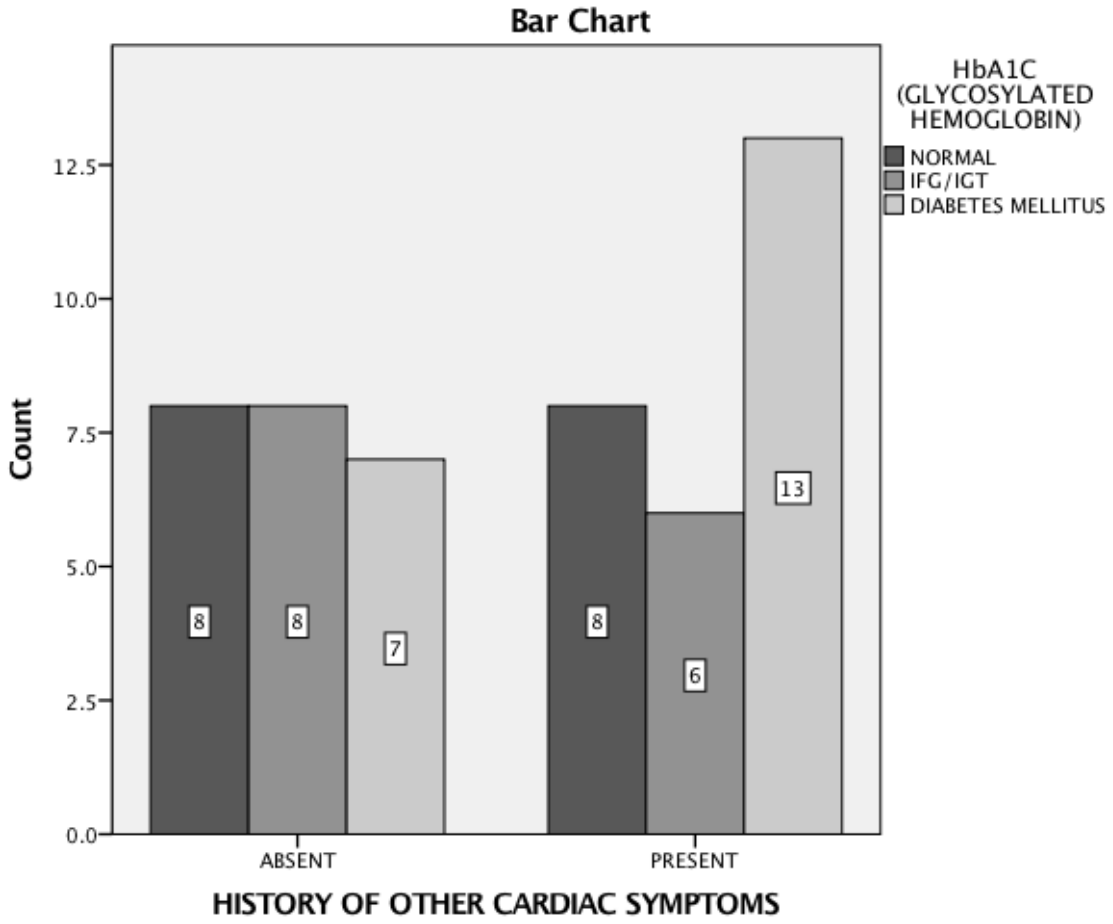


Figure 4: Bar chart of history of other cardiac symptoms in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

3. RISK FACTORS

Table 5. Distribution of other risk factor histories between groups in the study population.

S. No	Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value (odds ratio)
			N	%	n	%	n	%	
1)	Family history of CAD	Present	1	100	0	0	0	0	0.33 (NS)
		Absent	15	30.6	14	28.6	20	40.8	
2)	Known case of CAD	Present	1	100	0	0	0	0	0.33 (NS)
		Absent	15	30.6	14	28.6	20	40.8	
3)	Known case of systemic hypertension	Present	3	30	3	30	4	40	0.95 (NS)
		Absent	13	32.5	11	27.5	16	40	
4)	History of sedentary lifestyle	Present	2	33.3	2	33.3	2	33.3	0.92 (NS)
		Absent	14	31.8	12	27.3	18	40.9	
5)	History of cigarette smoking	Present	8	34.8	5	21.7	10	43.5	0.66 (NS)
		Absent	8	29.6	9	33.3	10	37	
6)	History of alcoholism	Present	0	0	4	33.3	8	66.7	0.01*
		Absent	16	42.1	10	26.3	12	31.6	

Data are expressed as percentages with absolute numbers.

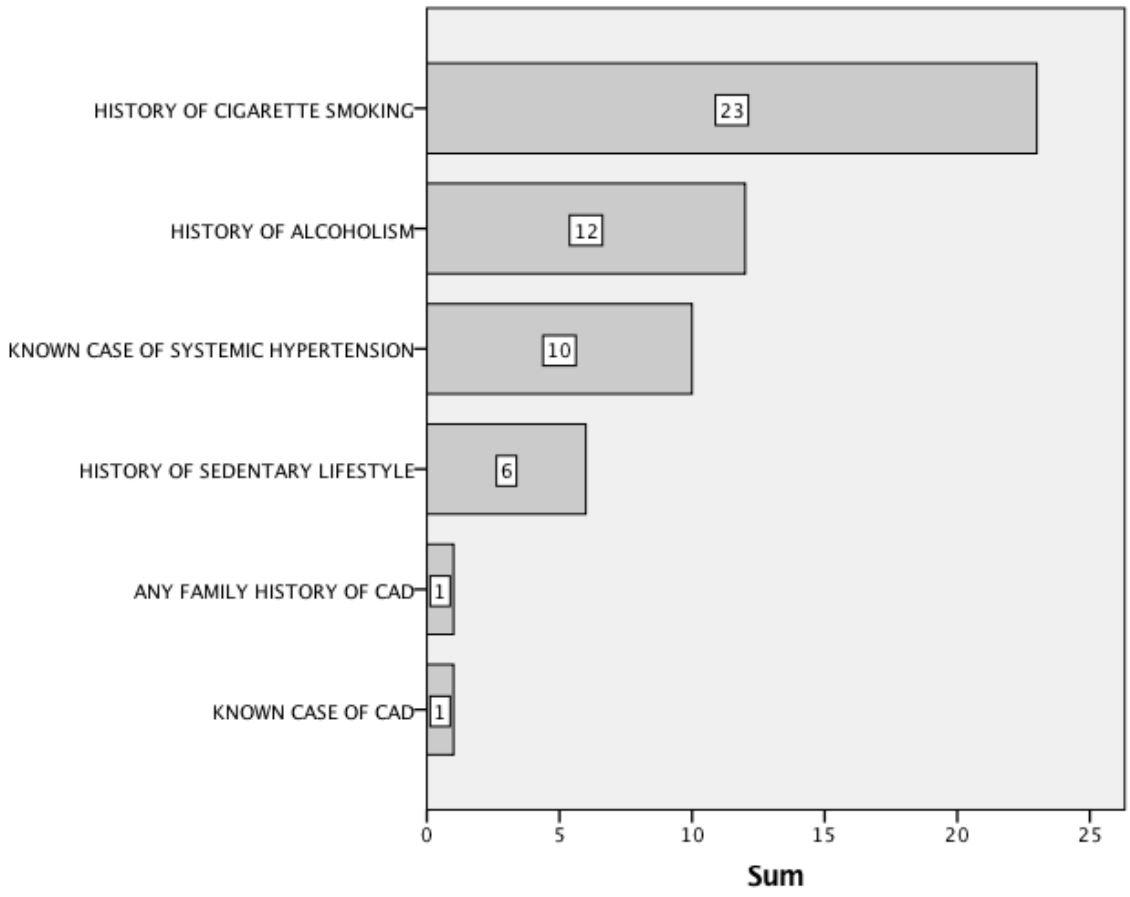


Figure5: Bar Chart showing numbers of distribution of risk factors in study population

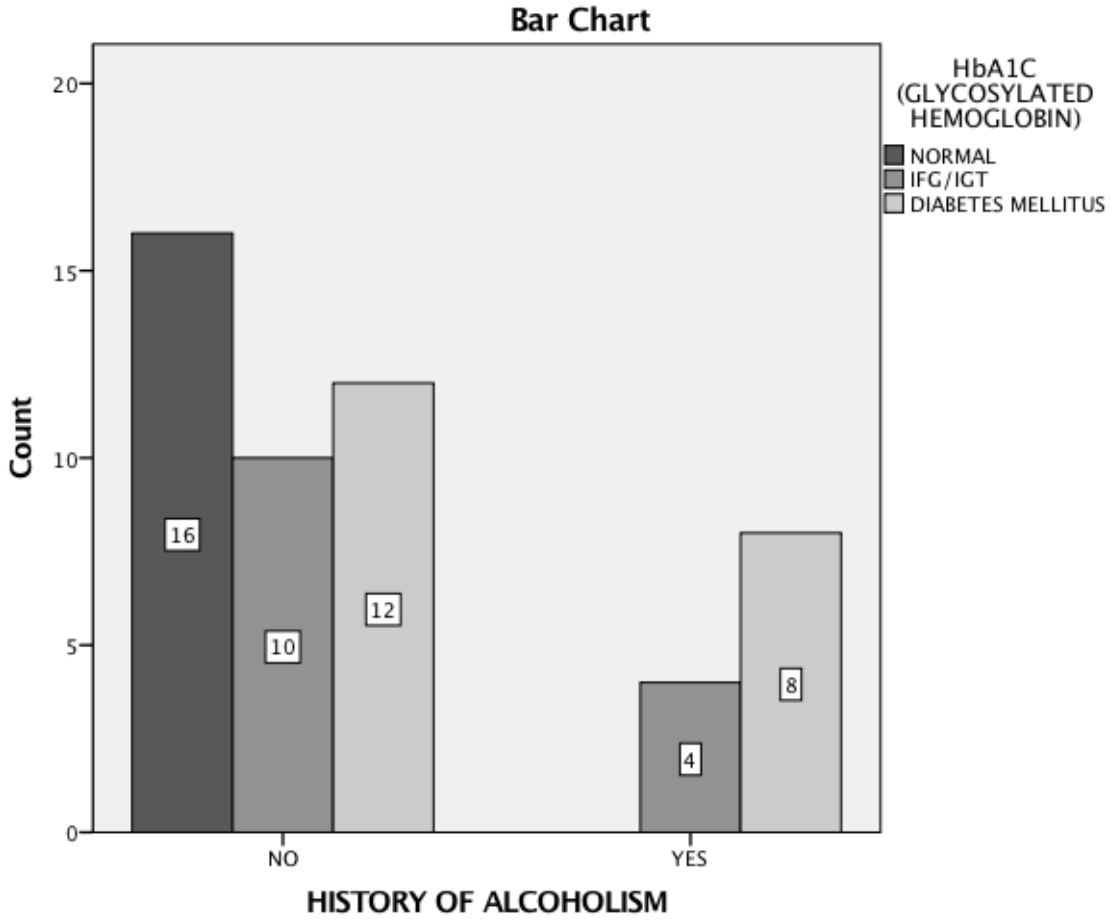


Figure 6: Bar chart of history of alcoholism in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

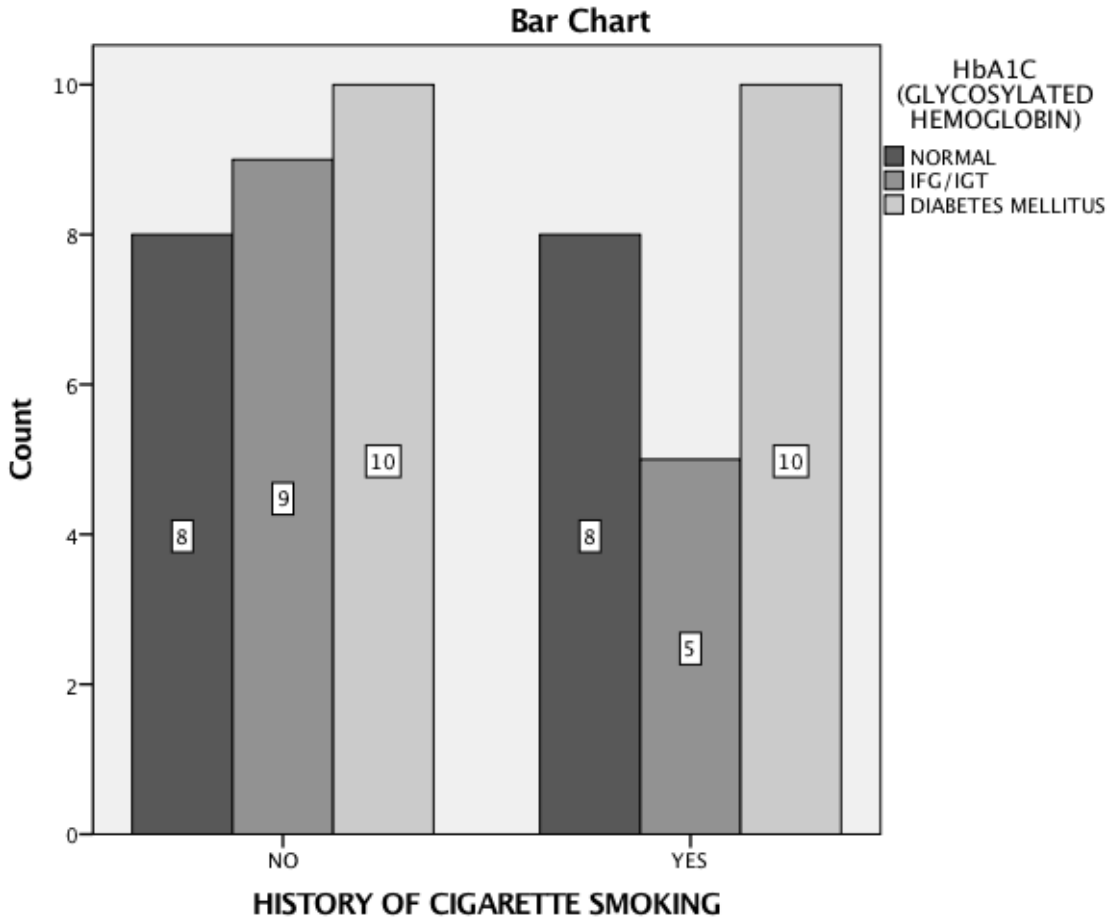


Figure 7: Bar chart of history of cigarette smoking in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

4. ADMISSION RANDOM BLOOD SUGAR AND LIPID PROFILE

Table 6.Distribution of Random blood sugar and abnormal lipid profile in study population

S. No	Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value
			N	%	n	%	n	%	
1	Random blood sugar	Hypoglycemia	7	46.7	4	26.7	4	26.7	0.2 (NS)
		Normal	8	26.7	10	33.3	12	40	
		Hyperglycemia	1	20	0	0	4	80	
2	Abnormal lipid level	Present	6	35.3	3	17.6	8	47.1	0.49 (NS)
		Absent	10	30.3	11	33.3	12	36.4	

Data are expressed as percentages with absolute numbers.

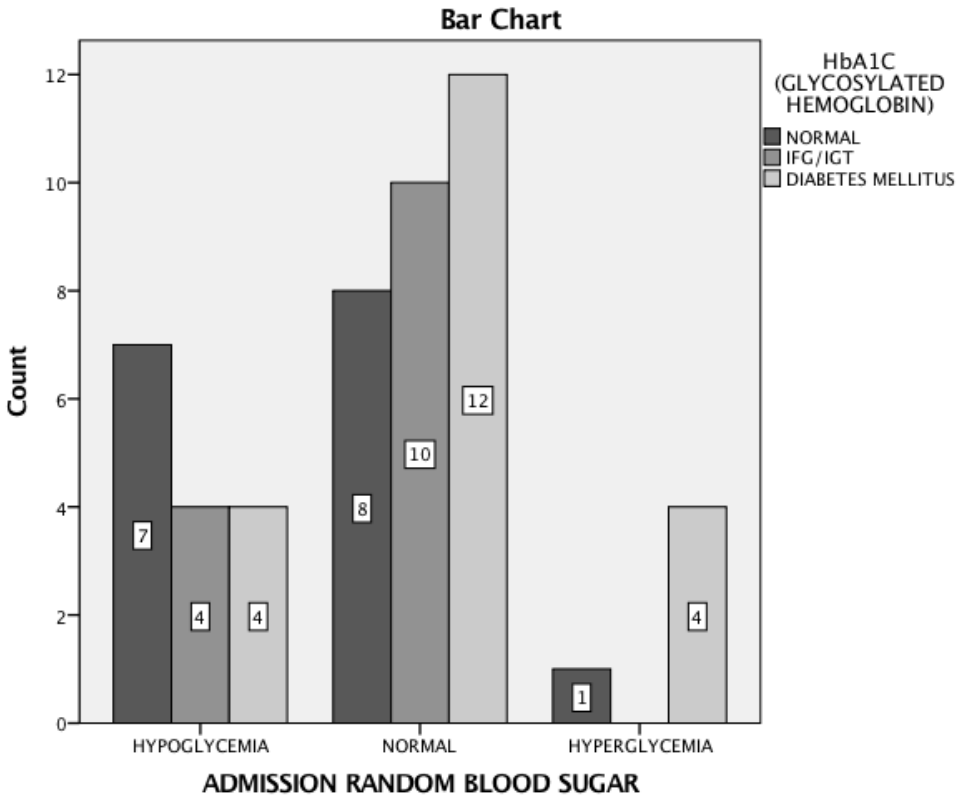


Figure 8: Bar chart of admission random blood sugar in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

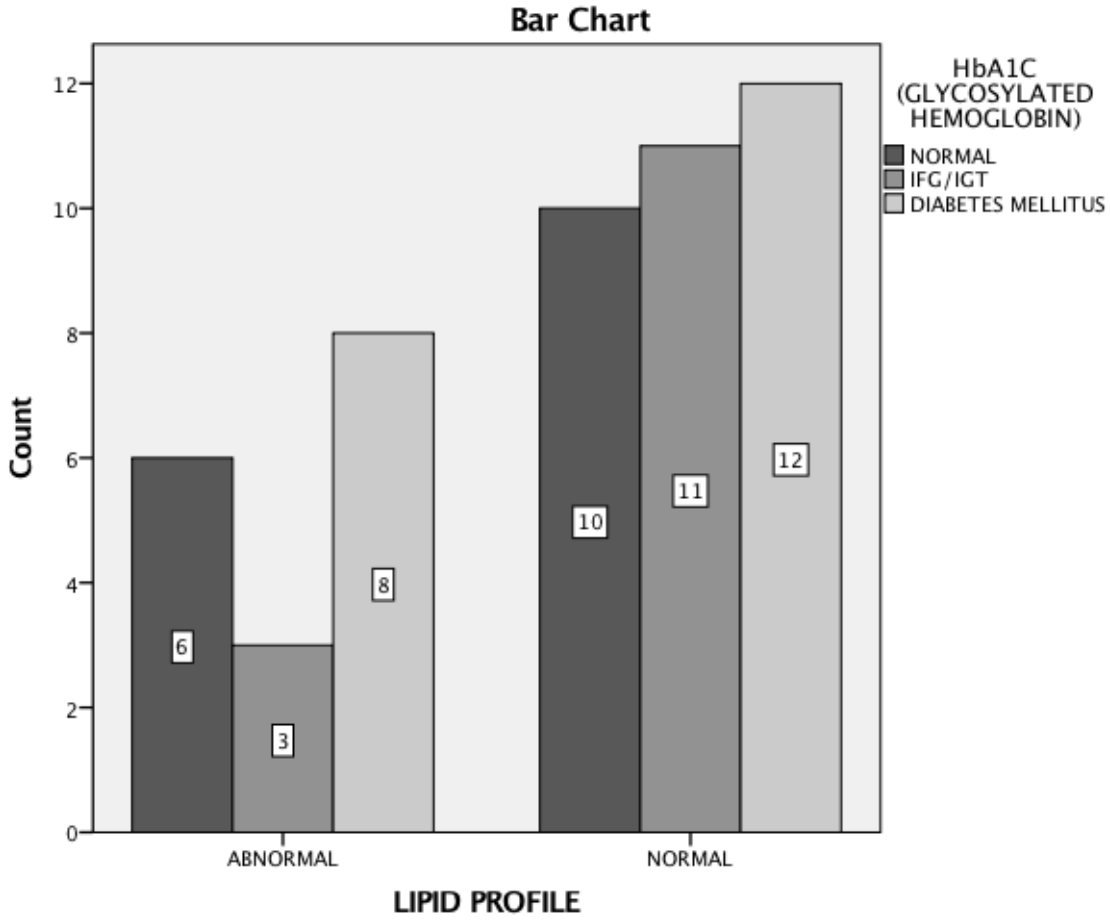


Figure 9: Bar chart of lipid profile in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

5. COMPLICATIONS OF MYOCARDIAL INFARCTION

Table 7: Distribution of complications of myocardial infarction among the groups of abnormal and normal HbA1c and RBS in the study population.

S. No	Parameter		COMPLICATIONS OF MI		P value
			Present	Absent	
1	HbA1c	Abnormal	21	13	0.032*
		Normal	4	12	
2	Admission RBS	Abnormal	4	1	0.349 (NS)
		Normal	21	24	

Data is expressed in absolute numbers. * indicates $p<0.05$ and considered statistically significant.

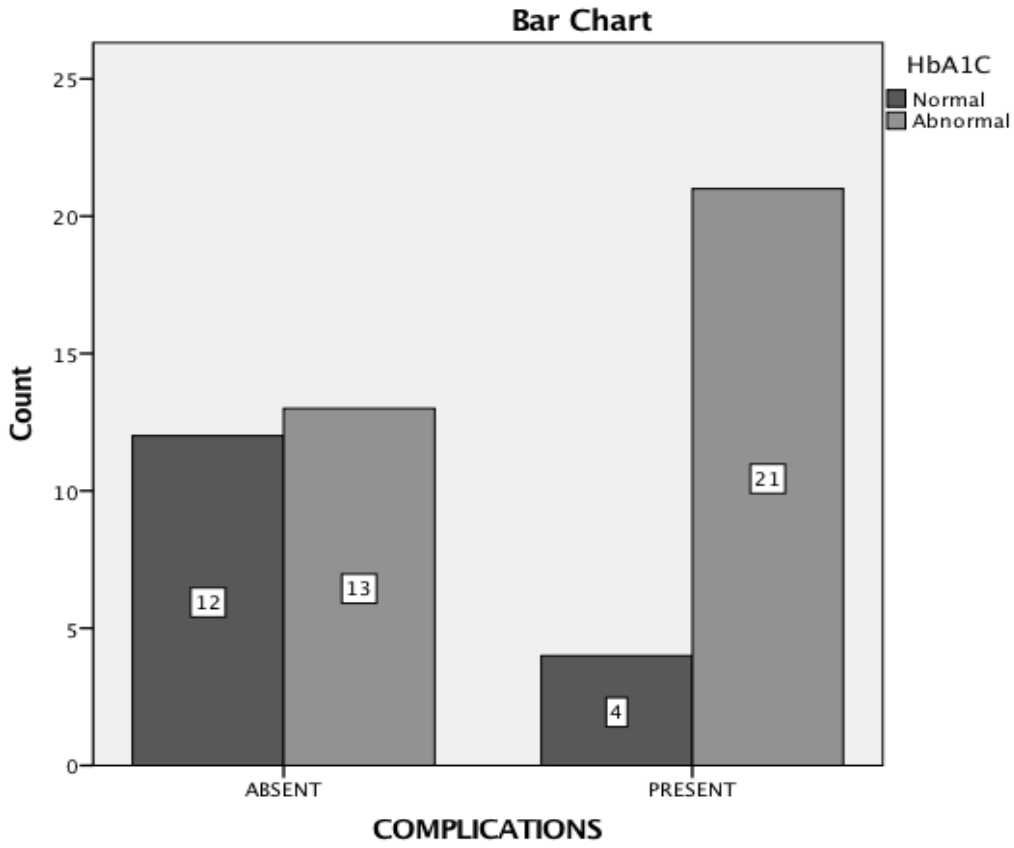


Fig 10: Bar diagram showing complications of Myocardial Infarction in the study population against the number of patients with normal or abnormal HbA1c

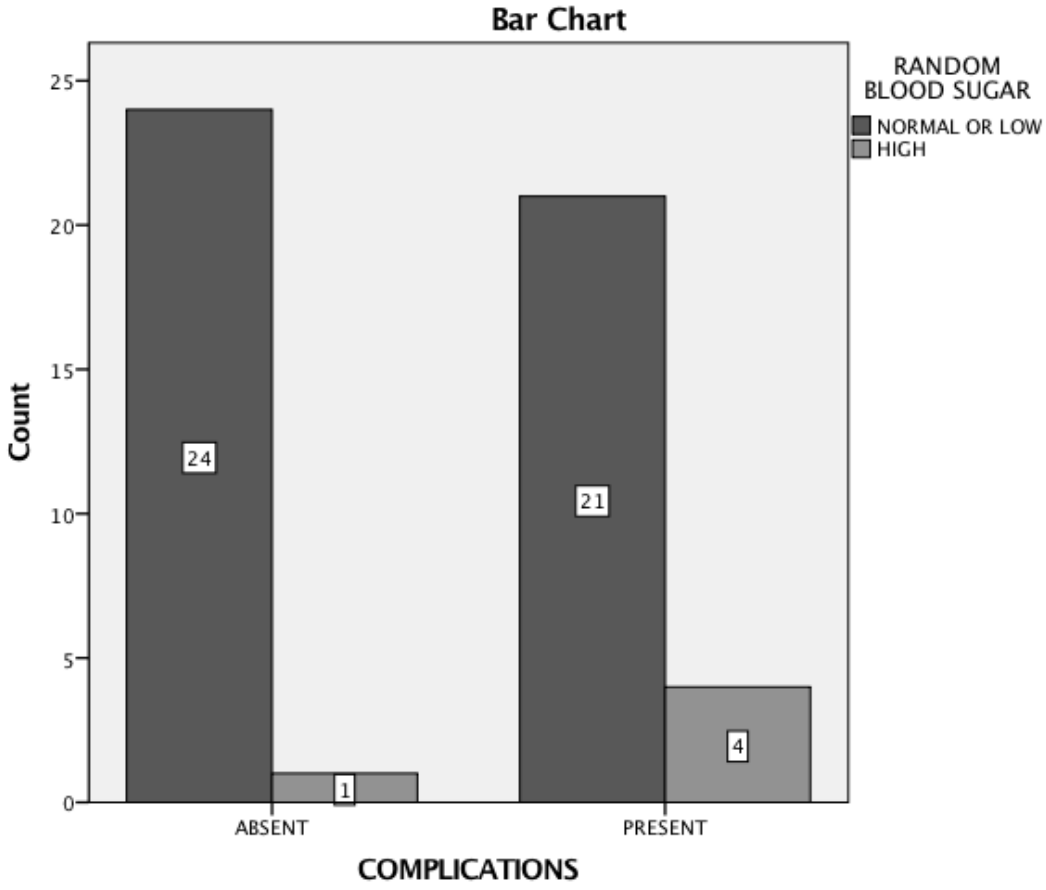


Fig 11: Bar diagram showing complications of Myocardial Infarction in the study population against the number of patients with normal or abnormal admission RBS

Table8. Distribution of major complications of CAD between groups in the study population

S. No	Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value
			N	%	n	%	n	%	
1	Cardiogenic shock	Present	1	8.3	2	16.7	9	75	0.015*
		Absent	15	39.5	12	31.6	11	28.9	
2	Cardiac Failure	Present	2	13.3	4	26.7	9	60	0.1 (NS)
		Absent	14	40	10	28.6	11	31.4	
3	Pulmonary edema	Present	1	50	0	0	1	50	0.65 (NS)
		Absent	15	31.3	14	29.2	19	39.6	
4	Arrhythmias	Present	2	18.2	3	27.3	6	54.5	0.45 (NS)
		Absent	14	35.9	11	28.2	14	35.9	

Data are expressed as percentages with absolute numbers.

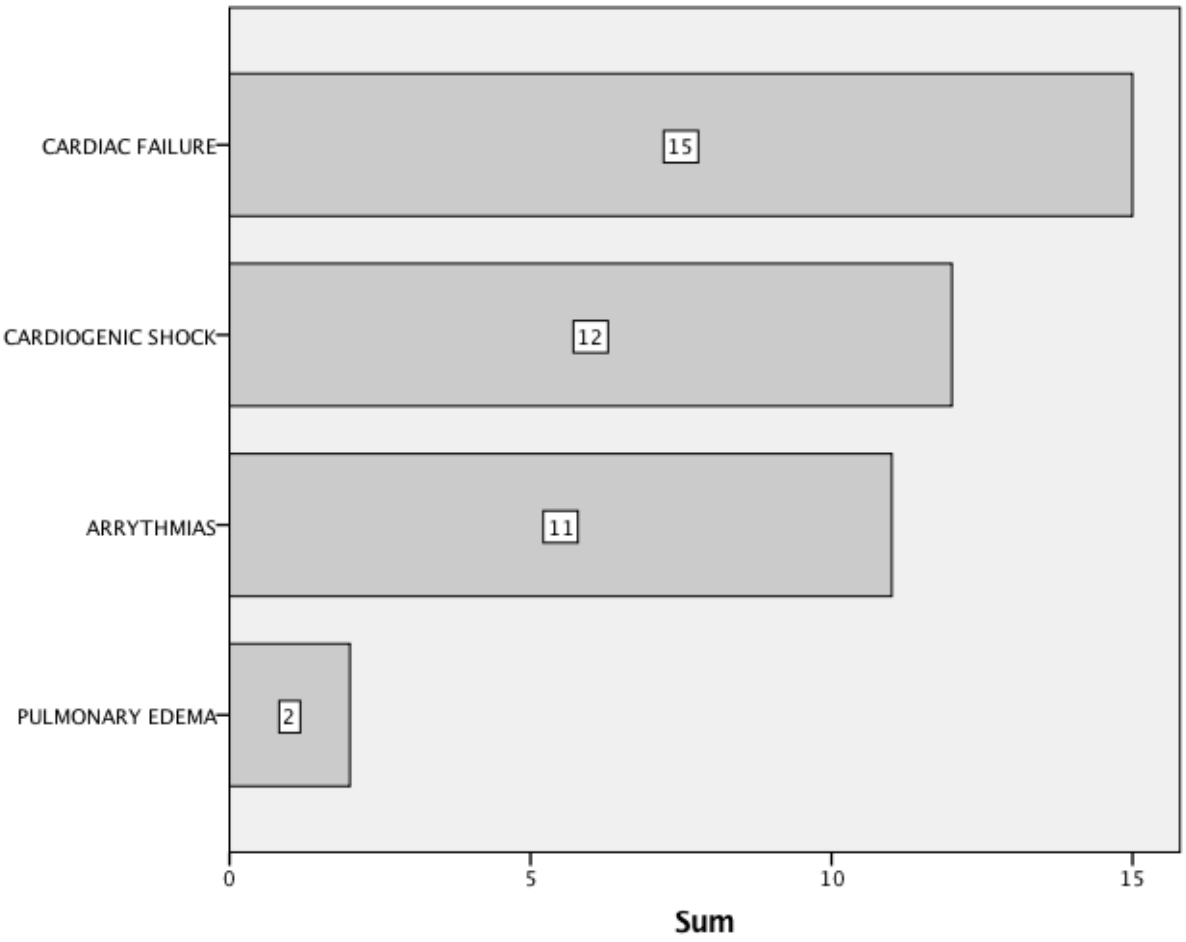


Figure12: Bar Chart showing numbers of distribution of complications of CAD in study population

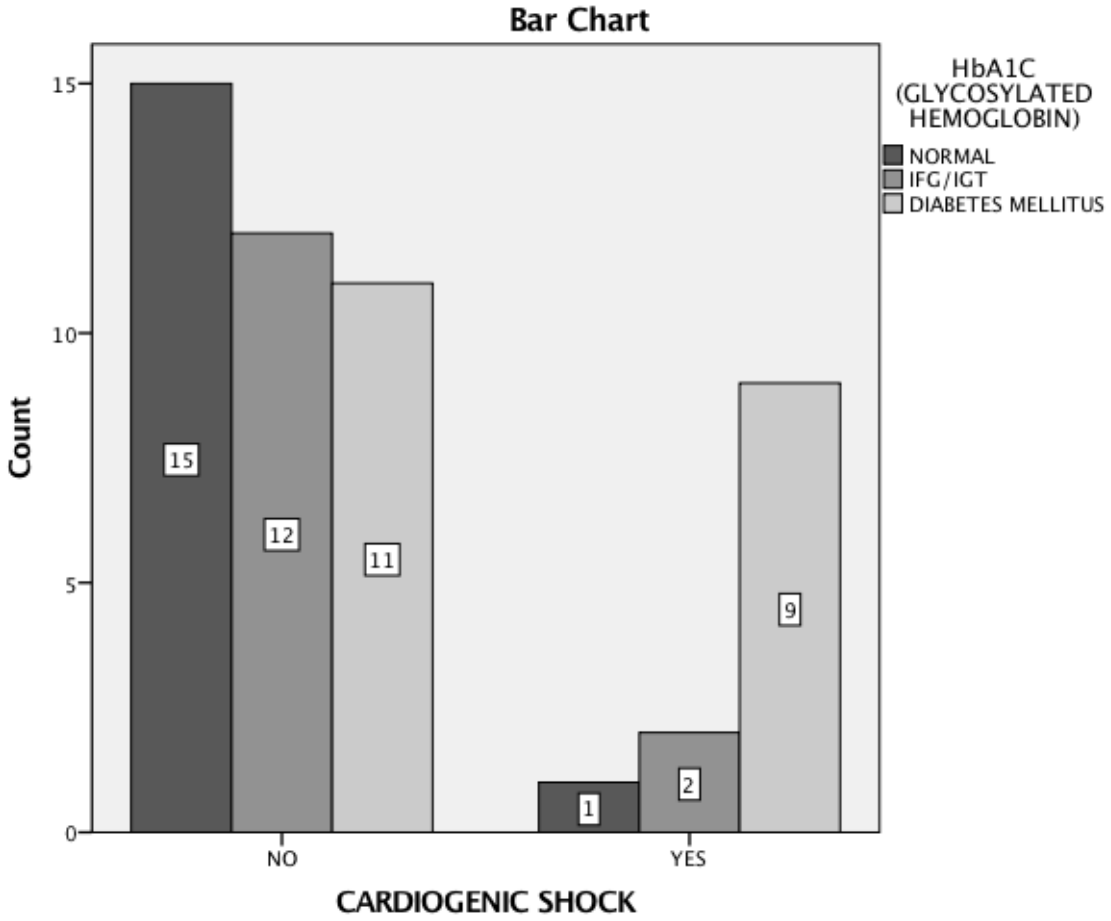


Figure 13: Bar chart of cardiogenic shock in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

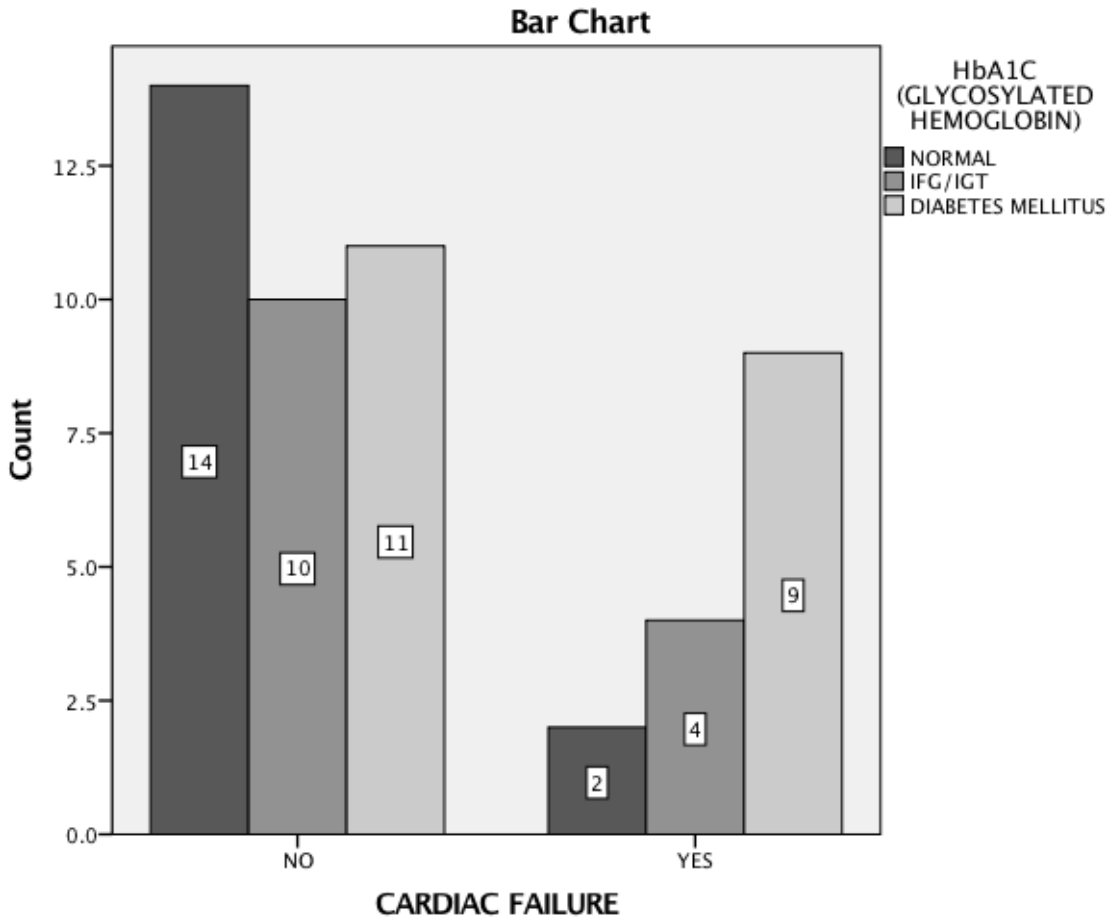


Figure 14: Bar chart of Cardiac Failure in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

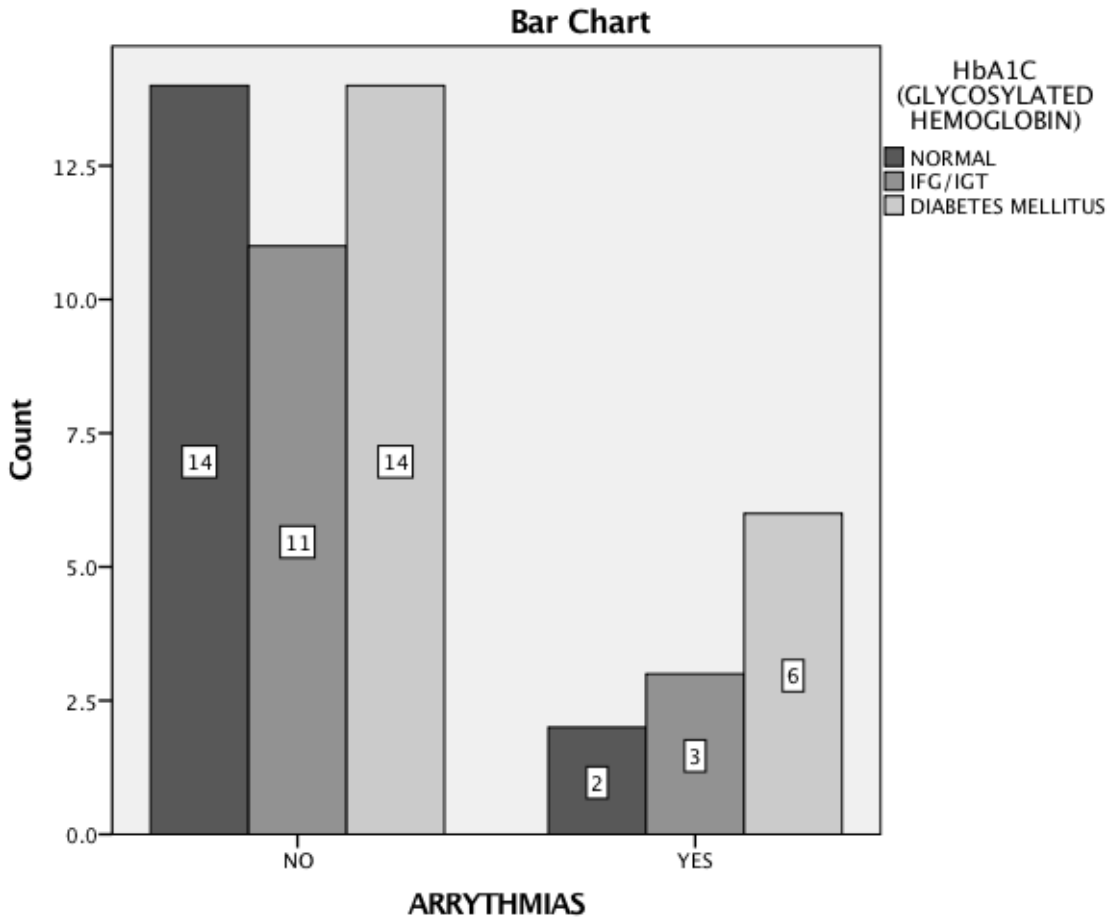


Figure 15: Bar chart of Arrhythmias in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

Table 9.Complications of CAD vs Wall involved

S. No	Parameter		Anterior Wall (n=27)		Inferior Wall (n=23)		P value
			n	%	n	%	
1	Cardiogenic shock	Present	7	58.3	5	41.7	0.73 (NS)
		Absent	20	52.6	18	47.4	
2	Cardiac Failure	Present	9	60	6	40	0.57 (NS)
		Absent	18	51.4	17	48.6	
3	Pulmonary edema	Present	1	50	1	50	0.9 (NS)
		Absent	26	54.2	22	45.8	
4	Arrhythmias	Present	8	72.7	3	27.3	0.15 (NS)
		Absent	19	48.7	20	51.3	

Data are expressed as percentages with absolute numbers.

Table 10 Complications of CAD vs admission RBS

S. No	Parameter		Hypoglycemia(n=16)		Normal (n=14)		Hyperglycemia group (n=20)		P value
			n	%	n	%	n	%	
1	Cardiogenic shock	Present	2	16.7	8	66.7	2	16.7	0.41 (NS)
		Absent	13	34.2	22	57.9	3	7.9	
2	Cardiac Failure	Present	0	0	12	80	3	20	0.007*
		Absent	15	42.9	18	51.4	2	5.7	
3	Pulmonary edema	Present	0	0	1	50	1	50	0.13 (NS)
		Absent	15	31.3	29	60.4	4	8.3	
4	Arrhythmias	Present	1	9.1	9	81.8	1	9.1	0.2 (NS)
		Absent	14	35.9	21	53.8	4	10.3	

Data are expressed as percentages with absolute numbers.

Table 11.Ejection Fraction and Mortality

S. No	Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value
			n	%	n	%	n	%	
1	Ejection fraction	Normal	4	44.4	2	22.2	3	33.3	0.43 (NS)
		Mild	8	30.8	10	38.5	8	30.8	
		Moderate	4	33.3	1	8.3	7	58.3	
		Severe	0	0	1	33.3	2	66.7	
2	Mortality	Present	0	0	0	0	2	100	0.2 (NS)
		Absent	16	33.3	14	29.2	18	37.5	

Data are expressed as percentages with absolute numbers.

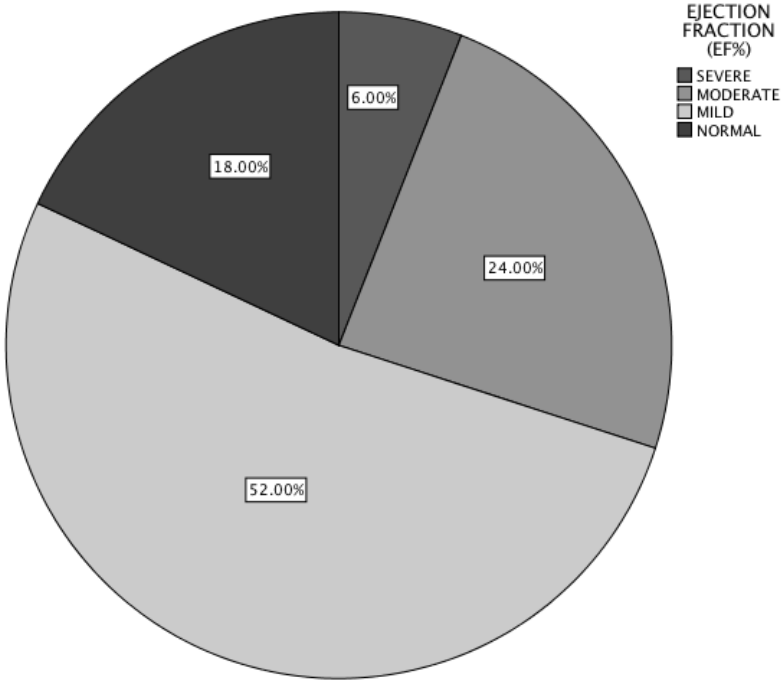


Figure 16: Pie Chart representation of Ejection Fraction in the study population.

Numbers indicate percentage of the total.

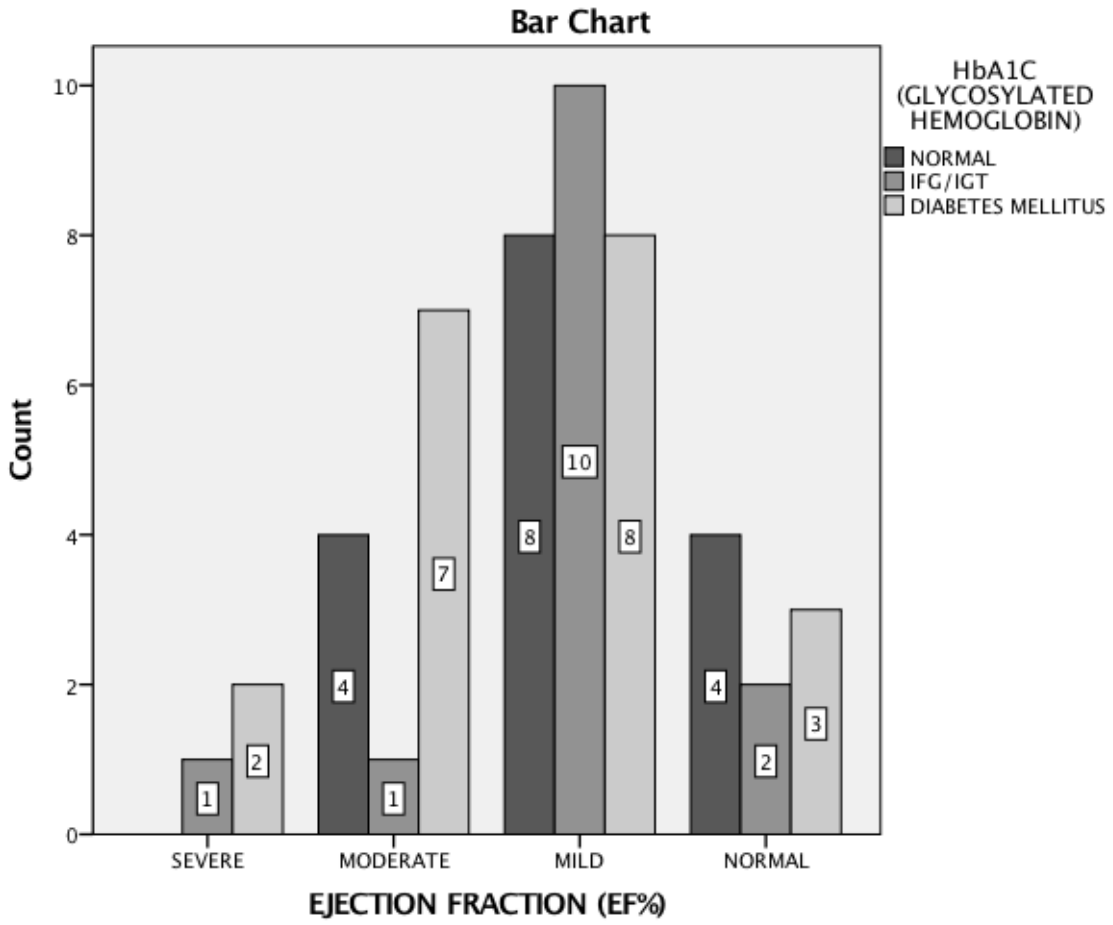


Figure 17: Bar chart of Ejection Fraction in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

Table12.Wall of LV involved

Parameter		Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value
		N	%	n	%	n	%	
Wall Involved	Anterior Wall	7	25.9	9	33.3	11	40.7	0.52 (NS)
	Inferior Wall	9	39.1	5	21.7	9	39.1	

Data are expressed as percentages with absolute numbers.

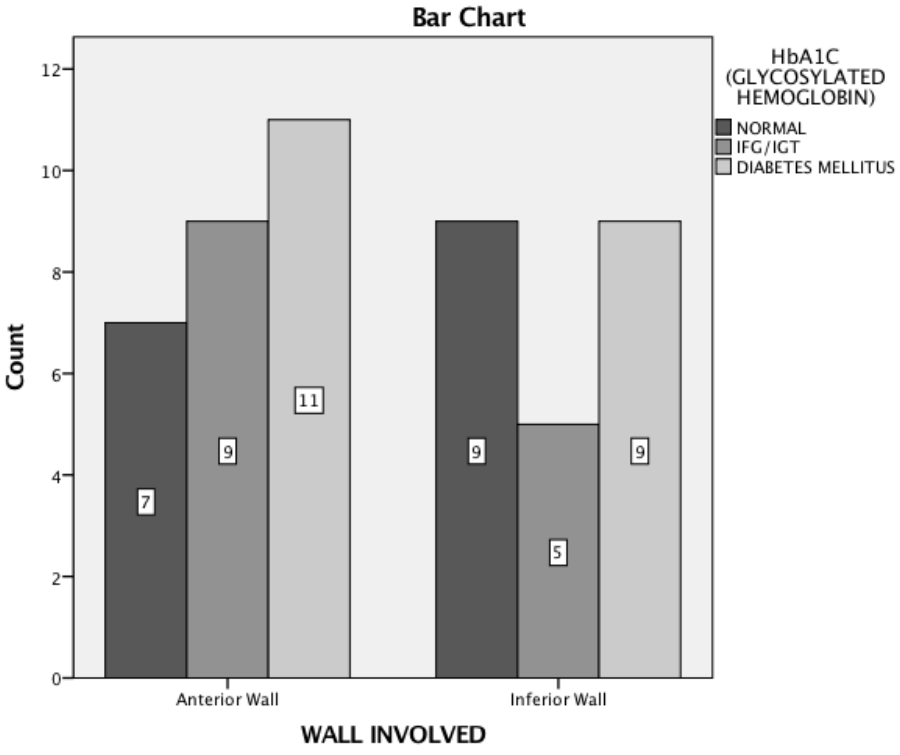


Figure18: Bar chart of Wall of LV involved in study population against the number of patients with normal, impaired glucose tolerance and diabetes with HbA1c values.

Table13.Comparison of different parameters between the groups in the study population

S. No	Parameter	Normal group (n=16)		Prediabetes group (n=14)		Diabetic group (n=20)		P value
		Mean	SD	Mean	SD	Mean	SD	
1	Average Blood Glucose (mg/dl)	87.3	17.2	125.6	0.68	182.9	35.7	<0.001*#
2	Random blood glucose at admission (mg/dl)	101.8	64.9	112.3	40.6	148.3	79.8	0.09 (NS)
3	Ejection fraction (%)	42.9	8.5	43	6.78	38.3	8.46	0.14 (NS)
4	HBA1C glycosylated	4.64	0.55	6.09	0.23	7.92	1.19	<0.0001*#

Data are expressed as mean with standard deviation. One way ANOVA with post hoc multiple comparison was used to test the level of significant difference. * indicates p< 0.0001 when diabetic group is compared with normal group and # indicates p<0.0001 when prediabetes group is compared with the normal group.

Table14: Diagnostic test values of various risk factors and complications in the study between normal and diabetic groups

S. No	Variables (if positive)	Odd's ratio (%)	95% Confidence interval (%)	P value
1	Cardiogenic shock	12.27	1.3 to 111.7	0.02*
2	Arrhythmia	3	0.5 to 17.5	0.25 (NS)
3	Pulmonary edema	0.78	0.04 to 13.7	0.99 (NS)
4	Cardiac failure	5.7	1.02 to 32.1	0.06 (NS)

Table 15: significance of different study variables

VARIABLES	P VALUE	SIGNIFICANCE
GENDER	0.9	NON-SIGNIFICANT
HISTORY OF OTHER CARDIAC SYMPTOMS	0.41	NON-SIGNIFICANT
FAMILY HISTORY OF CAD	0.33	NON-SIGNIFICANT
KNOWN CASE OF CAD	0.33	NON-SIGNIFICANT
KNOWN CASE OF SYSTEMIC HYPERTENSION	0.95	NON-SIGNIFICANT
HISTORY OF SEDENTARY LIFE STYLE	0.92	NON-SIGNIFICANT
HISTORY OF CIGARETTE SMOKING	0.66	NON-SIGNIFICANT
HISTORY OF ALCOHOLISM	0.01	SIGNIFICANT
RANDOM BLOOD SUGAR	0.2	NON-SIGNIFICANT
ABNORMAL LIPID PROFILE	0.49	NON-SIGNIFICANT
CARDIOGENIC SHOCK	0.015	SIGNIFICANT
CARDIAC FAILURE	0.1	NON-SIGNIFICANT
PULMONARY EDEMA	0.65	NON-SIGNIFICANT
ARRHYTHMIAS	0.45	NON-SIGNIFICANT
EJECTION FRACTION	0.43	NON-SIGNIFICANT
WALL INVOLVED	0.52	NON-SIGNIFICANT
MORTALITY	0.2	NON-SIGNIFICANT

Table 16: Correlation of HBA1C value with the RBS value and average blood glucose value in different groups of the study

S. No	Para meter	Overall (n=50)			Normal group (n=16)			Prediabetes group (n=14)			Diabetic group (n=20)		
		r value	95 % CI	P value	r value	95 % CI	P value	r value	95% CI	P value	r value	95% CI	P value
1	Average Blood glucose	0.98	0.97 to 0.99	<0.0001**	0.97	0.93 to 0.99	<0.0001**	0.98	0.95 to 0.99	<0.0001**	0.98	0.96 to 0.99	<0.0001**
2	Random Blood sugar at admission	0.33	0.05 to 0.56	0.01*	0.17	-0.3 to 0.61	0.52 (NS)	0.33	-0.24 to 0.73	0.24 (NS)	0.73	0.42 to 0.89	0.0003*

Pearson correlation was used to determine the strength of association.

DISCUSSION

- Out of 50 cases included in this study, 2 died and the rest 43 were discharged for further follow up.
- Both of the deaths were in the diabetic group (100%)
- Among the patients discharged, 18 were in the diabetic group (37.5%), 14 in the prediabetes group (14%) and 16 in the normal group (33.3%).
- Majority of the cases (54%) were in the age group 40-60 years.
- Among the age group 40-60 years, most were males (77.8%)
- Among males the majority 39% belonged to the diabetic group.
- Among females the majority 44.4% belonged to the diabetic group.
- History of chest pain was present in all the cases (100%)
- History of other cardiac symptoms were present in 13 patients in diabetic group (48.1%), 6 in prediabetes group (22.2%) and 8 in normal HbA1c group (29.6%).
- Family history of CAD was present in only 1 patient and had normal HbA1c
- In the study population, only one case was a known case of CAD and had normal HbA1c.
- 10 cases in the study population were a known case of systemic hypertension (20%). Four patients in the diabetic group (40%), 3 in prediabetes group (30%) and 3 in normal group (30%)

- 6 patients in the study population had history of sedentary lifestyle (12%). They were equally divided in normal, prediabetes and diabetic group with 2 patients each (33.3%).
- 23 patients gave history of cigarette smoking (46%). 10 in the diabetic group (43.5%), 5 in prediabetes group (21.7%) and 8 in normal group (34.8%).
- 12 patients gave history of alcoholism (24%). 8 in the diabetic group (66.7%) and 4 in the prediabetes group (33.3%). None in the normal group had history of alcoholism.

According to RBS value at admission patients were divided in into hypoglycemia, normal RBS and hyperglycemia as previously mentioned.

- 4 patients in the diabetic group with high HbA1c had hypoglycemia on admission (26.7%), 4 patients in the prediabetes group (26.7%) had hypoglycemia on admission.
- 12 patients in the diabetic group (40%) had normal blood sugar on admission, 10 patients in the prediabetes group (33.3%) had normal blood sugar on admission.
- 4 patients with hyperglycemia on admission had high HbA1c. 1 patient with high random blood sugar on admission (20%) had high HbA1c.
- 47.1% of patients with dyslipidemia had high HbA1c. 35.3% with dyslipidemia had normal HbA1c and 17.6% with dyslipidemia had prediabetes.
- 15 patients had cardiac failure (30%), 12 with cardiogenic shock (24%), 11 with arrhythmias (22%) and 2 with pulmonary edema (4%) making cardiac failure the most common complication in the study population.

- A total of 12 patients went in for Cardiogenic shock. Among them 75% were in the diabetic group, 16.7% in prediabetes group and 8.3% in normal group.
- A total of 15 patients had cardiac failure and among them 60% were in the diabetic group, 26.7% in prediabetes group and 13.3% in normal group.
- Two patients had Pulmonary edema. One in diabetic group and other in normal group.
- 11 patients had Arrhythmias in the study population. 54.5% in the diabetic group, 27.3% in the prediabetes group and 18.2% in the normal group.

Ejection fraction was divided into normal, mild, moderate and severe based on degree of LV dysfunction mentioned previously. 9 patients had normal LV function (18%), 26 with mild LV dysfunction (52%), 12 with moderate (24%) and 3 with severe LV dysfunction (6%).

- Three patients had severe LV dysfunction. Two in diabetic group (66.7%) and 1 in prediabetes group (33.3%)
- 12 patients had moderate LV dysfunction. 7 patients in diabetic group (58.3%), 1 in prediabetes group (8.3%), 4 in normal group (33.3%).
- 26 patients with mild LV dysfunction, 8 were in the diabetic group (30.8%), 10 in prediabetes group (38.5%) and 8 in normal group (30.8%).
- Anterior wall was involved in 27 patients (54%). 11 were in the diabetic group (40.7%), 9 in the prediabetes group (33.3%) and 7 in the normal group (25.9%).

- Inferior wall was involved in 23 patients (46%). 9 were in the diabetic group (39.1%), 5 in the prediabetes group (21.7%) and 9 in the normal group (39.1%).

Complications of STEMI were compared to the wall of LV involved in STEMI

- Among 12 patients with shock, 7 had anterior wall STEMI (58.3%) and 5 had inferior wall STEMI (41.7%)
- Among 15 patients with cardiac failure, 9 had anterior wall STEMI (60%) and 6 had inferior wall STEMI (40%)
- Two patients with pulmonary edema, one had anterior wall and one had inferior wall STEMI.
- Among 11 patients with arrhythmia, 8 had anterior wall STEMI (72.7%) and 3 had inferior wall STEMI (27.3%).

Complications of the study population were compared to the admission RBS

- 15 patients with cardiac failure, all had normal or hyperglycemia. 3 had hyperglycemia (20%) and 12 with normal glycemic status (80%).
- 12 patients with cardiogenic shock, 2 had hyperglycemia (16.7%), 8 had normal glycemic status (66.7%), 2 had hypoglycemia (16.7%).
- Two patients with pulmonary edema, one had normal glycemic status, other with hyperglycemia.
- Among 11 patients with arrhythmias, 1 had hyperglycemia (9.1%), 9 had normal glycemic status (81.8%) and 1 had hypoglycemia (9.1%).

With the above primary data, analysis was done

1. Gender was not found to be statistically significant (p value 0.9)
2. History of other cardiac symptoms was not found to be statistically significant (p value 0.41)
3. Family history of CAD was not found to be statistically significant (p value 0.33)
4. Known case of CAD was not found to be statistically significant. (p value 0.33)
5. Known case of systemic hypertension was not found to be statistically significant. (p value 0.95)
6. History of sedentary lifestyle was not found to be statistically significant. (p value 0.92)
7. History of cigarette smoking was not found to be statistically significant. (p value 0.66)
8. History of alcoholism was found to be significant. (p value 0.01)
9. Random blood sugar at admission was not found to be statistically significant. (p value 0.2)
10. Abnormal lipid profile was not found to be statistically significant. (p value 0.49)
11. Cardiogenic shock was found to be statistically significant. (p value 0.015)
12. Cardiac failure was not found to be statistically significant. (p value 0.1)
13. Pulmonary edema was not found to be statistically significant. (p value 0.65)
14. Arrhythmias was not found to be statistically significant. (p value 0.45)
15. Ejection Fraction was not found to be statistically significant. (p value 0.43)

16. Complications of MI was found more in the abnormal HbA1c group with p value of 0.032 which is statistically significant.
17. No statistical difference was found for the occurrence of complications between normal and abnormal group of random blood sugar. (p value 0.349)

Comparison of different parameters like Average blood glucose, Random blood sugar at admission, Ejection fraction (%) were made among the groups in the study population using One way ANOVA with post hoc multiple comparison

1. The mean average blood glucose for the diabetic group was found to be 182.9, prediabetic (125.6), normal (87.3) (p value <0.001 Significant).
2. The mean Random blood sugar at admission for the diabetic group (148.3), prediabetes (112.3), normal (101.8) (p value <0.09 NS).
3. The mean ejection fraction was 38.3% in the diabetic group, 43 in the prediabetes group and 42.9 in the normal group. (P value 0.14 NS).

Diagnostic test values of various risk factors and complications of STEMI were compared between normal and the diabetic group.

1. Cardiogenic shock with an Odd's ratio of 12.27 with 95% confidence interval with p value of 0.02 (statistically significant)
2. Arrhythmia with Odd's ratio of 3 (p value 0.25 NS)
3. Pulmonary edema with Odd's ratio of 0.78 (p value 0.99 NS)
4. Cardiac failure with Odd's ratio of 5.7 (p value 0.06 NS)

Correlation of HbA1c value with the Admission RBS was done in the different groups of the study using Pearson correlation.

1. In the overall study population, the strength of association was weak with an r value of 0.33 (p value 0.01 significant).
2. In the diabetes group r value was 0.73, the strength of association was strong (p value 0.0003 significant)

SUMMARY

- Maximum number of patients in the study population belonged to the age group of 40 to 60 years (54%) with more number of males (82%).
- No age or gender preponderance were identified pertaining to the different groups.
- In the total study population of 50 based on the HbA1c values, 14 were in the prediabetic group,20 were in the diabetic group, thus presenting with a macrovascular complication even before diabetes was diagnosed.it was already proposed that HbA1c level is a stable indicator of unstressed long-term glucose control and is more useful to predict abnormal glucose tolerance in AMI patients compared with admission glucose[21]
- There was no difference in clinical presentation, previous history of CAD and family history of CAD of the patients in the different groups.
- There was no significant difference among the three groups regarding sedentary life style & the habit of smoking.
- The history of Alcoholism was significantly found more in patients who were in the diabetic group. Eight out of twenty in the diabetic group were using alcohol.(P value – 0.01)
- There was no significance for normal or abnormal lipid profile among the groups.
- The random blood sugar (whether normoglycemic, hypoglycemic or hyperglycemic) at the time of admission didn't show any significant difference among the three groups.

- The mean admission blood sugar was almost similar in the three groups.
- Even though it was statistically insignificant it was interesting to note that four out of 20 patients in the diabetic group had hypoglycaemia at presentation.
- The random blood sugar values had a correlation with the HbA1c values only in the diabetic group and in the overall study population but not with the prediabetes or the normal group. Thus random blood sugar value correlates well with diabetic group, it is poor in predicting a prediabetic or normoglycemic status.
- Complications of cardiac failure was high in admission RBS>200mg/dl (P value 0.007)
- The complications of STEMI were found more in Abnormal HbA1c group rather than the normal group (P value 0.032) with odds ratio of 4.84.
- There was no significant difference in occurrence of complications among the abnormal & normal RBS groups.
- Cardiogenic shock was found to be more in the diabetic group and was found statistically significant (P value 0.015). It was found that there was significant difference in risk for cardiogenic shock in patients belonging to diabetic group rather than normal group. There is 12.27% more risk for cardiogenic shock in patients belonging to the diabetic group than the normal group of the study population.
- There was no significant difference regarding the occurrence of arrhythmias , cardiac failure , pulmonary edema or difference in ejection fraction in ECHO among the three groups of study population.

- There was no increased risk for pulmonary edema , cardiac failure , arrhythmias in the diabetic group when compared to the normal group.
- Eventhough it was statistically insignificant , it was found that risk of cardiac failure was more in the diabetic group.(P value 0.06)
- Mortality was 4% in the study population. All of them belonged to the diabetic group.[149]

Vinita etal has mentioned that the correlation between higher HbA1c levels and increased cardio-vascular mortality occurs even before the diagnosis of clinical diabetes. [150]

LIMITATIONS OF THE STUDY

- The sample size of the study population was small due to the less number of nondiabetic patients presented to the institution during the study period.
- A large sample multicentre study will have the power to stratify the risk of complications among the three groups in the study population.
- This was an observational and nonrandomised study.
- The study was done till the patient was discharged from the hospital
- Further follow up is required for assessing the glycemic status and the long term morbidity.
- STEMI was not confirmed by cardiac biomarkers
- Angiographic evidence was not obtained since the procedure was not available in the institution.

CONCLUSION

- This study suggests that the occurrence of complications following Acute STEMI is more in non-diabetic patients with HbA1c more than 6.5.
- The risk for cardiogenic shock is 12.27 % more when compared to the normal population in non-diabetic patients with HbA1c more than 6.5.
- Occurrence of cardiac failure was more in patients with elevated admission blood glucose more than 200mg/dl but not the other complications.
- Prior history of alcoholism was significantly more seen in the diabetic group.
- Admission blood glucose correlates well only with HbA1c in predicting Diabetes in the study population but not normoglycemia or prediabetic state.

Hence HbA1c should be availed in all patients presenting with STEMI irrespective of their glycemic status as it helps in risk stratification for complications and diagnosing Diabetes or prediabetic state.

Further studies with larger sample size and comparative design are required to describe and reinforce the role of HbA1c in Nondiabetic patients with Acute STEMI.

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ANNEXURE 1

PROFORMA

A STUDY ON PROGNOSTIC VALUE OF ADMISSION HBA1C AND BLOOD GLUCOSE IN NON DIABETIC PATIENTS WITH STEMI

DEMOGRAPHIC DATA:

NAME: AGE/SEX:

ADDRESS:

PHONE NO: IP NO.:

DIAGNOSIS:

HISTORY:	**YES**	**NO**
CHEST PAIN		
DYSPNOEA		
PALPITATION		
HYPERTENSION		
H/O ACS		
IF YES DETAILS		
DYSLIPIDEMIA		
FAMILY H/O CVD		
SEDENTARY LIFE STYLE		
OBESITY		

SMOKING/TOBACCO USE		

PHYSICAL EXAMINATION:

BP PR JVP

CVS RESP

OTHER SYSTEMS

ANTHROPOMETRY:

HEIGHT: WEIGHT: BMI: WAIST/HIP RATIO:

INVESTIGATIONS:

ADMISSION BLOOD GLUCOSE:

ADMISSION HBA1C:

CBC:

LIPID PROFILE:

ECG:

ECHO:

COURSE IN THE HOSPITAL:

CONDITION AT DISCHARGE:

ANNEXURE 2

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR SWATHY RAJU ,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant

ANNEXURE 3

MASTER CHART

KEY TO MASTER CHART

1. NAME
2. GENDER – M – MALE, F - FEMALE
3. AGE IN YEARS
4. IP NUMBER – IN PATIENT NUMBER
5. CHEST PAIN – 1- PRESENT, 0 – ABSENT
6. OTHER SYMPTOMS - 1- PRESENT, 0 – ABSENT
7. HYPERTENSION - 1- PRESENT, 0 – ABSENT
8. DYSPLIPIDEMIA - 1- PRESENT, 0 – ABSENT
9. KNOWN CAD - 1- PRESENT, 0 – ABSENT
10. SEDENTARY LIFE STYLE - 1- PRESENT, 0 – ABSENT
11. SMOKING - 1- PRESENT, 0 – ABSENT
12. ALCOHOLISM - 1- PRESENT, 0 – ABSENT
13. JVP - 1- ELEVATED, 0 – NOT ELEVATED
14. SHOCK –CARDIOGENIC SHOCK- 1- PRESENT, 0 – ABSENT
15. FAILURE – LV FAILURE - 1- PRESENT, 0 – ABSENT
16. PULMONARY EDEMA - 1- PRESENT, 0 – ABSENT
17. ARRHYTHMIA - 1- PRESENT, 0 – ABSENT

18. ABG – AVERAGE BLOOD GLUCOSE – IN mg/dl

19. HBA – HBA1C – IN %

20. RBS – ADMISSION RBS – IN MG/DL

21. LIPID PROFILE – 1 – HIGH, 0 – NORMAL

22. WALL – AW – ANTERIOR WALL, IW – INFERIOR WALL

23. OUTCOME – DI – DISCHARGE, DH - DEATH

MASTER CHART

OUTCOME	DI	DI	DI	DI	DI
WALL	IW	AW	IW	IW	IW
EF%	50	30	40	45	45
LIPID Profile	N	H	H	N	N
RBS	69	84	91	331	120
HbA1c	7.38	4.09	4.52	7.8	6.38
ABG	154.2	68.1	96.8	182.9	125.5
ARRYTHMIAS	0	0	0	0	0
PULMEDEMA	0	0	0	0	0
FAILURE	0	0	0	1	0
SHOCK	0	0	0	1	0
JVP	0	0	0	0	0
ALCOHOLIC	1	0	0	1	0
SMOKER	1	0	0	1	0
SEDENTARY	1	0	0	0	0
FAMILY	0	0	0	0	0
KNOWN CAD	0	0	0	0	0
DYSLIPIDEMIA	0	0	0	0	0
SHT	0	0	0	1	0
OTHERS	1	1	1	0	0
CHESTPAIN	1	1	1	1	1
IP NO:	12323	12345	13245	28190	28875
GENDER	M	F	M	M	M
AGE	63	65	63	40	61
NAME	MURUGESAN	RANI	NATARAJAN	GURUMOORTHY	SAMBATH

DI	DI	DI	DI	DI	DI	DI	DI
AW	IW	IW	IW	IW	IW	AW	IW
40	40	45	35	50	50	30	48
N	N	H	N	N	H	N	N
118	90	84	158	69	243	103	82
6.58	5.59	9.043	6.05	5.72	6.833	9.321	4.965
154.2	125.5	211.6	125.5	125.5	154.2	211.6	96.8
1	0	0	1	0	0	0	0
0	0	0	0	0	0	0	0
0	1	1	1	0	0	0	0
1	0	0	1	0	0	0	0
0	0	0	0	0	0	0	0
0	0	0	1	0	0	0	0
1	1	0	1	0	0	0	0
0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0
1	1	1	1	1	0	0	0
1	1	1	1	1	1	1	1
28467	28159	34500	28385	29069	35065	34485	34577
M	M	M	M	M	M	M	M
53	78	60	60	60	35	53	37
ANBALAGAN	SILUVARIMUTHU	KARUPPAIYYA	THANGAVEL	KARUNANITHI	RAJKUMAR	MARIYA JOSEPH	SATHYAMOORTHY

DI	DI	DI	DI	DI	DI	DI	DI
IW	AW	IW	IW	AW	AW	AW	AW
40	35	48	50	40	40	35	50
N	N	H	H	N	N	N	N
195	64	175	173	318	52	98	76
6.31	7.51	5.94	4.46	4.51	5.39	4.36	4.07
125.5	182.9	125.5	68.1	96.8	96.8	68.1	68.1
1	0	1	0	0	0	1	0
0	0	0	0	1	0	0	0
0	0	0	0	1	0	0	0
0	1	1	0	0	0	1	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0
0	1	0	1	1	0	1	1
0	0	1	0	0	0	0	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0
0	0	1	1	0	0	0	1
0	1	1	1	1	1	0	1
1	1	1	1	1	1	1	1
32561	32685	27742	27756	25503	25552	25851	26175
F	M	M	M	M	M	M	M
55	65	59	64	36	40	56	70
THAIYYALNAYAGI	KUNJAPPA	KRISHNAMOORTHY	SUNDARAMOORTHY	PANDIYAN	BARATHI	RAMADOSS	ALAGAPPAN

xxx

DI	DI	DI	DI	DI	DI	DI	DI
IW	IW	AW	IW	AW	IW	AW	AW
48	47	48	30	30	60	35	43
N	N	H	N	N	H	N	N
90	131	66	286	186	58	78	146
6.81	4.94	4.71	7.59	9.84	5.36	3.79	6.68
154.2	96.8	96.8	182.9	240.3	96.8	68.1	154.2
1	1	0	1	0	0	0	0
0	0	0	0	0	0	0	0
1	0	0	0	1	0	0	1
0	0	0	1	1	0	0	0
0	0	0	0	0	0	0	0
1	0	0	0	1	0	0	1
1	0	1	0	1	0	0	1
0	0	0	0	1	0	1	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	1
1	0	0	1	1	0	1	0
1	1	1	1	1	1	1	1
25359	28125	28246	32348	32456	24097	24567	23456
M	M	M	M	M	F	F	M
53	67	28	65	56	65	65	53
VADIVEL	NOOR MUHAMMED	SATHIYARAJ	PALANIYAPPAN	KAMARAJ	KALAVATHI	JANAKI	PALANISAMY